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Abstract

The use of fibrin sealant during non-emergency surgery: a systematic review of evidence of benefits and harms

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Background: Fibrin sealants are used in different types of surgery to prevent the accumulation of post-operative fluid (seroma) or blood (haematoma) or to arrest haemorrhage (bleeding). However, there is uncertainty around the benefits and harms of fibrin sealant use.

Objectives: To systematically review the evidence on the benefits and harms of fibrin sealants in non-emergency surgery in adults.

Data sources: Electronic databases [MEDLINE, EMBASE and The Cochrane Library (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment database and the Cochrane Central Register of Controlled Trials)] were searched from inception to May 2015. The websites of regulatory bodies (the Medicines and Healthcare products Regulatory Agency, the European Medicines Agency and the Food and Drug Administration) were also searched to identify evidence of harms.

Review methods: This review included randomised controlled trials (RCTs) and observational studies using any type of fibrin sealant compared with standard care in non-emergency surgery in adults. The primary outcome was risk of developing seroma and haematoma. Only RCTs were used to inform clinical effectiveness and both RCTs and observational studies were used for the assessment of harms related to the use of fibrin sealant. Two reviewers independently screened all titles and abstracts to identify potentially relevant studies. Data extraction was undertaken by one reviewer and validated by a second. The quality of included studies was assessed independently by two reviewers using the Cochrane Collaboration risk-of-bias tool for RCTs and the Centre for Reviews and Dissemination guidance for adverse events for observational studies. A fixed-effects model was used for meta-analysis.

Results: We included 186 RCTs and eight observational studies across 14 surgical specialties and five reports from the regulatory bodies. Most RCTs were judged to be at an unclear risk of bias. Adverse events were inappropriately reported in observational studies. Meta-analysis across non-emergency surgical specialties did not show a statistically significant difference in the risk of seroma for fibrin sealants versus standard care in 32 RCTs analysed [$n = 3472$, odds ratio (OR) 0.84, 95% confidence interval (CI) 0.68 to 1.04; $p = 0.13$; $I^2 = 12.7\%$], but a statistically significant benefit was found on haematoma development in 24 RCTs ($n = 2403$, OR 0.62, 95% CI 0.44 to 0.86; $p = 0.01$; $I^2 = 0\%$). Adverse events related to fibrin sealant use were reported in 10 RCTs and eight observational studies across surgical specialties, and 22 RCTs explicitly stated that there were no adverse events. One RCT reported a single death but no other study reported mortality or any serious adverse events. Five regulatory body reports noted death from air emboli associated with fibrin sprays.

Limitations: It was not possible to provide a detailed evaluation of individual RCTs in their specific contexts because of the limited resources that were available for this research. In addition, the number of RCTs that were identified made it impractical to conduct independent data extraction by two reviewers in the time available.

Conclusions: The effectiveness of fibrin sealants does not appear to vary according to surgical procedures with regard to reducing the risk of seroma or haematoma. Surgeons should note the potential risk of gas embolism if spray application of fibrin sealants is used and not to exceed the recommended pressure and spraying distance. Future research should be carried out in surgery specialties for which only limited data were found, including neurological, gynaecological, oral and maxillofacial, urology, colorectal and orthopaedics surgery (for any outcome); breast surgery and upper gastrointestinal (development of haematoma); and cardiothoracic heart or lung surgery (reoperation rates). In addition, studies need to use adequate sample sizes, to blind participants and outcome assessors, and to follow reporting guidelines.

Study registration: This study is registered as PROSPERO CRD42015020710.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CO_2	carbon dioxide
CRD	Centre for Reviews and Dissemination
EMA	European Medicines Agency
ENT	ear, nose and throat
FDA	Food and Drug Administration
GI	gastrointestinal
ITT	intention to treat
MD	mean difference
MHRA	Medicines and Healthcare products Regulatory Agency
OR	odds ratio
RCT	randomised controlled trial
SD	standard deviation

Plain English summary

Surgeons use fibrin sealants during operations in place of stitches. The sealants act like a biological glue, joining tissues together and stopping tissues leaking fluids. Using a fibrin sealant might lower the risk of having a seroma (a collection of fluids) or a haematoma (a collection of blood outside a blood vessel). It is not clear if fibrin sealants are more effective in operations at some body sites than at others, or in different types of operation. In addition, there have been reports of fibrin sealants causing serious harm to people.

This study brings together the evidence on the benefits and harms related to the use of fibrin sealants in different types of surgery. A total of 186 randomised controlled trials and eight observational studies were found that looked at the use of fibrin sealants during surgery at various body sites, including the liver, stomach, pancreas, heart and lungs. The evidence suggests a benefit for fibrin sealants in reducing the likelihood of haematomas, particularly in hernia surgery, but there is uncertainty regarding whether or not there is a benefit in surgery at all sites. Harms related to fibrin sealant use were reported in 10 randomised controlled trials and eight observational studies across surgical specialties, whereas 22 randomised controlled trials stated no harmful events. One randomised controlled trial reported a death caused by a large bleed that was possibly related to fibrin sealant use, but other studies did not report deaths or serious harms. However, holding the spray too close to a wound during application of the sealant has been found to introduce air into the body, which could increase the risk of dying, but this is rare.

We found a large number of studies that showed a reduction in the risk of developing haematoma during non-emergency surgery when fibrin sealant is used. Overall, the quality of the evidence found was unclear, mostly because the methods used in studies were not reported clearly. Future research is needed to improve the confidence of decision-making.

Scientific summary

Background

Fibrin sealants are used in different surgery procedures to arrest haemorrhage (bleeding) or prevent the accumulation of post-operative fluid (seroma) or blood (haematoma). It is unclear whether or not all surgical procedures benefit from fibrin sealants and there is concern that use of fibrin sealants could be associated with substantial harm.

Objectives

To systematically review the evidence on the clinical effectiveness and harms of fibrin sealants in non-emergency surgery in adults.

Data sources

Electronic databases [MEDLINE, EMBASE and The Cochrane Library (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Review of Effects, the Health Technology Assessment database and the Cochrane Central Register of Controlled Trials)] were searched from inception to May 2015. Ongoing and unpublished randomised controlled trials (RCTs) were identified from clinicaltrials.gov, controlledtrials.com and clinicaltrialsregister.eu. The Medicines and Healthcare products Regulatory Agency (MHRA), the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) websites were also searched to identify evidence of harms.

Methods

This review included RCTs and observational studies using any type of fibrin sealant compared with standard care in non-emergency surgery in adults that assessed at least one of the specified outcomes. The primary outcome was risk of seroma and/or haematoma, and secondary outcomes were haemorrhage (bleeding), infection, pain levels, complications arising from the use of drains, resource use (reoperation, length of hospital stay, duration of drainage and use of analgesics), health-related quality of life and adverse events related to the use of fibrin sealants. Only RCTs were used to review clinical effectiveness and both RCTs and observational studies were used for the assessment of harms related to the use of fibrin sealant.

Randomised controlled trials and observational studies were included based on pre-specified inclusion criteria. Two reviewers independently screened all titles and abstracts to identify potentially relevant studies for inclusion in the review. Full-text publications were evaluated independently by two reviewers. Data from included studies were extracted into a standardised data extraction form by one reviewer and validated by a second reviewer. The quality of included studies was assessed independently by two reviewers using the Cochrane Collaboration risk-of-bias tool for RCTs and Centre for Reviews and Dissemination guidance on adverse events for observational studies. Extracted data and quality assessment for each study were presented in structured tables. A fixed-effects model was used for the primary meta-analysis and a random-effects model was used for the sensitivity analysis. Subgroup analyses for different surgical specialties were conducted. Treatment effects were analysed as odds ratios (ORs) for dichotomous data and as mean difference (MD) for continuous outcomes. Data that could not be appropriately combined by meta-analysis were summarised in a narrative overview and presented in tables.

Changes between the protocol and this review include the addition of risk of haematoma as a co-primary outcome because haematoma was frequently reported and the mechanism of haematoma and seroma formation was found to be similar based on clinical advice.

Results

The search for benefits and harms of fibrin sealants in RCTs resulted in 1428 full papers and abstracts being screened for inclusion in the review. Full publications for 443 studies were evaluated, of which 186 RCTs were included. The search for harms identified 4714 studies and 93 reports that were screened for inclusion, of which eight observational studies and five reports of death in patients treated with fibrin sealants during surgical procedures from the MHRA, EMA and FDA were included.

Thirty-seven trials across different surgical areas (breast and axillary/inguinal lymph nodes, hernia, plastic, hepatic and otolaryngology surgery) reported the incidence of seroma as a study outcome. A meta-analysis of data from 32 RCTs ($n = 3472$) did result in a non-significant reduction in risk of seroma with fibrin sealant over standard procedures [OR 0.84, 95% confidence interval (CI) 0.68 to 1.04; $p = 0.13$; $I^2 = 12.7\%$). The co-primary outcome, risk of haematoma, was reported in 26 RCTs in breast and axillary/inguinal lymph nodes, hernia, plastic, orthopaedic, upper gastrointestinal (GI), oral and otolaryngology surgery. A meta-analysis of 24 RCTs ($n = 2665$) demonstrated a statistically significant reduction in risk for fibrin sealant versus standard care (OR 0.62, 95% CI 0.44 to 0.86; $p = 0.01$; $I^2 = 0\%$) that was driven by the results for hernia surgery in four RCTs ($n = 794$, pooled OR 0.22, 95% CI 0.06 to 0.74; $p = 0.01$; $I^2 = 0\%$). Furthermore, there was a trend towards a reduction in the risk of haematoma in the remaining surgical specialties, but this was not statistically significant ($p = 0.87$ for breast, $p = 0.20$ for orthopaedic and $p = 0.88$ for upper GI tract). The random-effects models for the primary outcomes showed similar results.

Secondary dichotomous outcomes of this review were risk of haemorrhage, reoperation and infections, use of analgesics and complications arising from the use of drains. There was no statistically significant difference between patients receiving fibrin sealants and those receiving standard care in the risk of haemorrhage in a meta-analysis of 2125 patients in 17 RCTs (OR 0.64, 95% CI 0.40 to 1.02; $p = 0.08$; $I^2 = 0\%$) or in the rate of infections in a meta-analysis of 3902 patients in 25 RCTs (pooled OR 0.76, 95% CI 0.54 to 1.06; $p = 0.12$; $I^2 = 0\%$). However, a meta-analysis of six RCTs of upper GI surgery ($n = 995$) found a statistically significant reduction in risk of haemorrhage when using fibrin sealants (OR 0.39, 95% CI 0.19 to 0.80; $p = 0.01$; $I^2 = 0\%$). In a meta-analysis of 15 RCTs ($n = 3789$), the risk of reoperation was statistically significantly lower in patients receiving fibrin sealants than in control subjects (OR 0.65, 95% CI 0.48 to 0.87; $p < 0.01$; $I^2 = 0\%$). Use of analgesics was reported by only three RCTs that could not be meta-analysed; there appeared to be no difference between fibrin sealant and standard care in two RCTs, but patients with trans-sphincteric anal fistulas treated with fibrin sealant did not require analgesics, whereas all those who received standard treatment did. No RCTs reported on complications arising from the use of drains.

Secondary continuous outcomes included duration of operation, length of hospital stay, use of drains, pain levels and health-related quality of life. A statistically significant benefit of fibrin sealants compared with standard care was identified in the mean duration of operations for eyes in eight RCTs ($n = 519$, MD –12.13 minutes, 95% CI –12.59 to –11.67 minutes; $p < 0.01$; $I^2 = 99.1\%$) and hernia surgery in two RCTs ($n = 784$, MD –2.56 minutes, 95% CI –3.57 to –1.56 minutes; $p < 0.01$). However, in surgery with liver mobilisation, two RCTs showed a statistically significant longer duration of surgery when fibrin sealants were used ($n = 364$, MD 19.07 minutes, 95% CI 2.75 to 35.38 minutes; $p = 0.02$). Fibrin sealants were shown to reduce the length of hospital stay for people undergoing upper GI surgery involving the pancreas in two RCTs ($n = 181$, MD –1.40 days, 95% CI –1.72 to –1.09 days; $p < 0.01$), cardiothoracic lung surgery in three RCTs ($n = 269$, MD –1.37 days, 95% CI –1.93 to –0.81 days; $p < 0.01$; $I^2 = 91.9\%$) and breast surgery in eight RCTs ($n = 440$, MD –0.73 days, 95% CI –0.95 to –0.50 days; $p < 0.01$; $I^2 = 88.7\%$).

Fibrin sealants slightly reduce the duration of post-operative drainage for breast and axillary lymph nodes in 12 RCTs ($n = 953$, MD –0.50 days, 95% CI –0.68 to –0.33 days; $p < 0.01$; $I^2 = 90.6\%$) and the duration of lung surgery in five RCTs ($n = 399$, MD –0.46 days, 95% CI –0.53 to –0.39 days; $p < 0.01$; $I^2 = 91.0\%$) than standard care. These results were not consistent across surgical procedures, with fibrin sealants showing no beneficial effect when compared with standard care in the following specialties: duration of operation in surgery without liver mobilisation in four RCTs ($p = 0.46$); gastric surgery in two RCTs ($p = 0.07$); length of hospital stay in gastric and bowel surgery in two RCTs ($p = 0.82$); joint surgery in four RCTs ($p = 0.87$); and duration of drainage in hepatic surgery in four RCTs ($p = 0.33$). The high level of heterogeneity warrants caution when interpreting the results of the secondary continuous outcomes. Pain levels were reported in 20 RCTs but the large differences in the different scales used, time points at which assessments took place and the lack of data on variability did not permit a meta-analysis. Health-related quality of life was not reported in any of the RCTs.

Adverse events were reported in 10 RCTs in various surgical procedures (liver, kidney, mixed, oral and maxillofacial, hernia, plastic and reconstructive, vascular and orthopaedic) that were reported as related to the use of fibrin sealants by the investigators, and 22 RCTs explicitly reported that there were no adverse events related to fibrin sealant use. Only one RCT reported a death as possibly related to fibrin sealant application in upper-GI surgery caused by a large bleed, but bleeding did not occur at the target site and no further information was provided. Other RCTs reported on various non-severe adverse events including mild cellulitis and mild seroma, anaemia, extravasation of urine, incision site complication and mild generalised skin rash. Severity was unclear for excessive pain, scar pain, testicular pain hydrocele, post-procedural haemorrhage and antibodies to hepatitis B. The eight observational studies reported adverse events that appeared to be fibrin related in the view of primary study investigators and reviewers, but there were no reports of death or serious adverse events.

Most full-text publications presented limited details on trial methodology and, as a consequence, were judged to be at an unclear risk of bias. Overall, 154 RCTs were assessed as having an 'unclear risk of bias', eight RCTs as having a 'high risk of bias' and 24 RCTs as having a 'low risk of bias'. Therefore, study quality was not used in the meta-analyses as a sensitivity analysis. The validity of the eight observational studies was compromised by a general failure to report whether or not adverse events were assessed independently and if blinding to the assigned treatment was performed.

Limitations

It was not possible to provide a detailed evaluation of individual RCTs in their respective contexts because of the limited resources that were available for this research. In addition, the number of RCTs that were identified made it impractical to conduct independent data extraction by two reviewers in the time available.

Conclusions

The effectiveness of fibrin sealants does not appear to vary according to surgical procedures, as there was virtually no heterogeneity in the meta-analyses of primary and secondary dichotomous outcomes. Fibrin sealants appear to reduce the risk of haematoma development when used in non-emergency surgical procedures compared with standard care, but the reduction in risk of post-operative seroma development remains unproven.

Randomised controlled trials and observational studies mostly reported on no or minor adverse events that appeared to be related to the use of fibrin sealants in the view of primary study investigators and reviewers, but poor reporting of adverse events in primary studies warrants caution when interpreting these results. Surgeons should note the potential risk of gas embolism if spray application is not performed

in accordance with manufacturers' recommendations and take the necessary precautions detailed in the updated prescribing advice for these medicines.

It is necessary for those who undertake future RCTs to capture all important outcomes in the same population of patients. Researchers should plan RCTs that collect data for biological outcomes (e.g. seroma, haematoma, duration of drainage) as well as more service-related outcomes (e.g. length of hospital stays and rates of reoperations) in order to reach a balanced view of the benefits or harms arising from these products. Future research should be carried out in surgery specialties where only limited data were found, including neurological, gynaecological, oral and maxillofacial, urology, colorectal and orthopaedics knee or hip surgery (for any outcome); breast and upper-GI surgery (for development of haematoma); and cardiothoracic heart or lung surgery (for reoperation rates). Furthermore, reporting of methodological aspects of studies, particularly for adverse events, should improve while following existing reporting guidelines.

Study registration

This study is registered as PROSPERO CRD42015020710.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Description of the health problem

Fibrin sealants are commercial products used during surgical procedures in many sites of the body (including the liver, breast, pancreas, thorax and nervous system) and are widely regarded as useful adjuncts to make blood clot, seal tissues and help the body repair mechanisms that can aid haemostasis and reduce seroma formation. However, the benefits and harms of fibrin sealants remain controversial and seem to be dependent on the surgical procedure.

Seroma and repair

Seroma is formed by acute inflammatory exudates in response to surgical trauma and in the acute phase of wound healing.[1] After surgery, the body's natural response to the removal of organs or tissues is to fill the space with fluid and blood cells. During this process, a collection of fluid and cells can result in the formation of a seroma (collection of a clear, yellow fluid). Some parts of the body are especially prone to seroma, for example the breasts and parts of the digestive tract.

Avoidance of post-operative drains

Post-operative drains are intended to prevent the build-up of fluid or seroma after some types of surgery by filling 'dead space'. The main concerns with seroma are that they can become infected or leak fluid and, if they remain, over time become swollen, hard and uncomfortable. Both additional surgery to remove the seroma and fine-needle aspiration are associated with increased resource use, such as nursing time, hospital stay and analgesic or antibiotic use. There is contradictory evidence from two small randomised controlled trials (RCTs)[2,3] ($n = 100$ and $n = 75$) about the use of fibrin sealants as an alternative to post-operative drains during thyroid surgery. In one trial, patient outcomes were best in the fibrin sealant group; pain was significantly reduced, as was the length of time spent in hospital.[2] However, no statistically different effects on any outcome was observed in a second trial.[3] The findings from individual RCTs also suggest that post-operative pain can be reduced when fibrin sealants are used in skin graft surgery.

Fibrin sealants are not recommended for surgical use in some sites; they were reported to be ineffective in reducing post-operative leakage from oesophago-gastric anastomoses.[4]

Tissue adhesion or sealing

A systematic review summarised the evidence for fibrin glue in the repair of pilonidal disease (the invasion of hair into the skin of the natal cleft).[5] The review included five RCTs in which fibrin glue was used to fill dead space and sinus tracks during surgery. The reviewers reported equivalent or better healing times at an average of 2–6 weeks and low recurrence rates between 0% and 17% at follow-up periods between 4 and 28 months for all patients treated with fibrin glue than for those treated with conventional therapies. However, no statistically significant differences between those who received fibrin glue and those who did not were observed. Furthermore, fibrin sealants are commonly used to prevent fistula during pancreatic surgery.[6–8]

Hernia repair

A systematic review of randomised and non-randomised studies evaluating fibrin sealants used in the surgical management of hernia repair concluded that fibrin sealants are an effective alternative to mechanical approaches.[9]

Dural repair in neurosurgery

Fibrin sealants can be used as an adjunct to dura (the outer-most layer of the brain and spinal cord) repair to achieve intraoperative watertight closure of the dura and to reduce post-operative cerebrospinal fluid leak.

A RCT ($n = 139$) showed the fibrin sealant EVICEL® (Ethicon, Livingston, UK) to be effective as an adjunct to dural sutures. Intra-operative watertight closure was achieved in 82 out of 89 participants (92.1%) in the EVICEL group, compared with 19 out of 50 participants (38.0%) in the control group ($p < 0.001$).[10]

Haemorrhage (bleeding)

Perioperative or post-operative haemorrhage is a common complication of surgery. Unexpected, excessive perioperative bleeding can be due to a pre-existing undetected bleeding disorder, or to coagulation abnormalities arising from massive blood loss and/or various coexisting pathologies.[11] It can be related to the nature of the operation itself. Red blood cell transfusion is often required as a result of perioperative bleeding, but this resource can be scarce and there has been worldwide concern regarding its safety.

Assisting the arrest of haemorrhage (haemostasis) perioperatively is an important function of fibrin sealant preparations. In a previous systematic review[12] researchers demonstrated that fibrin use during the removal of uterine fibroids in premenopausal women reduced blood loss and, consequently, the rate of blood transfusions. However, the quality of evidence was assessed as low. This effect was also reported in a systematic review of surgical interventions for liver, orthopaedic, vascular, prostate, thoracic, renal, pancreatic and cardiac conditions.[13] A RCT evaluating the use of fibrin sealants in total knee arthroplasty procedures also demonstrated statistically significant reductions in blood loss.[14]

Aetiology, pathology and prognosis

Incidence and/or prevalence and impact of the health problem

Seroma and repair

The development of seroma formation depends on the site of surgery. Approximately 50% of inpatients with a closed suction drain develop post-operative seroma,[15] and the incidence after breast cancer surgery and axillary node dissections ranges from 15% to 60%.[16] The most common complication of abdominoplasty is seroma formation, and the incidence in abdominal procedures, including abdominoplasty, panniculectomy and transverse rectus abdominis myocutaneous flap abdominal donor sites, ranges from 1% to 38%.[17] In a study of incisional hernia repair involving a combined fascial and prosthetic mesh repair in 35 patients (16 males and 19 females), the incidence of post-operative seroma formation was 17%.[18] One of the most common and serious complications of pancreatic surgery is post-operative pancreatic fistula, defined as a drain output of any measurable volume or fluid on or after post-operative day 3, with an amylase content greater than three times the serum amylase activity.[19–21] The estimated incidence of post-operative pancreatic fistula ranges between 2% and 24% based on different studies.[19,22]

Haemorrhage (bleeding)

The incidence of perioperative or post-operative bleeding also depends on the site or type of surgery. Severe bleeding occurs in about 7% of patients undergoing cardiac surgery.[23] Excess perioperative bleeding following surgery results in the increased use of red blood cell transfusions: between 60% and 70% of all red blood cell transfusions are used in surgical settings.[24,25] Moreover, bleeding perioperatively or post-operatively increases the risk of morbidity and mortality.[11] The mortality rate among patients undergoing elective vascular surgery who experience severe bleeding has been reported to be approximately 20%.[26] Uncontrolled bleeding has been reported to be the cause of 30–40% of all trauma-related deaths.[27]

Significance for patients in terms of ill health (burden of disease)

A seroma may cause problems because it can become infected or leak fluid and, over time, may also become swollen, hard and uncomfortable. After thoracic surgery the placement of a post-surgical drain can increase the length of hospital stay and cause discomfort. Problems arise when the drains do not work properly and, as a result, become blocked and infected.

Current service provision

Management of condition

Seroma and repair

To try to stop seroma formation, surgeons sometimes leave a drain (tube) in the wound to make sure fluid can escape and does not build up after the operation. Occasionally, the only way to cure the problem is further surgery to remove the seroma or drainage with a fine needle, which might increase the time spent in hospital.

To prevent post-operative pancreatic fistulas, a number of methods have been proposed, including application of duct stents, modification of anastomotic techniques and administration of somatostatin (a hormone that inhibits the secretion of pancreatic juice).[20,21,28,29]

Haemorrhage (haemostasis)

To look for ways to minimise the need for perioperative blood transfusion, a number of systematic reviews assessed the efficacy and safety of different interventions for the International Study of Perioperative Transfusion.[30–34] These reviews showed that techniques for reinfusing patients' own blood provided only relatively small reductions in the need for blood transfusion. However, interventions to reduce surgical blood loss resulted in significant improvements in reducing the need for blood transfusion.[35]

Variation in services and/or uncertainty about best practice

Relevant national guidelines

In 2012, a European review of the safety of sprayable fibrin sealants was started after reports of life-threatening events and deaths following administration of fibrin sealants using a pressure regulator.[36] The European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) stated that the benefits of fibrin sealants outweigh their risks, but that appropriate procedures have to be undertaken to optimise the safe use of fibrin sealant sprays during surgery.[36]

In 2013, four sprayable fibrin sealants were authorised in the UK: EVICEL, Tisseel Lyo® (Baxter Healthcare, Norfolk, UK), Tisseel Ready® to Use (Baxter Healthcare, Norfolk, UK) and Artiss® [Solutions for Sealant], deep frozen (Baxter Healthcare, Norfolk, UK). In all cases, the surface area of the wound should be dried with standard procedures before applying the fibrin sealants spray with a pressure regulator device.[37]

Description of technology under assessment

Summary of intervention

Fibrin sealants are commercial products that usually comprise two substances that occur naturally in mammals: (1) fibrinogen, a protein; and (2) thrombin, an enzyme that acts on fibrinogen to produce a fibrin clot, exactly as in normal blood clotting. The components used in these products are derived from either human or animal blood. There are different preparations of fibrin sealants: patches, sponges and bandage formulations, which can all be impregnated with fibrinogen and thrombin. Alternatively, fibrin glue is a mixture of the two substances in liquid form, which is dispensed via a 'gun' and there is also a liquid 'droplet' formulation that is delivered in an aerosol spray.[38]

Fibrin sealants are used during surgical procedures in many sites of the body (including the liver, breast, pancreas, thorax and nervous system) and are widely regarded as useful adjuncts to aid haemostasis and reduce seroma formation. They are used to seal tissues and prevent the accumulation of post-operative fluid and blood loss. Aerosol sprays, sponges, bandages and pad preparations are available, and all contain elements that make blood clot and help the body repair.

Concerns about safety

Fibrin sealants have been found to stop fluid collecting in the body after operations, but it is unclear if this 'good effect' works for all types of operations. There is concern that some types of fibrin sealants can have harmful effects, such as leaving pockets of air in the body, which can be dangerous.

The Food and Drug Administration (FDA) in the USA has issued warnings about life-threatening air or gas emboli developing after the use of fibrin sealant aerosol sprays during surgery. Users of the products have been advised about the dangers of using sprays too close to exposed tissue surfaces and at higher pressures than those recommended by the manufacturers.[39] However, despite concerns about safety, data from RCTs about harms are scarce.[40] A multicentre RCT[41] conducted in three Italian hospitals compared the rate of adverse events in a group of patients receiving fibrin sealants as an adjuvant for air leak control in patients undergoing lung resection. Air leakage and broncopleural fistulas in the lungs are both common complications after these procedures. With a follow-up period of 30–40 days the investigators found that the rate of adverse events was not statistically significantly different between patients who received fibrin sealant and those who did not.[41]

A review conducted in 2010[42] on the risks and complications of spinal fibrin sealants, included the two fibrin glues EVICEL and Tisseel. It concluded that Tisseel had been used in clinical studies without adverse events. However, the review found a lack of large clinical studies on the safety of EVICEL for neurosurgery. A more recent RCT evaluating the safety of EVICEL found that the incidence of adverse events and cerebrospinal leakage up to 30 days post surgery was similar in the EVICEL and control groups. No deaths or suspected unexpected serious adverse drug reactions occurred during the trial.[10]

The authors of a systematic review of RCTs have suggested that the beneficial patient outcomes that have been observed when using fibrin sealants are dependent on surgeon training in their use.[40]

Identification of important subgroups

Surgical specialties

The efficacy of fibrin sealants in different surgical specialties has been reported to differ. Therefore, where possible, after carrying out a meta-analysis combining all surgical specialties, additional subgroup analysis was carried out according to identified surgical specialties.

Type of intervention

For assessing the efficacy of fibrin sealant in reducing operative time, subgroup analysis according to interventions and comparators was carried out, as application times of different interventions was expected to vary.

Current usage in the NHS

Fibrin sealants are believed to be widely used by surgeons from many different disciplines working in the UK. There are no data collected at a national level about the cost of fibrin products to the NHS; costs data are likely to be available only at the level of NHS trust (NHS England, 2015, personal communication). It is anticipated that variations in the use of fibrin sealants are likely.

Chapter 2 Definition of the decision problem

Decision problem

The eligibility criteria pertaining to population, intervention, comparators and outcomes are summarised in *Table 1*.

Overall aims and objectives of assessment

Objectives

- To map the evidence of benefits (clinical effectiveness) of use of fibrin sealants from RCTs.
- To map the evidence of harms (adverse events) related to the use of fibrin sealants from RCTs, observational studies and regulatory body reports.

TABLE 1 Eligibility criteria

PICOS	Criteria
Population	People aged ≥ 18 years undergoing non-emergency surgery at any site in secondary care (hospital)
Intervention	Any fibrin sealant product including • fibrin glue • fibrin spray • fibrin sponges, bandages • fibrin aerosol • fibrin tissue adhesive
Comparators	Standard care
Outcomes	Primary outcomes • seroma development • haematoma development Secondary outcomes • haemorrhage (blood loss) • infections • pain levels • complications arising from the use of drains Resource use • use of analgesics • nurse or doctor time • length of hospital stay • use of drains Health-related quality of life Adverse events related to the use of fibrin sealant (attributed by the primary study authors and/or reviewers) In addition, an important output of the review will include an overview of gaps in knowledge to inform recommendations for future primary research, including specific outcomes for different conditions
Study design	RCTs and observational studies

PICOS, population, intervention, comparators, outcomes and study design.

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing clinical effectiveness

Evidence on the clinical effectiveness of fibrin sealants was identified by conducting a systematic review of the published research literature. The review was undertaken following the general principles published by the Centre for Reviews and Dissemination (CRD) and the Cochrane Collaboration.[43,44] The protocol for the systematic review is registered on PROSPERO (registration number CRD42015020710).[45] The protocol and review were developed with clinical experts who had experience with using fibrin sealants (Professor John MacFie, University of Hull, Hull, and Mr Alexander Green, John Radcliffe Hospital, Oxford). Guidance for systematic review reporting on benefits[46] and harms[47] was followed where possible.

Eligibility criteria

Eligibility criteria for the review of clinical effectiveness were as specified in the decision problem (see *Table 1* for a summary). The review included RCTs to assess both the benefits and harms, and observational studies and regulatory body reports to assess adverse events related to fibrin sealants in the view of primary study investigators and/or reviewers. Systematic reviews and other types of studies were excluded. The interventions of interest were any type of fibrin sealant. RCTs and observational studies were included if the treatments were evaluated in an adult population undergoing non-emergency surgery in a secondary care setting and compared with standard care. Regulatory body reports were included if they reported on deaths or serious adverse events related to fibrin sealants. RCTs were excluded if none of the outcomes of interest was reported. Observational studies were excluded if they did not report on adverse events that were thought to be related to the use of fibrin sealants.

Identification of studies

Search strategy

Two search strategies, one for RCTs and one for observational studies, were developed (see *Appendix 1*). Information on benefits and harms were extracted from RCTs. The searches for RCTs combined terms for the technology being assessed and the study design using the Cochrane Collaboration RCT filter.[44] Evidence of harms was obtained from observational studies with a search strategy focused on adverse events. For observational studies, the searches combine both controlled vocabulary terms (medical subject heading and EMTREE) and free-text terms for general adverse events from the CRD[43] and Cochrane guidance,[43,44] including the following: safe, safety, side effect, undesirable effect, treatment emergent, adverse effects, contraindications and complications.[48–51] Both search strategies for RCTs and observational studies included terms for the technology, which used both controlled vocabulary terms (medical subject heading and EMTREE) and free-text terms including the following: fibrin sealant, fibrin adhesive, fibrin glue, fibrin sponges, fibrin bandages or aerosol and commercial names. The search strategies were refined by scanning key papers identified during the review, through discussion with the review team, clinical experts and information specialists (see *Appendix 1*). No limits relating to inception date or language were applied to the searches.

The following searches were conducted in May 2015. The following electronic sources were searched: MEDLINE, EMBASE and The Cochrane Library (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment database and the Cochrane Central Register of Controlled Trials). Ongoing and unpublished RCTs were searched for in the following websites: clinicaltrials.gov, controlled-trials.com and clinicaltrialsregister.eu. For observational

studies websites from the following organisations were searched: Medicines and Healthcare products Regulatory Agency (MHRA) (www.gov.uk/search?q=fibrin+sealants), the EMA (www.ema.europa.eu/ema/index.jsp?curl=search.jsp&q=FIBRIN+SEALANT&spell=1&site=pfoi_collection&client=pfoi_frontend&ie=UTF-8&output=xml_no_dtd&proxystylesheet=pfoi_frontend&access=p) and the FDA (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=4277068). Relevant reviews and guidelines were identified through searching additional resources, including Clinical Evidence, National Institute for Health and Care Excellence, National Institute for Health Research Health Technology Assessment programme and the University of York Database of Abstracts for Reviews of Effectiveness. Additionally, reference lists of included papers were assessed and the abstracts from key conference proceedings were screened. Furthermore, clinical experts in the relevant therapy area were contacted to request details of RCTs and observational studies (published and unpublished) of which they may be aware.

Abstract appraisal

Titles and abstracts of studies identified by the search process were assessed for inclusion independently by two reviewers (GOA and MvV). In cases where the reviewers were unable to reach a consensus regarding whether or not the full text should be obtained for further appraisal, the full text was obtained. When potentially relevant data were identified, corresponding authors were contacted to obtain the full publications. A deadline for response to the initial contact of 1 calendar month was imposed. Studies were not screened on the basis of the presence or absence of harms-related terms in title or abstract as harms were expected to be reported in other sections of the primary study publications.[47]

Study inclusion assessment

Two teams of two reviewers (GOA and MvV, FSa and MB) independently assessed the full text of the RCTs and observational studies identified during the abstract assessment stage for inclusion, and differences in opinion were arbitrated by a third reviewer (FC). Studies rejected at this or subsequent stages were recorded in a 'characteristics of excluded studies table' and reasons for exclusion recorded.[46] Only RCTs reporting on one of the outcomes specified in *Table 1* and only observational studies or regulatory body reports of adverse events related to the use of fibrin sealants were included.

Data extraction and management

Data were extracted by one reviewer using a standardised data extraction form (items for which data were reported are presented in *Appendix 2*) and independently checked by another reviewer. Information extracted included details of the study's design and methodology; the intervention and comparators; baseline characteristics of participants and outcome measures, including clinical efficacy outcomes (variables for which data were sought are reported in *Table 20* in *Assessment of benefits*) and any type of adverse event related to the use of fibrin sealants as attributed by the primary study authors of studies or regulatory organisations. No data were sought for patient-underlying risk factors or for practitioner training or qualifications. When there was incomplete information, attempts were made to contact authors to request for further details. Discrepancies in the data extraction were resolved by discussion with involvement of a third reviewer.

Data from intention-to-treat (ITT) analyses were extracted. When a trial did not report ITT data for dichotomous outcomes, missing data were treated as treatment failures to allow analysis to conform to an ITT analysis.[50] For the purpose of this review, ITT analysis was defined as the analysis of patients according to the treatment group to which they were allocated at randomisation, irrespective of whether they received the allocated intervention, withdrew or were lost to follow-up.

Quality assessment strategy

The quality of included studies was assessed by one reviewer and independently checked by another. Any disagreements were resolved by consensus and the opinion of a third reviewer was sought.[43,46]

Randomised controlled trials were assessed according to the guidance published by the CRD[43] and the *Cochrane Handbook for Systematic Reviews of Interventions*,[44] and recorded using the Cochrane risk-of-bias tool. Seven domains were assessed for each included study:

1. random sequence generation
2. allocation concealment
3. blinding of participants and personnel
4. blinding of outcomes assessment
5. incomplete outcome data (study level)
6. selective reporting
7. 'other bias'.

Three bias assessment categories were used: low, high and unclear risk. Unclear risk was assigned because of poor reporting of how the trial was conducted rather than a poorly conducted trial. RCTs that were deemed to be at low or unclear risk of bias were included in the main analysis.

Within a study, a summary assessment of low risk of bias was given when there was a low risk of bias for all key domains, unclear risk of bias when there was an unclear risk of bias for one or more key domains and high risk of bias when there was a high risk of bias for one or more key domains. Across studies, a summary assessment of the risk of bias for the primary outcome (across domains) was undertaken.

For observational studies, guidance from the CRD[43] was used to inform the quality assessment of adverse event reporting in observational studies. Although criteria for quality assessment of adverse event data from observational studies are currently being developed, most tools have not been validated and there is currently no agreement on how these quality assessments should be used in systematic reviews.[49,51] Tools that have been validated for different types of observational studies seemed inadequate for the purpose of this systematic review.[51,52] Therefore, the relevant questions for quality assessment from the CRD[43] guidance were used:

1. Is there an adequate explanation of how adverse effects were identified?
2. Were the adverse effects assessed independently by someone other than the surgeon performing the procedure?
3. Are the measurement instruments described?
4. Is the timing and duration of follow-up reported?
5. Was a standardised or validated measurement instrument used?
6. How was the adverse effect(s) attributed to the intervention?
7. Was the process was blinded to assigned treatment?
8. Are the terms clearly explained?

The following question that was deemed relevant was also added: Are all adverse events from the population reported?

Publication bias

For each of the primary pairwise meta-analyses, a funnel plot was assessed for publication bias when at least 10 studies were included. A regression of normalised effect versus precision was calculated as a test for small study effects (using $p < 0.10$ as an indicator of a significant result), and Egger bias values are presented in *Quantity and quality of research available*.[53]

Methods of analysis/synthesis

For all study designs (RCTs and observational studies) data were tabulated and discussed in a narrative analysis. In this narrative the evidence is grouped according to shared characteristics relevant to the review

question. A meta-analysis was performed to estimate a summary measure of effect on relevant outcomes based on ITT analyses. For dichotomous outcomes, odds ratios (ORs) were used as the summary statistic. For continuous outcomes, mean difference (MD) was the summary statistic. Meta-analyses were conducted when clinically homogeneous studies of similar comparisons reporting the same outcome measures were identified. Standard pairwise meta-analysis was conducted when more than one RCT was identified. Meta-analysis of continuous outcomes was carried out with the inverse variance method.[44] For dichotomous outcomes meta-analysis was carried out using a fixed-effects model with the Mantel–Haenszel method.[54] Sensitivity analysis was conducted using a random-effects model with the DerSimonian and Laird method.[55] Subgroup analyses were performed for specific surgical indications, when possible. Studies with zero events in both the intervention and control group were reported in a narrative.

In RCTs with more than one control group, the control that was reported as standard care was included. However, in RCTs where standard care was unclear or variable, all control groups were included. In cases for which standard care was unclear or variable, the different control groups were compared with a respective proportion of patients of the intervention group; for example if there were three control groups, the fibrin population was divided by three and compared in a pairwise meta-analysis with each control. The same approach was undertaken in RCTs with more than one fibrin group (i.e. different concentrations) and one control group; all the fibrin sealant groups were included and the number of patients in the control group was divided appropriately. This procedure was followed to avoid double counting of events.

Heterogeneity

For pairwise meta-analysis, heterogeneity was explored through consideration of the study populations, methods and interventions, by visual inspection of results and, in statistical terms, by the chi-squared test for homogeneity and the I^2 statistic. Statistically significant heterogeneity was defined as $p < 0.10$. Levels of inconsistency were assessed using I^2 and were defined as follows: I^2 of 0–25% = low level of inconsistency; 26–50% = moderate level of inconsistency; and > 50% = high level of inconsistency.[56] In instances when statistically significant heterogeneity was detected in the analyses, a hypothesis-generating subgroup analysis was conducted.[57]

Sensitivity analysis

The sensitivity analysis was conducted using a random-effects model with the DerSimonian and Laird method.[55]

Changes between protocol and systematic review

Systematic reviews were not included and, therefore, the quality of systematic reviews was not assessed as was mentioned in the protocol. Haematoma is an additional post hoc primary outcome that was not reported in protocol. As the mechanism of haematoma and seroma formation is similar and is reported in some studies interchangeably, it was deemed important to include haematoma as a primary outcome. In addition, a post hoc analysis of combined seroma and haematoma development was undertaken. Haemorrhage, pain levels and infections were described in the protocol as adverse events, but have been moved to secondary outcomes as these were found to be adverse events of surgery, but not adverse events related to fibrin sealant (and fibrin sealants are used to reduce these adverse events related to surgery). Duration of the operation was used to reflect the outcome 'nurse or doctor time' instead of the previously mentioned 'dressing or fine-needle aspirations'. Sensitivity analyses were planned for aspects of the review that might have an impact on the results; for example, including studies where there is a high risk of bias.[53] However, most studies were assessed as having an unclear risk of bias and, therefore, these analyses were not deemed to be appropriate. Sensitivity analysis using a random-effects model was conducted, but because of the large number of RCTs identified in the review, it was not possible to perform additional analyses in the time available.

Results

Quantity and quality of research available

Quantity of randomised controlled trials

A total of 2509 records were identified by searching MEDLINE, EMBASE and The Cochrane Library (*Figure 1*). After deduplication and screening records, 443 full-text papers were assessed for inclusion. After reviewing the full text, 257 studies were excluded for various reasons, as outlined in *Figure 1* (for details of excluded studies see *Appendix 3*). We included 186 RCTs, which are summarised in *Table 2*. These RCTs were undertaken in 14 different surgical specialties (classification based on the Royal College of Surgeons of England[58]) or included a mix of different surgical specialties (four papers combined different surgical specialties), and are presented in *Table 2*.

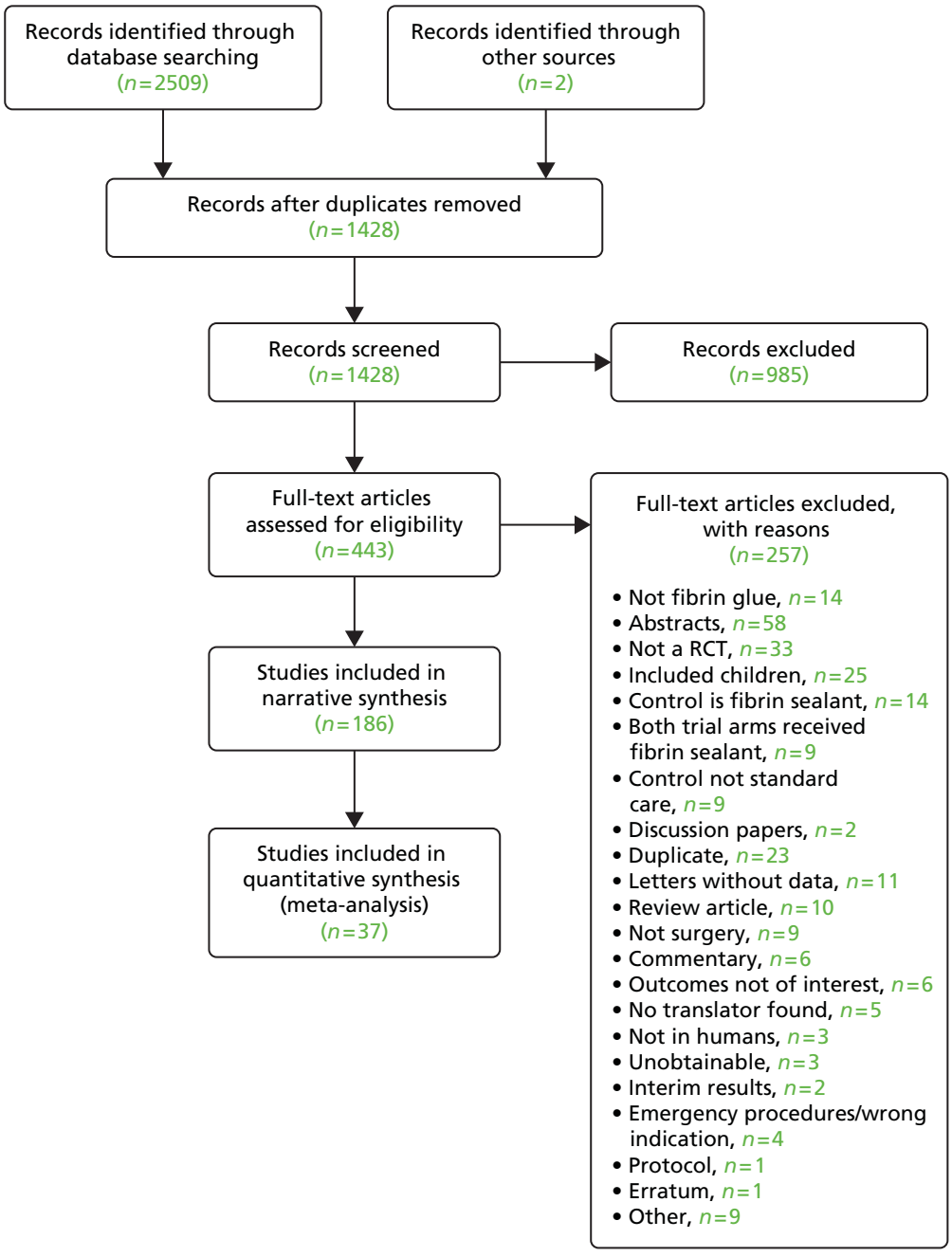

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for RCTs.

TABLE 2 Overview of surgical specialties and number of RCTs

Surgical area	Number of RCTs
Upper GI tract (digestive system)	33
Stomach	11
Liver	13
Gallbladder	3
Pancreas	6
Breast and lymph nodes	30
Breast and/or axillary lymph nodes	19
Inguinal and/or axillary lymph nodes	9
Pelvic and/or para-aortic lymph nodes	1
Thorax/oesophagus lymph nodes	1
Cardiothoracic	20
Lung	16
Heart	4
Orthopaedic (joints)	17
Shoulder	1
Hip	5
Knee	11
Eye	15
Hernia	14
Otolaryngology (ENT)	7
Nose	6
Tonsils	1
Vascular	13
Plastic or reconstructive	10
Skin (graft and ulcer)	5
Buttock (pilonidal disease)	2
Abdomen (lipoabdominoplasty)	2
Ischial region	1
Colorectal (anus)	5
Urology (urinary tract)	5
Kidney	3
Prostate	1
Urethra	1
Oral (mouth) and maxillofacial	7
Mixed	4
Gynaecological	4
Neurological	2
Total	186

ENT, ear, nose and throat; GI, gastrointestinal.

Sample sizes ranged from seven participants in Nativ *et al.*[59] to 1436 participants in Tavilla *et al.*,[60] with a median sample size of 62 participants and most values at the lower end. RCTs were published over the past 30 years, since 1985. The main fibrin sealants used were Tisseel ($n = 37$)/Tissucol® (ImmunoAG, Vienna, Austria) ($n = 16$), Quixil® (Johnson & Johnson Wound Management, Somerville, NJ, USA) ($n = 23$), TachoSil® (Takeda Austria GmbH, Linz, Austria) ($n = 18$), Beriplast® (Behringwerke, Marburg, Germany; FSBP, Aventis Behring, Strasbourg, France) ($n = 12$), Vivostat® (Vivolution A/S, Birkerød, Denmark) ($n = 8$) and EVICEL ($n = 6$).

In addition, 87 RCTs from clinicaltrials.gov were identified, of which 11 relevant trials started since January 2013 (see *Appendix 4*). Seven trials from controlled-trials.com were found, of which none was recent (since January 2013). A total of 26 trials from clinicaltrialsregister.eu were found, of which 4 were relevant, recent RCTs (see *Appendix 4*).

In the following subsections the quantity of RCTs and their characteristics for each of the 14 surgical specialties are described.

Upper gastrointestinal (digestive system) surgery

A total of 33 upper gastrointestinal (GI) tract surgery RCTs were identified:[61–93] 13 liver surgeries,[65–75,77,250] three cholecystectomies,[78–80] seven pancreatic surgeries,[81–86,93] five gastric surgeries[63,64,89,90,92] and five surgeries in other areas of the digestive tract[61,62,87,88,91] (*Table 3*). Fibrin sealants had a range of indications in the RCTs reporting GI tract surgeries: improving haemostasis, reducing leakage and wound drainage, and preventing post-operative complications. A variety of different fibrin sealants were used. The sample size ranged from 13[61] to 320[62] participants, with a mean size of 116 participants. The follow-up duration varied from approximately 7 days in Fernandez *et al.*[63] to 53 months in Huang *et al.*,[64] but was infrequently reported.

TABLE 3 Summary of included RCTs in upper GI tract (digestive system) surgery

Study (author, year)	Sample size	Surgery	Intervention	Control
Bektas *et al.*, 2014[65]	31	Liver resection	Tisseel spray	Compression
de Boer *et al.*, 2012[66]	45	Liver resection	Quixil/Crosseal (Johnson & Johnson Wound Management, Somerville, NJ, USA)	Standard care
Chapman *et al.*, 2000[67]	60	Hemihepatectomy or segmental liver resection	CoStasis Surgical Hemostat (Cohesion Technologies Inc., Palp Alto, CA, USA)	Standard care
Uetsuji *et al.*, 1994[68]	96	Hepatectomy	IMMUNOAG spray (IMMUNO AG, Vienna, Austria)	Liver mobilisation
Liu and Lui, 1993[69]	118	Liver resection	Fibrin sponge/bandage	Standard care
Noun *et al.*, 1996[70]	137	Liver resection	Biocol glue (Bio-transfusion, Lille, France)	Standard care
Figueras *et al.*, 2007[71]	143	Liver and contralateral resection	Tissucol	Standard care
Fischer *et al.*, 2011[72]	146	Liver resection	TachoSil patch	Argon beam coagulation
Frilling *et al.*, 2005[73]	148	Liver resection	TachoSil	Argon beam coagulation
Kakaei *et al.*, 2013[74]	166	Liver resection	TachoSil patch	Surgicel (Ethicon, Somerville, NJ, USA)
Kohno *et al.*, 1992[75]	174	Liver resection	Beriplast	Bovine microcrystalline collagen powder

continued

TABLE 3 Summary of included RCTs in upper GI tract (digestive system) surgery (*continued*)

Study (author, year)	Sample size	Surgery	Intervention	Control
Moench *et al.*, 2014[76]	187	Liver resection	TachoSil patch	Collagen hemostat sangustop fleeces (B. Braun Surgical S.A., Barcelona, Spain)
Schwartz *et al.*, 2004[77]	207	Liver resection	Crosseal/Quixil spray	Haemostatic agents
Fu *et al.*, 2009[78]	60	Laparoscopic cholecystectomy	Fibrin sealant	Fibrin sealant and ropivacaine hydrochloride
Danielsen *et al.*, 2010[79]	51	Laparoscopic cholecystectomy	Vivostat	Human albumin
Dimo *et al.*, 1989[80]	80	Cholecystectomy	Beriplast spray	Standard care
Carter *et al.*, 2013[81]	101	Pancreatectomies	Vitagel injection (Stryker, Kalamazoo, MI, USA)	Staples or sutures
Suzuki *et al.*, 1995[82]	56	Distal pancreatectomy	Tisseel glue	Standard care
Lillemoe *et al.*, 2004[83]	124	Pancreaticoduodenectomy	Hemaseel glue (Baxter Healthcare Corp, Deerfield, MA, USA)	Standard care
Montorsi *et al.*, 2012[84]	275	Pancreatectomy	TachoSil patch	Standard suturing or stapling
Suc *et al.*, 2003[85]	182	Pancreaticoduodenectomy	Tissucol spray	Standard care
Martin and Au, 2013[86]	57	Pancreaticoduodenectomy	Tisseel adhesive	Standard care
Hwang and Chen, 1996[61]	13	Closure of low-output enterocutaneous fistula	Fibrin tissue glue, infused	Conservative treatment
Huang *et al.*, 2015[64]	42	Locally advanced gastric cancer without peritoneal metastases	Fibrin sealant spray	Cisplatin hyperthermic intraoperative chemotherapy
Fernandez Fernandez *et al.*, 1996[63]	86	Total gastrectomy for gastric adenocarcinoma	Tissucol fibrin glue	Standard care
Oliver *et al.*, 2012[87]	104	Anastomosis of the digestive tract	Tissucol Duo (1 ml)	Standard care
Musella *et al.*, 2014[88]	100	Laparoscopic sleeve gastrectomy	Tiseel spray	Standard care
Silecchia *et al.*, 2008[62]	320	Laparoscopic Roux-en-Y antecolic antegastric gastric bypass	Tissucol/Tisseel	Sutures
Pilone *et al.*, 2012[89]	30	Laparoscopic sleeve gastrectomy for bariatric surgery	TachoSil spray	Standard care
Sroka *et al.*, 2015[90]	165	Laparoscopic sleeve gastrectomy	EVICEL spray	Sutures
Fékété *et al.*, 1992[91]	100	Surgery requiring oesophageal anastomosis	Quick-setting fibrin glue	Standard care
Bulbuller *et al.*, 2013[92]	65	Gastrectomy	Tisseel	Without suture
Huang and Qian, 2014[93]	95	Radical gastrectomy	Fibrin spray	Standard care

Breast and lymph node surgery

A total of 30 breast and lymph nodes surgery RCTs[94–123] were identified: 19 in breast and/or axillary lymph nodes,[95–112,123] nine in inguinal and/or axillary lymph nodes,[94,113–120] one in pelvic and/or para-aortic lymph nodes[121] and one in thorax/oesophagus lymph nodes[122] (*Table 4*). Fibrin sealants were used as a wound sealant in all RCTs apart from Zhibo and Miaobo,[95] when a local anaesthetic was incorporated into the fibrin sealant. A variety of different fibrin sealants were used in different forms, such as patches [TachoComb (Takeda Pharma, Apotekerstien, Denmark) and TachoSil] and sprays (Vivostat, Tisseel and Beriplast). Control-group interventions included standard closure, lidocaine only, no fibrin and no drain. The sample size ranged from 26[114] to 159[110] participants, with a mean size of 66 participants. Individual randomisation took place in all the RCTs. The follow-up duration varied from approximately 3 days in Moore *et al.*[106] to 46 months in Swan *et al.*,[113] but was infrequently reported.

TABLE 4 Summary of included RCTs in breast and lymph nodes surgery

Study (author, year)	Sample size	Surgery	Intervention	Control
Zhibo and Miaobo, 2009[95]	30	Breast: surgical augmentation	Fibrin glue and lidocaine	Lidocaine only
Ulusoy *et al.*, 2003[96]	54	Breast: mastectomy	Fibrin sealant, spray	Standard closure
Dinsmore *et al.*, 2000[97]	27	Breast: mastectomy	Autologous fibrin glue, spray	Standard closure
Nielsen *et al.*, 1985[123]	38	Breast: mastectomy	Tisseel, spray	Standard care
Udén *et al.*, 1993[98]	68	Breast and axillary lymph nodes	Tisseel, adhesive	Standard closure
Jain *et al.*, 2004[99]	116	Breast and axillary lymph nodes	Tisseel spray; no drains	No fibrin, no drain
Johnson *et al.*, 2005[100]	82	Breast and axillary lymph nodes	Hemaseel APR, spray	Standard closure
Llewellyn-Bennett *et al.*, 2012[101]	101	Breast and axillary lymph nodes	Tisseel, spray	Standard closure
Ko *et al.*, 2009[102]	95	Breast and axillary lymph nodes	Greenplast kit (Green Cross Corp., Seoul, Korea), spray	Standard closure
Miri Bonjar *et al.*, 2012[103]	60	Breast and axillary lymph nodes	Hemaseel, spray	Standard closure
Mustonen *et al.*, 2004[104]	40	Breast and axillary lymph nodes	Tisseel, spray	Standard closure
Segura-Castillo *et al.*, 2005[105]	45	Breast and axillary lymph nodes	Quixil, spray	Standard closure
Moore *et al.*, 1997[106]	63	Breast and axillary lymph nodes	Autologous fibrin sealant, spray	Standard closure
Berger *et al.*, 2001[107]	60	Axillary lymph nodes	TachoComb H, patch	Standard closure
Gillly *et al.*, 1998[108]	108	Axillary lymph nodes	Tissucol, unclear application	Standard closure
Benevento *et al.*, 2014[109]	60	Axillary lymph nodes	Fibrin sealant	Standard closure
Cipolla *et al.*, 2010[110]	159	Axillary lymph nodes	Fibrin sealant, spray	Standard closure
Moore *et al.*, 2001[111]	80	Axillary lymph nodes	Fibrin sealant VI Guard spray (V.I. Technologies, Inc. Vitex, Watertown, MA, USA) 4/8/16 ml	Standard closure

continued

TABLE 4 Summary of included RCTs in breast and lymph nodes surgery (*continued*)

Study (author, year)	Sample size	Surgery	Intervention	Control
Vaxman *et al.*, 1995[112]	40	Axillary lymph nodes	Tisseel, spray	Standard closure
Swan *et al.*, 2011[113]	74	Axillary or inguinal lymph nodes	Tisseel, spray	Standard closure
Siim *et al.*, 1994[114]	26	Axillary or inguinal lymph nodes	Tisseel, unclear application	Standard closure
Gilly *et al.*, 1994[115]	40	Axillary or inguinal lymph nodes	Tissucol, spray	Standard closure
Furrer *et al.*, 1993[116]	30	Axillary or inguinal lymph nodes	Tissucol, spray	Standard closure
Di Monta *et al.*, 2012[117]	70	Axillary or ilioinguinal lymph nodes	TachoSil, patch	Standard closure
Neuss *et al.*, 2009[118]	58	Inguinal lymph nodes	Tissucol, spray	Standard closure
Simonato *et al.*, 2009[119]	60	Inguinal lymph nodes	TachoSil, patch	Standard closure
Carlson *et al.*, 2008[94]	137	Inguinal lymph nodes	Tisseel, spray	Standard closure
Mortenson *et al.*, 2008[120]	30	Inguinofemoral lymph nodes	Tisseel, unclear application	Standard closure
Scholz *et al.*, 2002[121]	93	Pelvic or pelvic and para-aortic lymph nodes	Tissucol, spray	Standard closure
Tachibana *et al.*, 2003[122]	43	Thorax/oesophagus lymph nodes	Bohleal (Kaketsuken Pharmaceutical, Kumamoto, Japan), spray	Standard closure

Cardiothoracic surgery

A total of 18 cardiothoracic surgery RCTs[60,124–140] were identified, of which 14 were in lung surgery[124–137] and four were in heart surgery[60,138–140] (*Table 5*). In lung surgery, fibrin sealants were used to prevent or reduce air leakage, whereas in heart surgery the indication for fibrin sealants was to stop bleeding. A variety of different fibrin sealants were used, such as patches (TachoComb and TachoSil) and sprays (Vivostat, Tisseel or Beriplast). Control-group interventions included sutures, stapling, clips, standard patches, fleece material, electrocautery or no additional procedures. The sample size ranged from 23[138] to 346[129] participants, with a mean size of 115 participants.

TABLE 5 Summary of included RCTs in cardiothoracic surgery

Study (author, year)	Sample size	Surgery	Intervention	Control
Lung				
Fabian *et al.*, 2003[128]	100	Pulmonary resection	Fibrin glue spray	Stapling
Droghetti *et al.*, 2008[124]	40	Pulmonary resection	Fibrin patch	Stapling
Lopez *et al.*, 2013[129]	346	Pulmonary resection	TachoSil patch	Suturing
Rena *et al.*, 2009[127]	60	Pulmonary resection	TachoSil patch	Standard treatment
Gonfiotti *et al.*, 2011[130]	186	Pulmonary resection	Fibrin sealant	No additional interventions

TABLE 5 Summary of included RCTs in cardiothoracic surgery (*continued*)

Study (author, year)	Sample size	Surgery	Intervention	Control
Moser *et al.*, 2008[126]	25	Pulmonary resection	Vivostat system	No additional interventions
Belcher *et al.*, 2010[131]	102	Pulmonary resection	Vivostat system, spray	BioGlue (CryoLife, Kennesaw, GA, USA)
Mouritzen *et al.*, 1993[132]	114	Pulmonary resection (pneumonectomies, lobectomies, bilobectomies, segmental resections, subsegmental resections or decortications)	Beriplast P spray	Not specified
Belboul *et al.*, 2004[133]	40	Pulmonary resection (lobectomy)	Vivostat system	No additional interventions
Lang *et al.*, 2004[134]	186	Pulmonary resection (lobectomy)	TachoComb, fleece-bound sealant	Sutures
Anegg *et al.*, 2007[125]	152	Pulmonary resection (lobectomy, segmentectomy)	TachoSil, fleece-bound sealant patch	Sutures with absorbable patches or staples
Marta *et al.*, 2010[135]	299	Pulmonary resection (lobectomy)	TachoSil, surgical patch	Resuturing, stapling or no treatment
Filosso *et al.*, 2013[136]	24	Pulmonary resection (thoracotomy, lobectomy)	TachoSil, patch	Stapling/suturing
Czerny *et al.*, 2004[137]	80	Lobectomy and mediastinal lymph node dissection	TachoComb, bandage/ patch	Conventional surgical haemostasis
Heart				
Kjaergard and Trumbull, 1998[138]	23	Primary coronary artery bypass surgery/grafting	Vivostat system	Sutures, clips and electrocautery
Kjaergard and Trumbull, 2000[139]	60	Median sternotomy	Vivostat system	No additional interventions
Maisano *et al.*, 2009[140]	119	Elective surgery on the heart, ascending aorta or arch requiring a cardiopulmonary bypass procedure	TachoSil, patch	Standard haemostatic fleece material

Orthopaedic (joint) surgery

A total of 17 RCTs[14,141–156] in orthopaedic surgery were identified (*Table 6*). Eleven reported fibrin usage for knee arthroplasty,[14,142–151] whereas five reported on hip arthroplasty[141,152–154,156] and one on shoulder surgery.[155] In knee and hip arthroplasty, fibrin was used as a haemostatic agent. The most commonly reported sealant used was Quixil spray, which was used in eight RCTs.[14,144–148,154,156] The remaining RCTs reported using EVICEL,[149–151] Vivostat[141] and Omrixil® spray (Omrix Biopharmaceuticals, Tel Hashomer, Israel),[153] whereas two RCTs did not specify the product that was used.[152,155] Control groups mostly constituted patients receiving standard care. The sample size ranged from 24[145] to 198[142] participants, with a mean size of 81 participants. Within-patient randomisation took place in Kjaergard and Trumbull[139] and individual randomisation was undertaken in the remaining RCTs. Duration of follow-up ranged from 7 days in Randelli *et al.*[149] to 3 years in Mawatari *et al.*[152]

TABLE 6 Summary of included RCTs in orthopaedic (joint) surgery

Study (author, year)	Sample size	Surgery	Intervention	Control
Knee				
Aguilera *et al.*, 2013[143]	166	Total knee arthroplasty	Fibrin glue, Tissucol	None
Levy *et al.*, 1999[14]	58	Total knee arthroplasty	Quixil, spray	Standard care
Wang *et al.*, 2001[144]	46	Knee arthroplasty	Quixil, spray	Standard care
Kluba *et al.*, 2012[145]	24	Total knee arthroplasty	Quixil, spray	Anaesthesia and fluid regimen
McConnell *et al.*, 2012[146]	65	Knee arthroplasty	Quixil, spray	Tranexamic acid
Molloy *et al.*, 2007[147]	150	Total knee arthroplasty	Quixil, spray	Tranexamic acid
Sabatini *et al.*, 2012[148]	70	Total knee, cement-less arthroplasty	Quixil	Dideco blood recovery device (Liva Nova, London, UK)
Randelli *et al.*, 2014[149]	62	Total knee arthroplasty	EVICEL, spray	Electrocautery
Skovgaard *et al.*, 2013[150]	48	Total knee arthroplasty	EVICEL, spray	Saline
Choufani *et al.*, 2015[151]	60	Total knee arthroplasty	EVICEL, spray	Standard care
Heyse *et al.*, 2014[142]	198	Total knee arthroplasty	Fibrin, spray	Standard care
Hip				
Mawatari *et al.*, 2006[152]	100	Total hip arthroplasty	Autologous fibrin tissue adhesive, spray	Standard care
Wang *et al.*, 2003[153]	81	Total hip arthroplasty	Omrixil, spray	Standard care
Lassen *et al.*, 2006[141]	58	Hip arthroplasty	Vivostat, spray	Standard care
Falez *et al.*, 2013[154]	95	Hip arthroplasty	Quixil, spray	Bipolar sealer (Medtronic, Minneapolis, MN, USA)
McConnell *et al.*, 2011[156]	66	Hip arthroplasty	Quixil, spray	Tranexamic acid
Shoulder				
Antuña *et al.*, 2013[155]	28	Arthroscopic massive rotator cuff tears repair	Platelet-rich fibrin	Standard care

Eye surgery

A total of 15 eye surgery RCTs[157–171] were identified, of which 13 were on pterygium surgeries,[157–163,165–169,171] one was a cataract surgery[170] and one a corneal perforation surgery[164] (*Table 7*). In pterygium surgery, fibrin adhesives were used to attach conjunctival autografts. For cataracts and perforation, fibrin sealants were used for wound closure and perforation closure, respectively. The most commonly reported sealant used within the RCTs was Tisseel (used in seven RCTs[157,160–163,167,171]). Quixil[159,166,169] and Beriplast[158,168] were also used, whereas the product was not specified in three RCTs.[164,165,170] Control group interventions were sutures in all the RCTs except for one in which cyanoacrylate tissue adhesive was used (Sharma *et al.*[164]). The sample size ranged from 22[168] to 116[165] participants, with a mean size of 63 participants.

TABLE 7 Summary of included RCTs in eye surgery

Study (author, year)	Sample size	Surgery	Intervention	Control
Ocular surface				
Kucukerdonmez *et al.*, 2010[157]	70	Pterygium surgery with autograft	Tisseel VH, glue	Sutures
Eye				
Yüksel *et al.*, 2010[158]	58	Pterygium surgery with autograft	Beriplast P/Combi-set (Aventis Hehring GmbH, Marburg, Germany)	Sutures
Bahar *et al.*, 2006[159]	65	Pterygium surgery	Quixil	Sutures
Rubin *et al.*, 2011[166]	42	Pterygium surgery with autograft	Quixil, glue	Sutures
Conjunctiva				
Hall *et al.*, 2009[160]	50	Pterygium surgery with autograft	Tisseel, glue	Sutures
Karalezli *et al.*, 2008[161]	50	Pterygium surgery with autograft	Tisseel, glue	Sutures
Koranyi *et al.*, 2005[162]	43	Pterygium surgery with autograft	Tisseel, glue	Sutures
Sati *et al.*, 2014[163]	90	Pterygium surgery with autograft	Tisseel, spray	Sutures
Ratnalingam *et al.*, 2010[165]	137	Pterygium surgery with autograft	Fibrin, glue	Sutures
Srinivasan *et al.*, 2009[167]	40	Pterygium surgery with autograft	Tisseel	Sutures
Uy *et al.*, 2005[168]	22	Pterygium surgery with autograft	Beriplast P, glue	Sutures
Mellin and Kondler, 1989[170]	100	Cataract surgery	Fibrin, glue	Sutures
Malik and Kumar, 2010[171]	50	Pterygium surgery with autograft	Tisseel Duo Quick	Sutures
Cornea				
Sharma *et al.*, 2003[164]	40	Corneal perforation	Fibrin, glue	Cyanoacrylate tissue adhesive
Bahar *et al.*, 2007[169]	81	Pterygium surgery with autograft	Quixil	Sutures

Hernia surgery

A total of 14 hernia surgery RCTs[172–185] were identified (*Table 8*). Fibrin sealants were used mostly for prosthetic mesh fixation (12 RCTs[172–176,178,181–186]). The most commonly reported sealant used was Tisseel/Tissucol (10 RCTs[172,176–178,180–185]). Quixil (two RCTs[174,179]) and Vivostat (one RCT[173]) were also used, whereas one RCT did not report which fibrin product was used.[175] Three papers reported using fibrin sealant in spray form[176,177,179] and three reported using laparoscopic applicators.[172,178,180] One paper reported using a needle applicator,[174] another reported using a manual application catheter[183] and the remaining six papers did not specify how it was applied.[173,175,181,182,184,185] Fibrin was compared with a range of interventions across the RCTs including sutures, staples, tacks and self-gripping mesh. The sample size ranged from 22[173] to 600[185] participants, with a mean size of 172 participants. Within-patient randomisation took place in Boldo[173] and individual randomisation was undertaken in the remaining RCTs. The follow-up duration varied from approximately 3 months in Cambal *et al.*[175] to 26 months in Olmi *et al.*[185]

Ear, nose and throat surgery

Seven RCTs[186–192] were identified in ear, nose and throat (ENT) surgery: six nasal surgeries[186–191] and one tonsillectomy[192] (*Table 9*). Fibrin adhesives were mostly used to aid haemostasis (five RCTs[188–192]) and to improve healing. The most commonly reported sealant used was Quixil (spray/glue) and was used in four

TABLE 8 Summary of included RCTs in hernia surgery

Study (author, year)	Sample size	Surgery	Intervention	Control
Inguinal canal				
Lau, 2005[172]	93	Endoscopic totally extraperitoneal inguinal hernioplasty	Tisseel VH	Staples
Boldo, 2008[173]	22	Laparoscopic hernioplasty	Vivostat	Staples
Bracale *et al.*, 2014[174]	102	Hernioplasty	Quixil	Sutures
Cambal *et al.*, 2012[175]	100	Laparoscopic hernioplasty	Fibrin glue	Self-gripping (or self-anchoring) mesh
Campanelli *et al.*, 2012[176]	316	Hernioplasty	Tissucol/Tisseel	Sutures
Canonico *et al.*, 1999[177]	50	Hernioplasty	Tissucol	Standard care
Chan *et al.*, 2014[178]	129	Total extraperitoneal hernioplasty	Tisseel spray	Staples
Lionetti *et al.*, 2012[179]	148	Hernioplasty	Quixil spray	Sutures
Wong *et al.*, 2011[182]	56	Hernioplasty	Tisseel glue	Sutures
Damiano *et al.*, 2014[184]	468	Herniorrhaphy	Tissucol	Sutures
Olmi *et al.*, 2007[185]	600	Laparoscopic transabdominal pre-peritoneal hernia repair	Tissucol/Tisseel	Staples
Inguinal and femoral canals				
Lovisetto *et al.*, 2007[180]	197	Hernioplasty	Tissucol/Tisseel	Staples
Tolver *et al.*, 2013[181]	100	Laparoscopic groin hernia	Tisseel spray	Tacks
Umbilicus				
Eriksen *et al.*, 2013[183]	34	Laparoscopic ventral hernia repair	Tisseel Duo Quick	Tacks

TABLE 9 Summary of included RCTs in ENT surgery

Study (author, year)	Sample size	Surgery	Intervention	Control
Nose				
Prado *et al.*, 2006[187]	22	Rhinoplasty	Beriplast	Standard care
Pryor *et al.*, 2008[186]	10	Rhinoplasty	EVICEL	Compression
Vaiman *et al.*, 2005[189]	64	Endoscopic sinus surgery	Quixil/Crosseal (Johnson & Johnson Wound Management, Somerville, NJ, USA) spray	Nasal packing
Yu *et al.*, 2014[190]	41	Rhinosinusitis refractory	Fibrin spray	Sponge packing
Vaiman *et al.*, 2005[191]	513	Endonasal surgery	Quixil glue	Nasal packing
Nose and septum				
Vaiman *et al.*, 2002[188]	204	Septoplasty and conchotomy	Quixil aerosol glue	Quixil aerosol glue and trans-septal suturing
Tonsils				
Vaiman *et al.*, 2006[192]	80	Tonsillectomy	Quixil spray	Electrocautery

RCTs,[188,189,191,192] whereas Beriplast[187] and EVICEL[186] were also used. Control-group interventions included packing, compression, sutures and standard care. The sample size ranged from 10[186] to 513[191] participants, with a mean size of 133 participants. Within-patient randomisation took place in two RCTs,[186,190] whereas individual randomisation was undertaken in the remaining RCTs. The follow-up duration varied from approximately 21 days in Pryor *et al.*[186] to 1 year in Prado *et al.*[187]

Vascular surgery

A total of 13 vascular surgery RCTs[193–205] were identified (*Table 10*). Fibrin sealant was used in all cases to control suture hole bleeding from placing the graft for vascular access or vascular reconstruction surgery. In Bajardi *et al.*[194] Poly(ethyl benzene-1,4-dicarboxylate) [Dacron® (Ethicon Inc., Somerville, NJ, USA)] grafts were used, whereas in all other RCTs[193,195–204] polytetrafluoroethylene grafts were used. These materials are frequently used for vascular replacement or bypass when no autologous venae are available. All RCTs used different fibrin sealants apart from the Joseph *et al.*[200] and Czerny *et al.*[205] RCTs that used TachoComb patches. Control group interventions were manual compression[194,196–198,200,204,205] or use of thrombin,[196] thrombin-soaked materials,[196,199] Surgicel[195,196] or Kalkostat.[202] The sample size ranged from 24[200] to 199[199] participants, with a mean size of 66 participants. Individual randomisation was undertaken in all RCTs. Follow-up duration varied from approximately 30 days in Sintler *et al.*[202] to 6 months in Schenk *et al.*,[195] but was infrequently reported.

TABLE 10 Summary of included RCTs in vascular surgery

Study (author, year)	Sample size	Surgical area	Surgery	Intervention	Control
Schenk *et al.*, 2003[195]	48	Upper extremity; artery and vein in the upper arm or forearm	Vascular access surgery using PTFE graft placement (dialysis required for end-stage renal failure)	Bioplasma (ZLB, Bioplasma AG, Bern, Switzerland) glue	Surgicel (Johnson & Johnson, Somerville, NJ, USA)
Schenk *et al.*, 2002[196]	28	Upper extremity; artery and vein in the upper arm or forearm	Vascular access surgery using PTFE graft placement	Hemaseel spray (Haemacure Corp., Sarasota, FL, USA)	Thrombin ($n = 8$); pressure ($n = 6$); thrombin-soaked Gelfoam (Pfizer Inc., New York City, NY, USA) ($n = 2$); Surgicel ($n = 2$)
Saha *et al.*, 2012[197]	140	Upper and lower extremity: axillofemoral, iliofemoral, femorofemoral, iliopopliteal, proximal femoropopliteal, distal femoropopliteal and femorotibial vessel bypass	Arterio-arterial bypasses and arteriovenous shunting for dialysis access with expanded PTFE graft placement	Fibrin sealant	Compression
Chalmers *et al.*, 2010[198]	147	Femoral or upper extremity arteries	PTFE grafts	EVICEL	Compression
Taylor *et al.*, 2003[199]	199	Femoral artery	PTFE grafts	Beriplast P gel	Thrombin-soaked gelatin sponge
Joseph *et al.*, 2004[200]	24	Femoral or carotid artery	Femoral anastomosis and femoral or carotid patch angioplasty with PTFE grafts	TachoComb patch	Compression

continued

TABLE 10 Summary of included RCTs in vascular surgery (*continued*)

Study (author, year)	Sample size	Surgical area	Surgery	Intervention	Control
Jackson *et al.*, 1999[193]	47	Carotid artery	Elective carotid endarterectomy with expanded PTFE patch angioplasty (atherosclerotic occlusive diseases)	Investigational new drug number 4353, human fibrin sealant	Gelfoam
Milne *et al.*, 1995[201]	17	Carotid artery	Endarterectomy with a PTFE patch	Fibrin spray	No treatment
Sintler *et al.*, 2005[202]	20	Carotid artery	Endarterectomy with an expanded PTFE patch	Quixil	Kaltostat (ConvaTec, Flintshire, UK)
Milne *et al.*, 1996[203]	39	Artery or aorta	Arterial bypass surgery with a PTFE bypass graft and aortic aneurysm repair with a woven Dacron graft	Fibrin injection	No treatment
Saha *et al.*, 2011[204]	73	Anastomoses (junction) of arterio-arterial bypasses and arteriovenous shunts	Bypass vessel PTFE grafts	Tisseel	Compression
Czerny *et al.*, 2000[205]	60	Aortofemoral, femoropopliteal and crossover bypasses, femoral artery, arteria carotis interna	Vascular reconstruction; anastomoses or patch angioplasties with PTFE prostheses	TachoComb H patch	Compression
Bajardi *et al.*, 2009[194]	20	Infrarenal abdominal aorta	Elective infrarenal abdominal aortic aneurysm replacement with a Dacron graft	TachoSil patch	Compression

PTFE, poly(1,1,2,2-tetrafluoroethylene).

Plastic or reconstructive surgery

Ten RCTs[206–215] in plastic/reconstructive surgery in various body sites were found (*Table 11*). Fibrin sealant had different indications within plastic/reconstructive surgery: haemostasis (four RCTs[207,208,211,212]), reduction of seroma formation (two RCTs[213,214]), reduction of drainage (two RCTs[210,215]) and wound healing (two RCTs[206,209]). Various types of fibrin sealants were used across the RCTs: sprays (Tisseel,[210,211] Cryoseal,[206,212] Quixil[213] and autologous sealant using a spraypen[207]) and a Bioseed fibrin net.[208] Control-group interventions included standard care,[206,210,212,214,215] pressure,[208,209] thrombogen kit,[207] fabric dressing[211] and suction drains.[213] The sample size ranged from 10[210] to 225[208] participants, with a mean size of 58 participants. Individual randomisation was undertaken in all RCTs except Drake and Wong,[207] which reported within-patient randomisation. The follow-up duration varied from 1 week[207] to 12 months[210] and was not reported in Oliver *et al.*[215]

Colorectal surgery

Five RCTs were found in colorectal surgery[216–220] (*Table 12*). Fibrin sealant was used mainly to minimise recurrence and prevent incontinence after anal fistula surgery. Three RCTs[216,217,219] reported the use of Tisseel/Tissucol in the fibrin group, whereas Beriplast was used in one RCT[218] and the remaining RCT[220] did not specify the product used. The sample size ranged from 28[219] to 62[217] participants and the mean

TABLE 11 Summary of included RCTs in plastic or reconstructive surgery

Study (author, year)	Sample size	Surgical area	Surgery	Intervention	Control
Drake and Wong, 2003[207]	34	Skin	Skin graft	Vivolution spraypen (Vivolution A/S, Birkerød, Denmark)	Thrombogen Kit (Johnson & Johnson Wound Management, Somerville, NJ, USA)
Vanscheidt *et al.*, 2007[208]	225	Lower legs	Treatment of recalcitrant venous leg ulcers	BioSeed fibrin net (BioTissue Technologies GmbH, Freiburg, Germany)	Pressure dressing pad
Danielsen *et al.*, 2008[209]	39/40	Legs	Treatment of leg ulcers	Vivolution	Gauze and pressure
Erba *et al.*, 2010[210]	10	Ischial region	Seal fasciocutaneous flaps to cover ischial pressure sore	Tisseel spray	Standard care
Healy *et al.*, 2013[211]	40	Thigh	Treat split skin graft donor sites	Tisseel spray	Mefix self-adhesive fabric dressing (MoInlycke Healthcare, Lancashire, UK)
Altinli *et al.*, 2007[206]	32	Buttock	Limberg flap procedure in pilonidal disease	CryoSeal spray (Thermogenesis, Rancho Cordova, CA, USA)	Standard care
Sözen *et al.*, 2011[212]	50	Buttock	Karydakis flap operation for pilonidal sinus	CryoSeal spray	Standard care
Bercial *et al.*, 2012[213]	43	Abdomen	Abdominoplasty	Quixil spray	Suction drains
Mabrouk *et al.*, 2013[214]	60	Abdomen	Lipoabdominoplasty	Fibrin glue	Standard care
Oliver *et al.*, 2002[215]	44	Axilla, groin, back and abdomen	Axillary dissection, groin dissection, latissimus dorsi flaps and abdominoplasty	Beriplast spray	Standard care

TABLE 12 Summary of included RCTs in colorectal surgery (anal fistula)

Study (author, year)	Sample size	Surgery	Intervention	Control
Ellis and Clark, 2006[216]	57	Mucosal or anodermal advancement flap for surgical management of anal fistulas	Tisseel injection	Flap repair
Altomare *et al.*, 2011[217]	62	Treatment of trans-sphincteric anal fistulas	Tissucol	Seton treatment
Lindsey *et al.*, 2002[218]	42	Treatment of anal fistulas	Beriplast glue	Fistulotomy or loose seton insertion
Hammond *et al.*, 2011[219]	28	Treatment of idiopathic anal fistula	Tisseel glue	Permacol (Covidien, Dublin, Ireland)
van der Hagen *et al.*, 2011[220]	30	Treatment of complex perianal fistulas	Fibrin sealant glue	Seton drainage

number of patients was 44. Individual randomisation was undertaken in all RCTs. The follow-up duration varied from approximately 1 year[217] to 60 months.[220]

Urology (urinary tract)

Five RCTs[59,221–224] were found in urological surgery (*Table 13*). Fibrin sealant was used for haemostasis in all the RCTs except for Schultz and Christiansen[224] in which it was used to reduce the post-operative drainage period. Various fibrin sealants were used across the RCTs: Siemer *et al.*[221] and Cormio *et al.*[222] used a TachoSil patch, Nativ *et al.*[59] used an Ethicon pad, Luke *et al.*[223] used Beriplast and Schultz and Christiansen[224] used Tisseel. Control groups received standard care in all the RCTs. The sample size ranged from 7[59] to 185[221] participants, and the mean number of patients was 67. Individual randomisation was undertaken in all RCTs. The follow-up duration varied from 1[59,221] to 3 months[223] but was not reported for Cormio *et al.*[222] and Schultz and Christiansen.[224] Randomisation was carried out at an individual level in all RCTs.

Oral and maxillofacial surgery

Seven RCTs[225–231] were found in oral and maxillofacial surgery (*Table 14*). Fibrin sealant was used mostly to reduce post-operative wound drainage in different types of procedures. A variety of fibrin sealants were used across RCTs: Tisseel,[225,226,230] Crosseal,[227] Beriplast spray,[228] autologous fibrin glue[229] and Artiss.[231] Control-group interventions included 'no sealant',[225,228,231] tranexamic acid[229] and sutures.[230] The sample size ranged from 9[227] to 75[231] participants, with a mean size of 41 participants. Within-patient randomisation was carried out in four RCTs,[226–228,231] whereas the remaining three reported individual-level randomisation.[225,229,230] The follow-up duration varied from 24 hours in Oliver *et al.*[228] to 3 weeks in Maharaj *et al.*[230]

Gynaecological surgery

Four RCTs[232–235] were found in gynaecological surgery (*Table 15*). Fibrin sealant was indicated for the following: the prevention of post-operative adhesions,[232,234] haemostasis around myomectomy suture sites[233] and prevention of a vesicovaginal fistula.[235] A variety of fibrin sealants were used across RCTs and control group patients received 'no sealant' procedures. The sample size ranged from 16[232] to 91 participants,[234] with a mean size of 54 participants. Follow-up duration was 3 months[235] to 1 year,[233] but not reported in Diamond *et al.*[232] and Takeuchi *et al.*[234]

TABLE 13 Summary of included RCTs in urology (urinary tract) surgery

Study (author, year)	Sample size	Surgery	Intervention	Control
Kidney				
Nativ *et al.*, 2012[59]	7	Open partial nephrectomy	Ethicon pad (Johnson & Johnson Wound Management, Somerville, NJ, USA)	Standard care
Siemer *et al.*, 2007[221]	185	Resection of small, superficial kidney tumours not extending into the collecting duct system; nephron-sparing surgery	TachoSil patch	Standard suturing
Cormio *et al.*, 2012[222]	96	Percutaneous nephrolithotomy	TachoSil patch	Nephrostomy tube
Prostate				
Luke *et al.*, 1986[223]	30	Transurethral resection of the prostate	Beriplast glue	Standard care
Urethra				
Schultz and Christiansen, 1985[224]	16	Closure of the ureterotomy after ureteral stone surgery	Tisseel adhesive	Dexon sutures (Syneture, Mansfield, MA, USA)

TABLE 14 Summary of included RCTs in oral and maxillofacial surgery

Study (author, year)	Sample size	Surgery	Intervention	Control
Face				
Marchac and Greensmith, 2005[226]	29	Rhytidectomy	Tisseel spray	Rhytidectomy using the vertical U incision technique without glue
Oliver *et al.*, 2001[228]	20	Rhytidectomy	Beriplast spray	No sealant
Face and neck				
Lee *et al.*, 2009[227]	9	Rhytidectomy	Crosseal	No Crosseal treatment
Hester *et al.*, 2013[231]	75	Rhytidectomy	Artiss	No application of fibrin sealant
Thyroid gland				
Uwiera *et al.*, 2005[225]	56	Hemithyroidectomy and total thyroidectomy	Tisseel	No sealant
Tooth socket				
Carter *et al.*, 2003[229]	49	Dental extraction	Autologous fibrin glue	Active 4.8% tranexamic acid solution
Parotid glands				
Maharaj *et al.*, 2006[230]	50	Superficial and total parotidectomy	Tisseel fibrin glue	Vicryl and Monocryl sutures (Johnson & Johnson Wound Management, Somerville, NJ, USA)

TABLE 15 Summary of included RCTs in gynaecological surgery

Study (author, year)	Sample size	Surgical area	Surgery	Intervention	Control
Diamond *et al.*, 2011[232]	16	Ovaries	Bilateral ovarian surgery	Adhexil spray/drip (Johnson & Johnson Wound Management, Somerville, NJ, USA)	Standard care
Maggiore *et al.*, 2011[233]	70	Uterus/endometrium	Laparoscopic removal of myomas (neoplasm)	TachoSil sponge	Standard care
Takeuchi *et al.*, 2005[234]	91	Uterus/abdomen	Laparoscopic myomectomy	Beriplast spray	TachoComb sheet
Safan *et al.*, 2009[235]	38	Vesicovaginal region	Treatment of vesicovaginal fistula	Fibrin adhesive	Standard care

Neurosurgery

Two RCTs[236,237] reporting on fibrin sealant for prevention of cerebrospinal fluid leakage were found in neurosurgery (*Table 16*). Beriplast adhesive was compared with autologous fibrin sealant in Nakamura *et al.*,[236] whereas collagen sponge was compared with standard care in Hutter *et al.*[237] Nakamura *et al.*[236] reported a sample size of 30 participants, whereas the sample size in Hutter *et al.*[237] was 229 participants, giving a mean sample size of 134 participants. Individual randomisation was undertaken in both RCTs. The follow-up duration was 32 days in Hutter *et al.*[237] and 8 weeks in Nakamura *et al.*[236]

TABLE 16 Summary of included RCTs in neurosurgery

Study (author, year)	Sample size	Surgical area	Surgery	Intervention	Control
Nakamura *et al.*, 2005[236]	39	Dura layer of spinal cord	Spinal cord tumours and related illnesses	Beriplast adhesive	Autologous fibrin sealant
Hutter *et al.*, 2014[237]	229	Dura mater of the brain	Elective cranial surgery involving a dural incision	Collagen sponge	Standard care

Mixed surgery

Four RCTs[238–241] across more than one surgical area were found (*Table 17*): Bochicchio *et al.*[239] and Verhoef *et al.*[240] were in spinal and vascular surgery, hepatic resection and soft tissue dissection; Hanks *et al.*[238] was cardiothoracic, general, obstetric and gynaecological and vascular surgery; and Fischer *et al.*[241] was in abdominal, retroperitoneal, pelvic and non-cardiac thoracic surgeries. Fibrin sealant was used for haemostasis in all the RCTs and different products were used across them. Raplixa fibrocaps powder was used in Bochiccio *et al.*[239] and Verhoef *et al.*[240] In Hanks *et al.*[238] autologous fibrin sealant derived from patients' blood was used, whereas in Fischer *et al.*[241] fibrin pads were used. The sample size ranged from 69[238] to 719[239] participants, with a mean size of 263 participants. Individual randomisation was undertaken in all RCTs. The follow-up duration was around 1 month in Bochicchio *et al.*[239] and Fischer *et al.*,[241] but was not reported in the other two RCTs.

Quality of randomised controlled trials

A risk-of-bias table for RCTs can be found in *Appendix 5*. Overall, 154 studies were assessed as having an 'unclear risk of bias', eight RCTs as having a 'high risk of bias' and 24 RCTs as having a 'low risk of bias' (see *Table 37*). The risk-of-bias table (see *Table 37*) shows a high level of uncertainty about the validity of data collected across all parameters, especially regarding the blind collection of patient outcomes. Owing to the nature of the intervention, surgeons could not be blinded to the intervention, as they had to apply the fibrin sealant; however, patients and outcome assessors who could be blinded to the intervention were frequently not blinded either.

TABLE 17 Summary of included RCTs in mixed surgery

Study (author, year)	Sample size	Surgical specialties	Surgery	Interventions	Control
Bochicchio *et al.*, 2015[239]	719	Spine, liver, arteries, soft tissues	Spinal procedures; vascular procedures with suture hole bleeding; hepatic resection; soft tissue dissection	Raplixa fibrocaps powder (ProFibrix BV – The Medicines Company, Leiden, The Netherlands)	Gelatin sponge
Verhoef *et al.*, 2015[240]	122	Spine, liver, arteries, soft tissues	Hepatic resections (46%), spinal procedures (30%), vascular procedures (24%) and soft tissue dissection (1%)	Raplixa fibrocaps powder	Pressure dressing pad
Hanks *et al.*, 2003[238]	69	Cardiothoracic, general, obstetric and gynaecological, and vascular	Not reported	Vivostat system	Dry surgical sponge
Fischer *et al.*, 2013[241]	90/141	Abdomen, retroperitoneum, pelvis and non-cardiothoracic surgery	Surgical operations in the abdomen, retroperitoneum, pelvis and non-cardiothoracics	Fibrin pad	Surgicel

Most of the funnel plots did not show publication bias (see *Appendix 6*); however, the funnel plot for development of haematoma meta-analysis [Egger bias –0.63, 95% confidence interval (CI) –1.20 to –0.06; $p = 0.03$] (see *Figure 43*) and duration of drainage for breast surgery meta-analysis (Egger bias –3.34, 95% CI –6.75 to –0.05; $p = 0.05$) (see *Figure 47*) showed a skewed figure of publications, which indicated the presence of small study effects.

Quantity of observational studies and regulatory body reports

The search of electronic databases identified 4714 potentially relevant articles about harms related to the use of fibrin sealants, of which 3709 references were excluded and 1005 full-text papers assessed (*Figure 2* and *Appendix 7*). There were an additional 93 reports, reviews or notifications about harms from the use of these products from the MHRA, EMA and FDA websites.

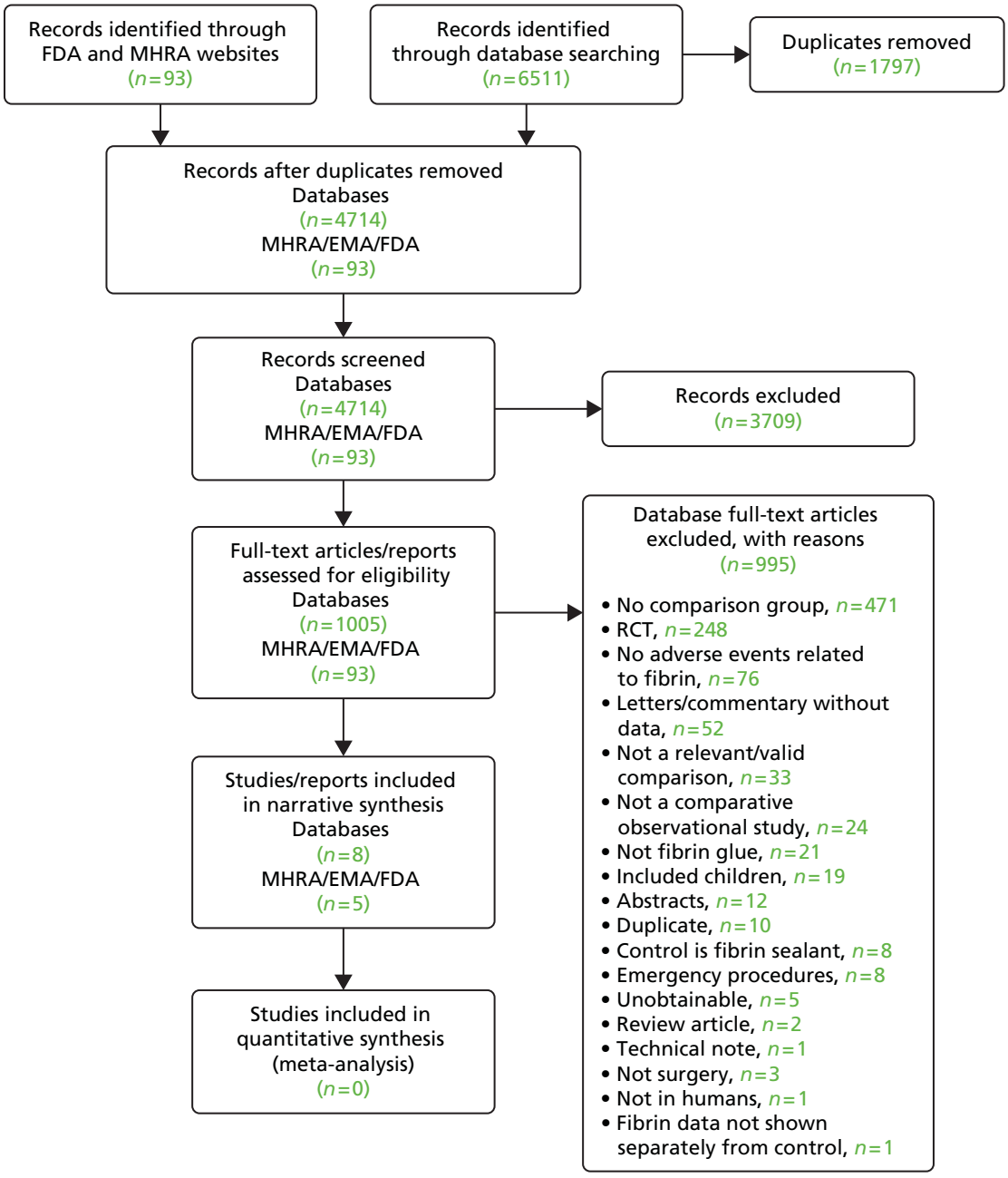

FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of observational studies and regulatory body reports.

After screening and applying the eligibility criteria, eight observational studies were included[242–249] (*Table 18*). Three observational studies were in eye surgery,[242–244] three in upper GI tract surgery,[245–247] one in plastic/reconstructive surgery[248] and one in vascular surgery.[249] There were three cohort studies,[243,245,249] three comparative studies[242,244,247] and two reviews of patient records.[246,248] The following fibrin sealants were used: unspecified fibrin glue in eye surgery,[242–244] Tiseel,[245] Beriplast,[247] aerosolised fibrin glue[248] and platelet-enriched fibrin glue sealant.[249] Comparator interventions were standard care[245–249] or sutures in eye surgery.[242–244] Sample sizes ranged from 40[243] to 529[246] participants.

Five reports from the regulatory body websites that reported on harms related to the use of fibrin sealants were included (see *Table 43*).

Quality of observational studies

The validity of the eight observational studies was compromised owing to a general failure to report whether or not adverse events were assessed independently and whether or not blinding to the assigned was performed (*Table 19*). Cagatay *et al.*[242] reported that harms were assessed independently. Five studies described measurement instruments,[243,245,246,248,249] but only three studies reported timing and duration of follow-up.[243,246,249] Only Sakic *et al.*[249] appeared to have used objective measures. All eight studies, except that by Jiang *et al.*,[243] attributed the harms to the use of fibrin sealants and seven studies explained terms used to identify harms.[242–246,248,249] No studies reported to have blinded the collection of outcomes to the treatment assignment.

TABLE 18 Overview of observational studies

Study (author, year)	Sample size	Type of comparative study	Surgery	Intervention	Control
Eye surgery					
Cagatay *et al.*, 2014[242]	103	Comparative study (consecutive sample)	Conjunctival autografting for pterygium surgery	Fibrin glue	Sutures
Jiang *et al.*, 2008[243]	40	Cohort study	Conjunctival autografting for pterygium surgery	Fibrin glue	Sutures
Choi *et al.*, 2010[244]	126	Comparative study	Pars plana vitrectomy (eye)	Fibrin glue	Sutures
Upper GI tract surgery					
Efthimiou *et al.*, 2010[245]	474	Cohort (consecutive sample supplemented with clinical observations and chart reviews)	Laparoscopic Roux-en-Y gastric bypass	Tisseel	Standard care
Ibele *et al.*, 2014[246]	529	Review of patient records (consecutive sample)	Laparoscopic Roux-en-Y gastric bypass	Autologous fibrin sealant	Standard care
Nanashima *et al.*, 2012[247]	341	Comparative study (consecutive sample)	Hepatobiliary pancreas surgery; hepatectomy and pancreatectomy	Beriplast fibrin glue spray	Standard care
Plastic/reconstructive surgery					
Marchac and Sándor, 1994[248]	200	Review of patient records (consecutive sample)	Rhytidectomy	Aerosolised fibrin glue	Standard care
Vascular surgery					
Sakic *et al.*, 2013[249]	418	Cohort study (consecutive sample)	Bilateral internal thoracic artery grafting	Platelet-enriched fibrin glue sealant	Standard care

TABLE 19 Quality of observational studies

Study (author, year)	AEs assessed independently?	Measurement instruments described?	Timing and duration of follow-up reported?	Standard or validated measurement instrument used?	Objective measures?	AEs attributed to the intervention?	Collection of outcomes blinded to assigned treatment?	Terms used to identify AEs clearly explained?	All AEs from the population reported?
Cagatay *et al.*, 2014[242]	Y	N	N	N	N	Y	N	Y	Y
Jiang *et al.*, 2008[243]	N	Y	Y	Y	UC	N	NA	Y	Y
Choi *et al.*, 2010[244]	N	N	N	N	N	Y	N	Y	Y
Efthimiou *et al.*, 2010[245]	N	Y	N	UC	UC	Y	UC	Y	Y
Ibele *et al.*, 2014[246]	N	Y	Y	Y	UC	Y	N	Y	Y
Nanashima *et al.*, 2012[247]	N	N	N	N	UC	Y	N	N	N
Marchac and Sándor, 1994[248]	N	Y	N	N	N	Y	N	Y	Y
Sakic *et al.*, 2013[249]	Y	Y	Y	Y	Y	Y	N	Y	Y

AE, adverse event; N, no; NA, not applicable; UC, unclear; Y, yes.

Assessment of benefits

The following sections present the analyses of benefits for the primary and secondary outcomes (*Table 20*). Fixed-effects model results are presented in the text and random-effects model results in *Appendix 8*. Data on primary and secondary outcomes used in the meta-analysis for all RCTs are presented in *Appendix 9*.

Primary outcomes

Seroma development

Development of seroma was reported in 37 RCTs, of which 33 ($n = 3472$) were included in the meta-analysis (*Figure 3*). The remaining four RCTs were excluded for the following reasons: Cipolla *et al.*[110] as all participants in the fibrin and control groups developed seroma; Erba *et al.*[210] and Uwiera *et al.*[225] because no patients developed seroma; and Siim *et al.*[114] because seroma development was not reported separately but combined with other complications reported as 'post-operative complications'. The included RCTs were across different surgical specialties: breast and axillary/inguinal (19 RCTs[94,96–105,107–109,111,113,115,118,120]), hernia (8 RCTs[172–174,178,181,182,184,185]), plastic, hepatic and otolayrngology.[202,204,227]

Patients receiving fibrin sealants rather than the control had a statistically non-significant reduced risk of developing seroma (OR 0.84, 95% CI 0.68 to 1.04; $p = 0.13$; $I^2 = 12.7\%$, fixed-effects model). The random-effects model showed a similar result (see *Appendix 8*). Two of the 32 RCTs with an unclear risk of bias showed a statistically significant difference in seroma development: Mabrouk *et al.*[214] reported a significant benefit of fibrin sealant, whereas Lau[172] reported more seroma development in patients receiving fibrin sealants.

TABLE 20 Overview of outcomes and analysis

Outcomes	Variables
Primary outcomes (dichotomous)	
Seroma development	Number of patients who developed seroma
Haematoma development	Number of patients who developed haematoma and a post hoc analysis in which the development of seroma and haematoma are combined
Secondary outcomes (dichotomous)	
Haemorrhage (blood loss)	Number of patients with bleeding
Reoperation	Number of patients with reoperation
Infections	Number of patients with wound infection
Use of analgesics	Number of patients (no meta-analysis as the data from RCTs were too heterogeneous)
Complications arising from the use of drains	Number of patients with complications (no data in RCTs reported)
Secondary outcomes (continuous)	
Duration of operation	Mean duration in minutes
Length of hospital stay	Mean duration in days
Use of drains	Mean duration of drainage in days
Pain levels	Mean level of pain (no meta-analysis as the data from RCTs were too heterogeneous)
Health-related quality of life	Mean health-related quality-of-life value (no data in RCTs reported)

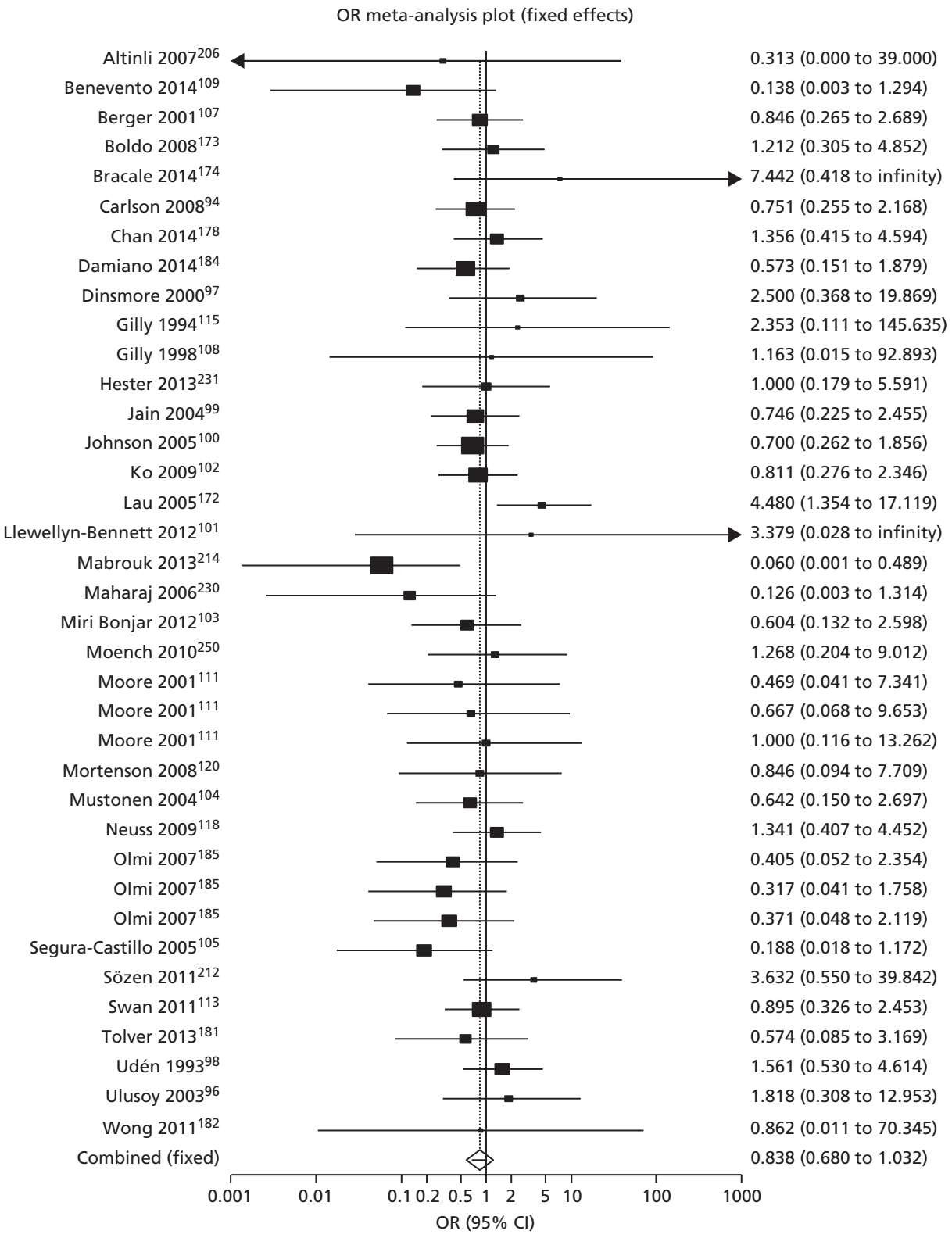

FIGURE 3 Seroma development in all surgical specialties: fibrin sealant vs. standard care.

There were some differences in how seroma was defined and at which time point it was reported; the data used in the meta-analysis were the first point at which seroma was reported for the hernia RCTs.[144,172–174,178,181,184,185] Jain *et al.*[99] had two control groups: (1) no drain and no fibrin, and (2) drain and no fibrin. The first was deemed to be most appropriate for analysis as the only difference from the intervention group was the addition of fibrin. In Moore *et al.*[111] three intervention groups were reported in which different amounts of fibrin were used; therefore, the control group was divided into three and compared accordingly. Olmi *et al.*[185] reported one intervention group and three control groups which were different types of fixation, and so the fibrin group was divided into three and compared with each control group. In cases where seroma development was reported at different time points, only the development at the first time point was included in the analysis.

Subgroup analysis was conducted for two surgical specialties that were deemed comparable: breast surgery RCTs (*Figure 4*) and hernia RCTs (*Figure 5*). In breast RCTs, patients ($n = 1277$) receiving fibrin sealants had a statistically non-significantly reduced risk of developing seroma than control group patients (OR 0.84, 95% CI 0.64 to 1.11; $p = 0.26$; $I^2 = 0.0\%$, fixed-effects model). In hernia RCTs, patients

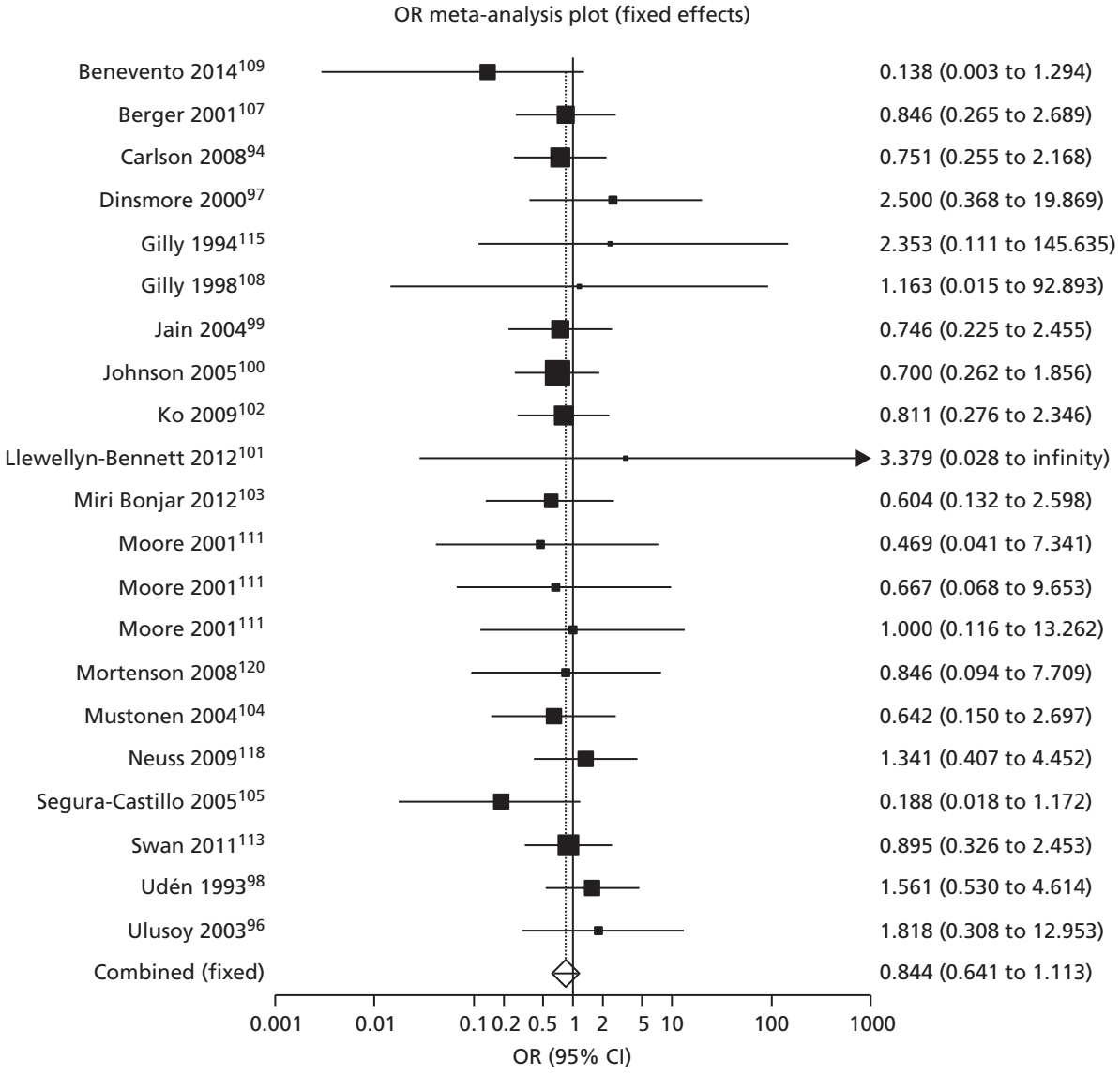

FIGURE 4 Seroma development in breast surgery: fibrin sealant vs. standard care.

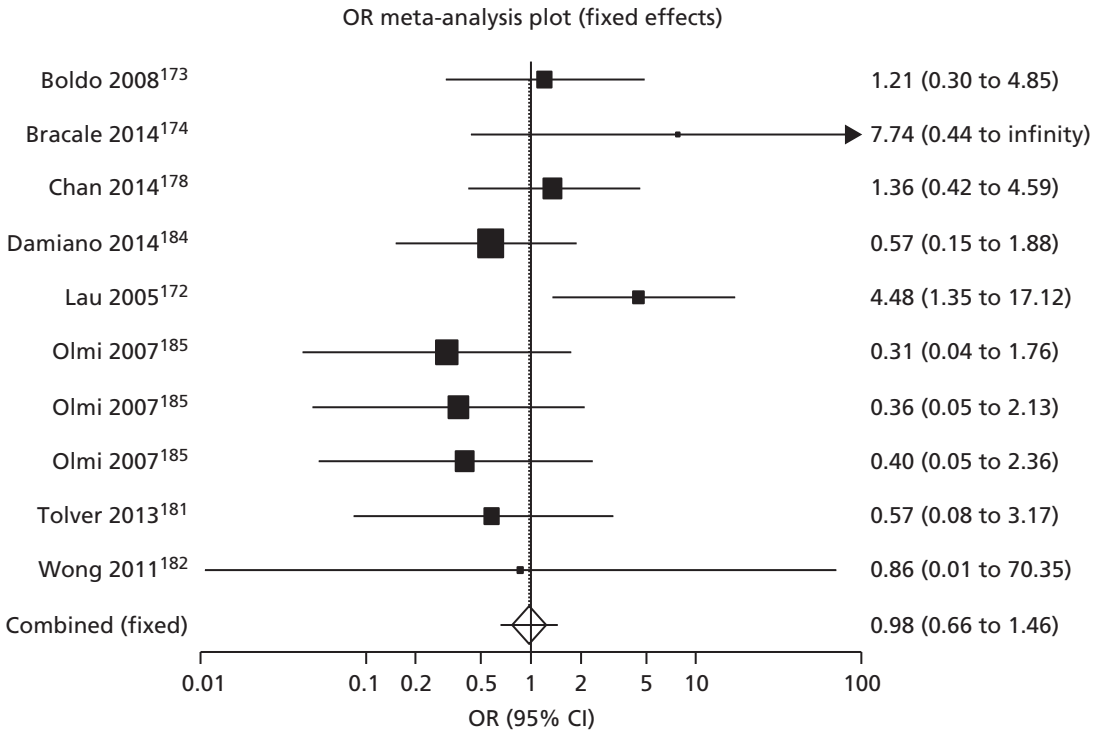

FIGURE 5 Seroma development in hernia surgery: fibrin sealant vs. standard care.

($n = 1592$) receiving fibrin sealants had no difference in risk of developing seroma than control group patients (OR 0.98, 95% CI 0.66 to 1.46; $p = 1.00$; $I^2 = 0.0\%$, fixed-effects model). The random-effects models showed similar results for these subgroups (see *Appendix 8*). These results are broadly consistent with the primary analysis that showed an apparent trend of a decrease in the risk of seroma development in patients receiving fibrin sealants.

Haematoma development

Development of haematoma was reported in 26 RCTs, of which 24 were included in the meta-analysis (*Figure 6*). Two RCTs were excluded from the primary analysis for following reasons: Prado *et al.*[187] reported only median, quartiles and ranges across a 12-month period and Lovisetto *et al.*[180] reported haematoma and seroma combined and not separately. The 24 included RCTs[65,70,90,100,101,103,110,111,113,118,141,143,144,148,173,177,181,185,188,221,222,227,228,231] ($n = 2665$) were within the following surgical specialties: breast and axillary/inguinal lymph nodes, hernia, plastic, orthopaedic, upper GI tract, oral and otolaryngology. Patients receiving fibrin sealant had a statistically significant lower risk of developing haematomas than control patients ($n = 2403$, OR 0.62, 95% CI 0.44 to 0.86; $p = 0.01$; $I^2 = 0\%$, fixed-effects model). The random-effects model showed a similar result (see *Appendix 8*).

Overall haematoma development was calculated by combining groin and axillary haematomas in Swan *et al.*,[113] and by combining hepatic and post procedural haematomas in Bektas *et al.*[65] Reviewers checked that different haematomas did not occur in the same person and, therefore, that data were not double-counted. Data from multiple intervention and control groups in Olmi *et al.*[185] and Moore *et al.*[111] were dealt with in the same manner as in the seroma analysis. As two different fibrin groups and two controls were reported in Aguilera *et al.*[143] it was decided for analysis purposes to compare fibrin glue to control and Tissucol to tranexamic acid.

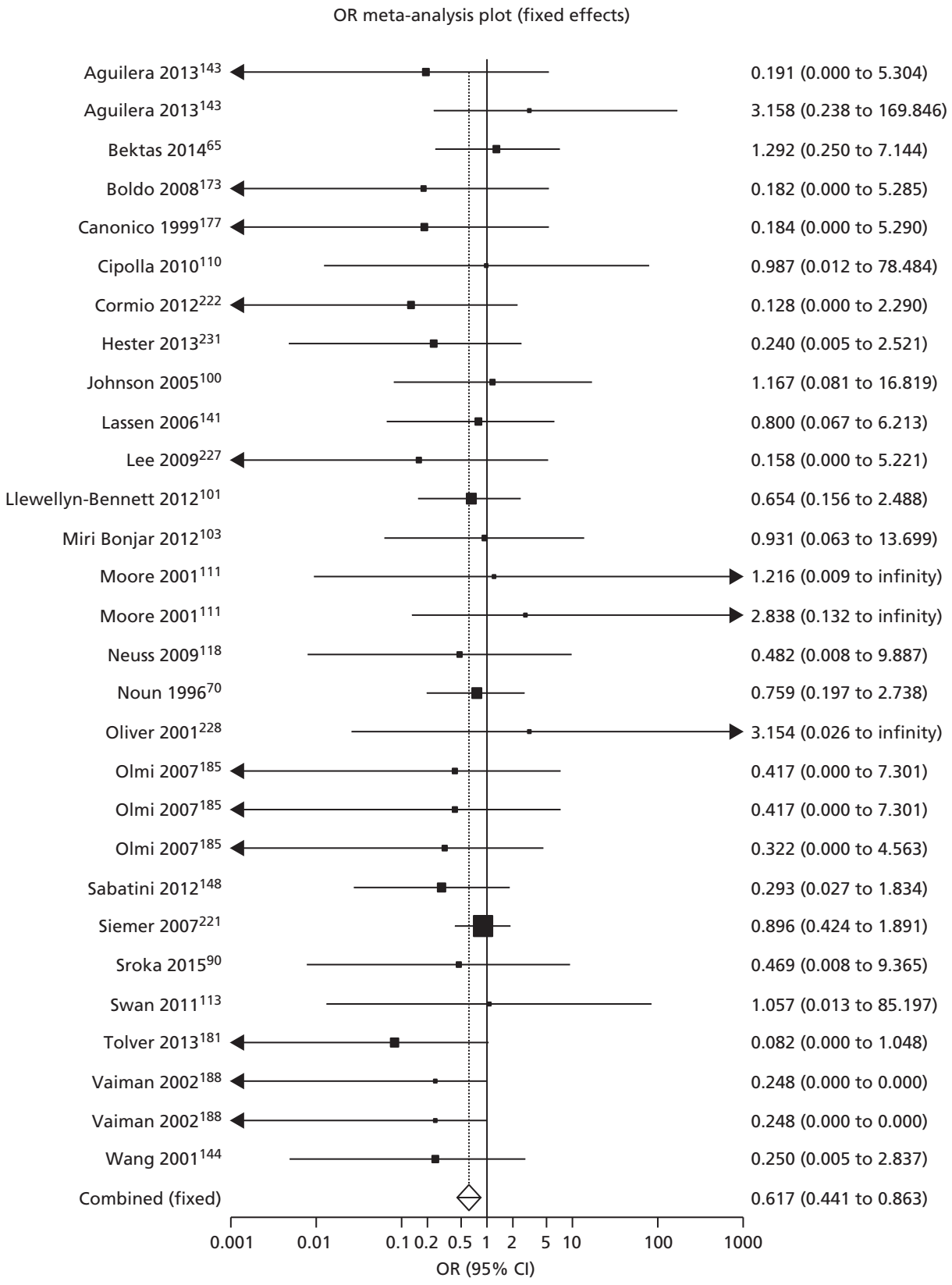

FIGURE 6 Haematoma development in all surgical specialties: fibrin sealant vs. standard care.

Subgroup analyses were conducted for the following areas: breast (*Figure 7*), hernia (*Figure 8*), orthopaedics (*Figure 9*) and upper GI tract (*Figure 10*). A statistically significant reduction in the risk of haematoma formation due to fibrin use occurred only in a meta-analysis of four hernia surgery RCTs[173,177,181,185] ($n = 794$, OR 0.22, 95% CI 0.06 to 0.74; $p = 0.01$; $I^2 = 0\%$, fixed-effects model). There was a trend of a decreased risk of haematoma when using fibrin sealants within the remaining surgical specialties, but these reductions were not statistically significant: $p = 0.87$ (seven breast RCTs,[100,101,103,110,111,113,118] $n = 588$), $p = 0.20$ (four orthopaedic RCTs,[141,143,144,148] $n = 347$) and $p = 0.88$ (three upper GI tract RCTs,[65,70,90] $n = 243$). The random-effects models showed similar results (see *Appendix 8*).

A post hoc analysis including 48 RCTs[65,70,90,94,96–105,107–111,113,115,118,120,141,143,144,148,172–174,177,178,180–182,184,185,188,206,212,214,221,222,227,228,230,231,250] ($n = 4876$) was carried out to explore impact of combining seroma and haematoma

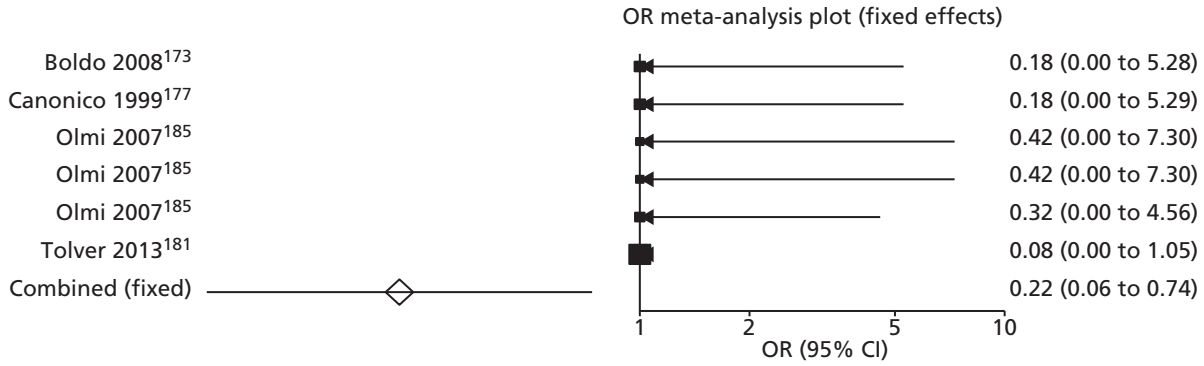

FIGURE 7 Haematoma development in hernia surgery: fibrin sealant vs. standard care.

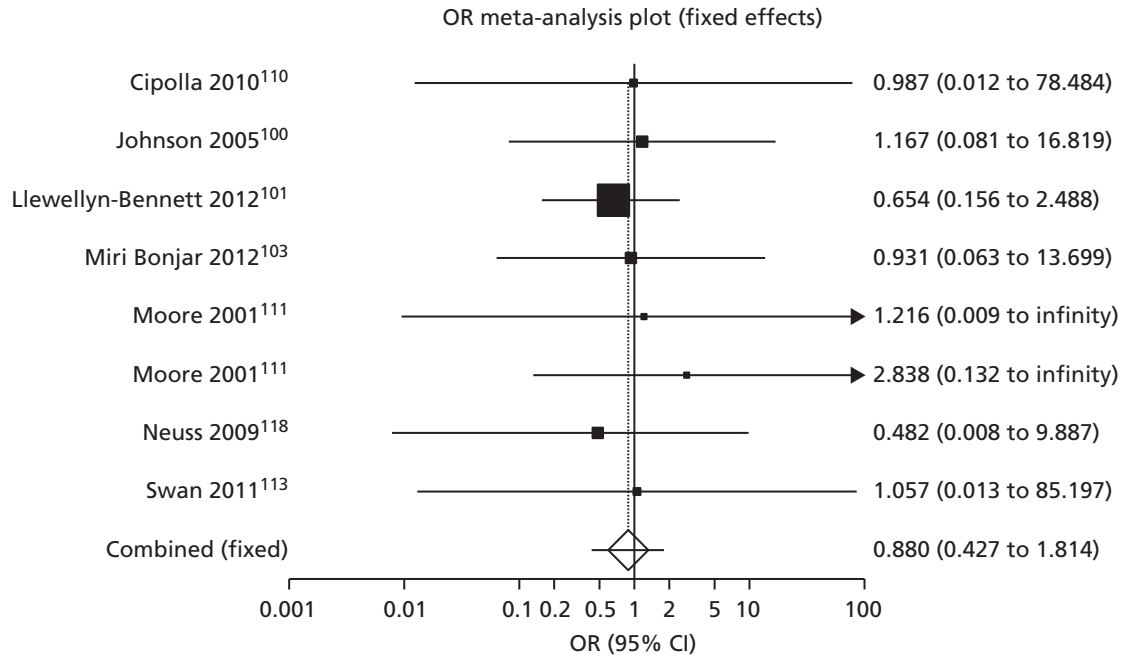

FIGURE 8 Haematoma development in breast surgery: fibrin sealant vs. standard care.

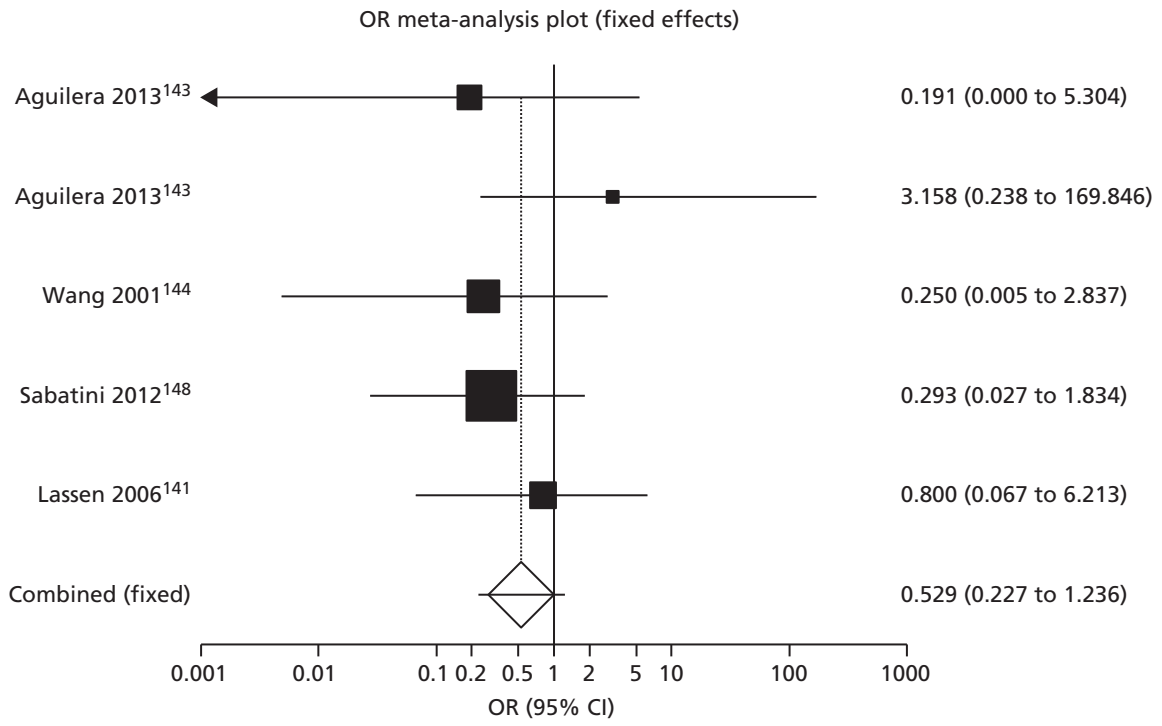

FIGURE 9 Haematoma development in orthopaedic surgery: fibrin sealant vs. standard care.

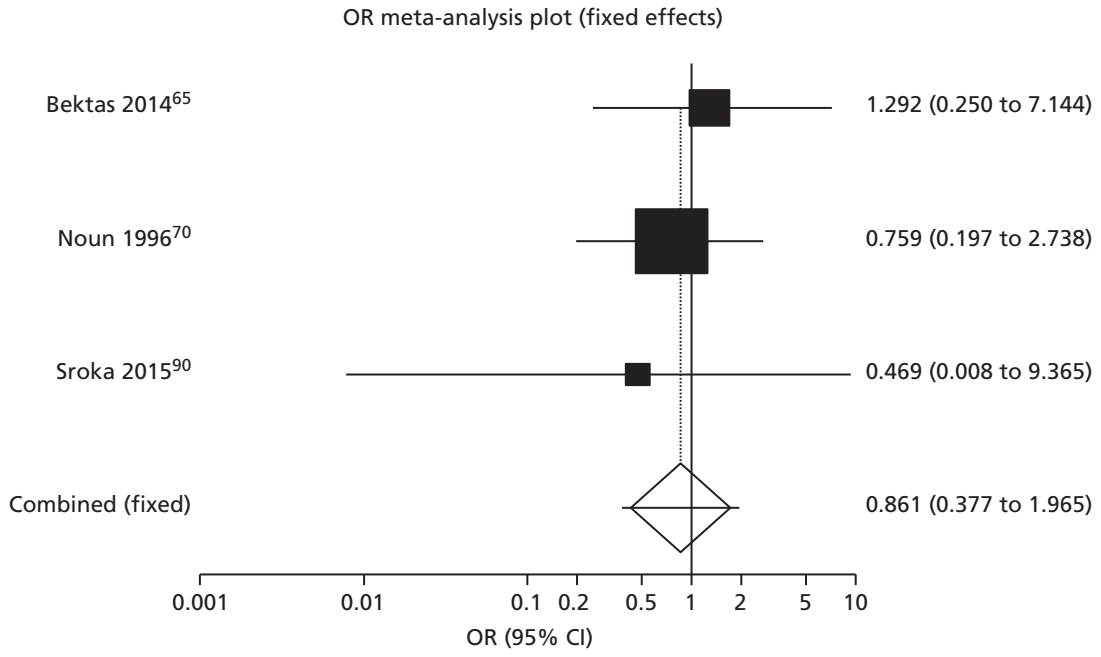

FIGURE 10 Haematoma development in upper GI tract surgery: fibrin sealant vs. standard care.

as an outcome (*Figure 11*). The study by Lovisetto *et al.*,[180] who reported only combined haematoma and seroma rates (and, therefore, was excluded from the haematoma analysis), was included in the combined analysis. This meta-analysis demonstrated a statistically significant reduction in the risk of developing seroma or haematoma with fibrin sealant compared with control (OR 0.77, 95% CI 0.64 to 0.92; $p = 0.01$; $I^2 = 6.7\%$, fixed-effects model). The random-effects model showed a similar result (see *Appendix 8*).

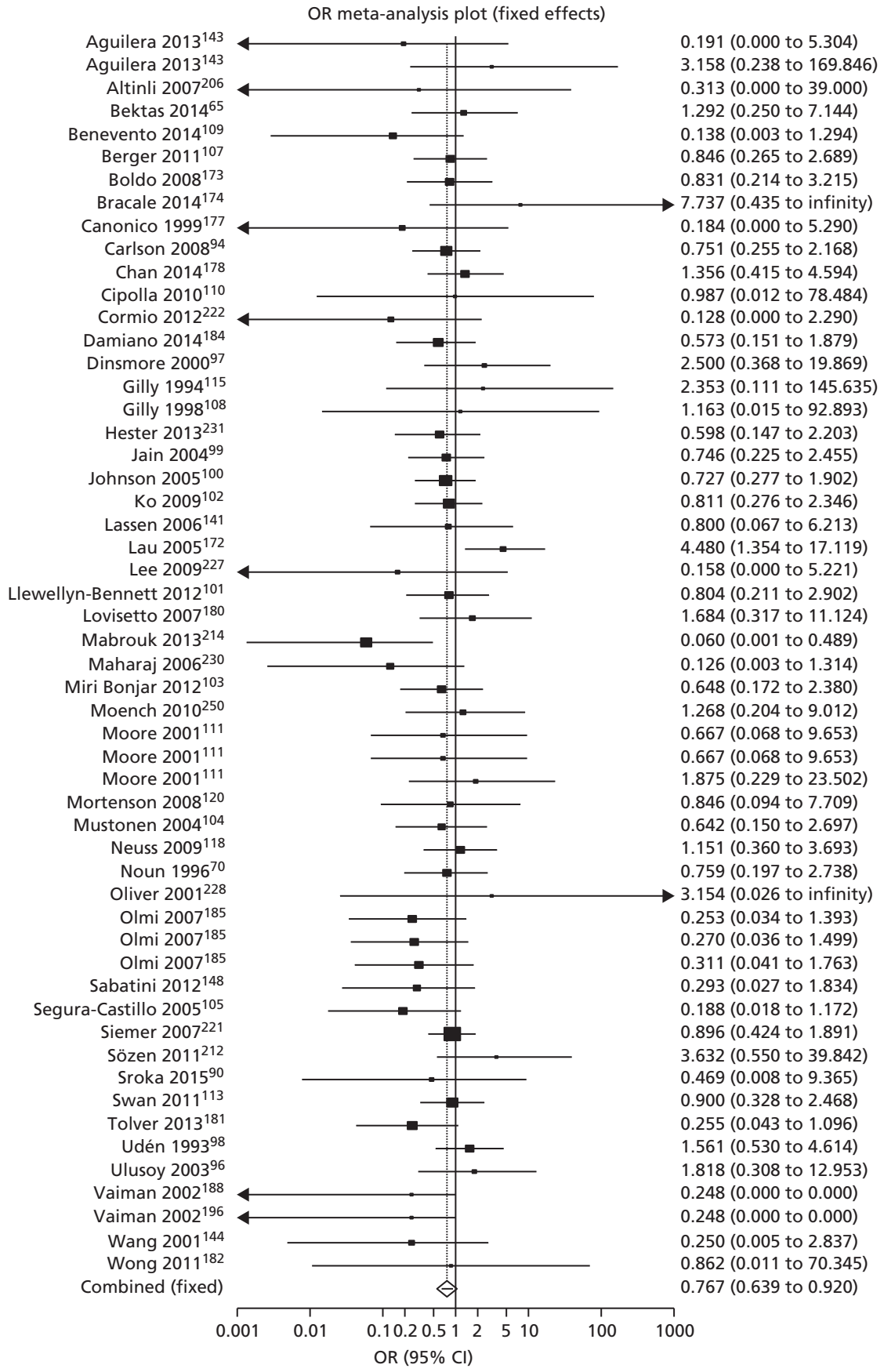

FIGURE 11 Seroma and haematoma development combined in all surgical specialties: fibrin sealant vs. standard care.

Secondary dichotomous outcomes

The following sections present the five dichotomous outcomes: haemorrhage (bleeding), reoperation, infections, use of analgesics and complications arising from the use of drains.

Haemorrhage (bleeding)

Haemorrhage was reported in 19 RCTs, of which 17[59,62,74,75,84,85,99,102,134,135,158,168,177,197,199,205,250] ($n = 2125$) were included in the meta-analysis (*Figure 12*). Two RCTs (Neuss *et al.*[118] and Jackson *et al.*[193]) were excluded because they reported that none of the participants experienced post-operative bleeding. The included RCTs were within several surgical specialties: cardiothoracic,[134,135,205] breast and axillary/inguinal lymph nodes,[99,102] hernia,[177] vascular,[197,199] eye,[158,168] upper GI tract[62,74,75,84,85,250] and urology.[59] There was statistically non-significant reduction in risk of post-operative bleeding between patients receiving fibrin sealants versus standard care (OR 0.64, 95% CI 0.40 to 1.02; $p = 0.08$; $I^2 = 0\%$, fixed-effects model). The random-effects model showed a similar result (see *Appendix 8*).

Randomised controlled trials that did not report the number of patients and only reported bleeding as total number of blood units were also excluded. In Jain *et al.*[99] two control groups (no drain and no fibrin; drain and no fibrin) were reported and the first group was deemed to be most appropriate for analysis as the only difference between the intervention and control group was the addition of fibrin.

Subgroup analyses were conducted for the following surgical specialties: upper GI tract (*Figure 13*), cardiothoracic lung (*Figure 14*), breast (*Figure 15*), vascular (*Figure 16*) and eye (*Figure 17*). There was a

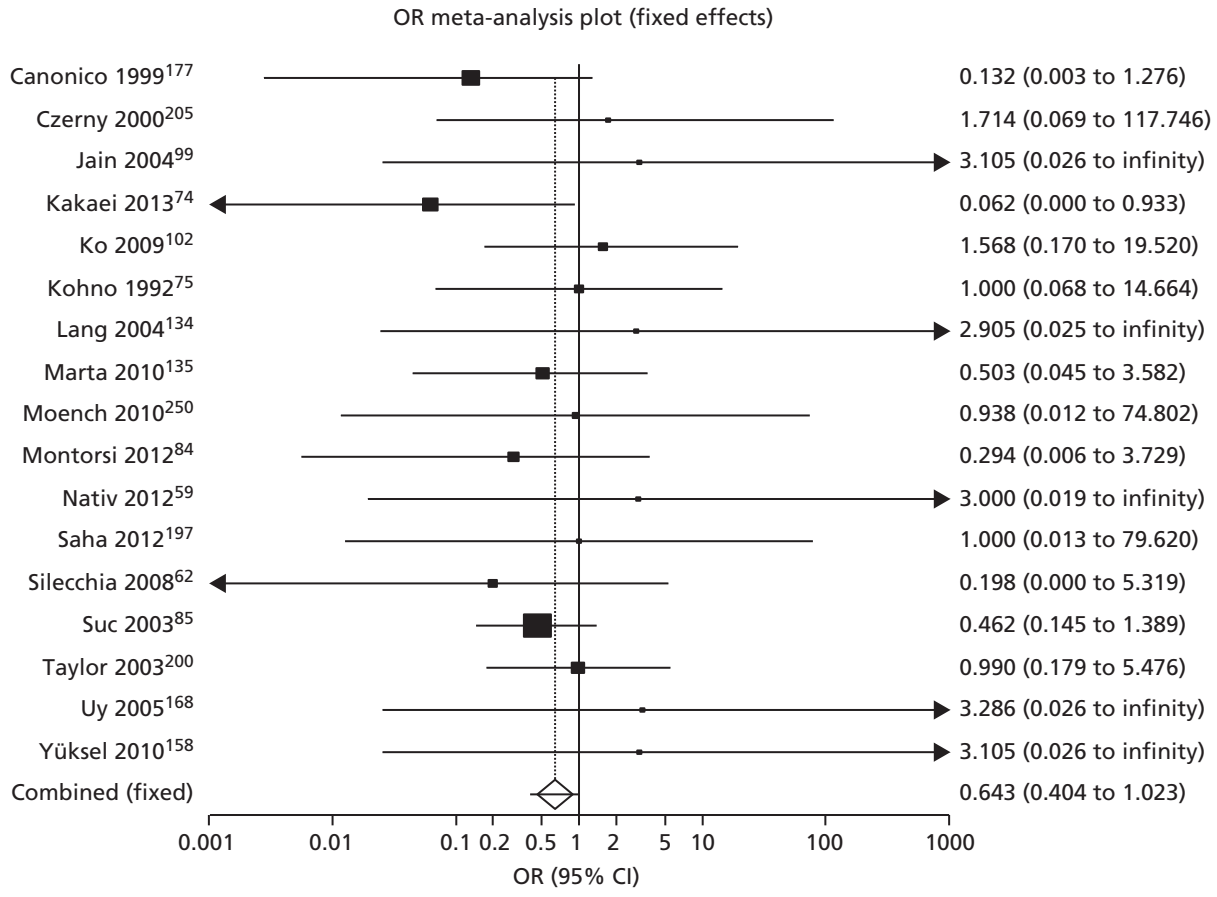

FIGURE 12 Haemorrhage (bleeding) in all surgical specialties: fibrin sealant vs. standard.

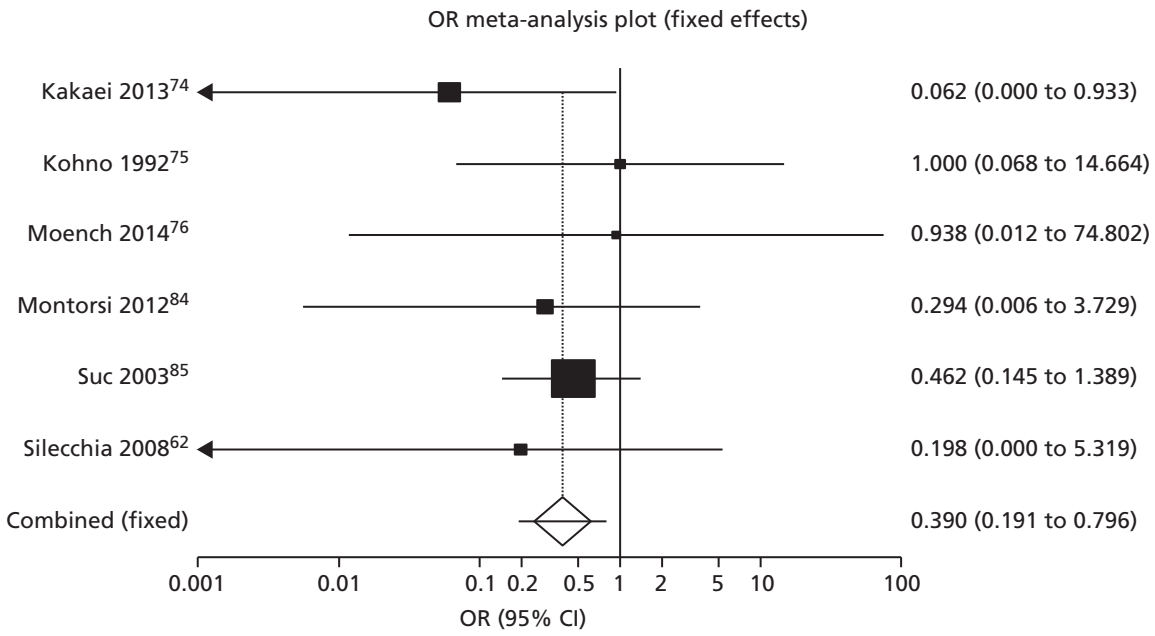

FIGURE 13 Haemorrhage (bleeding) in upper GI tract surgery: fibrin sealant vs. standard.

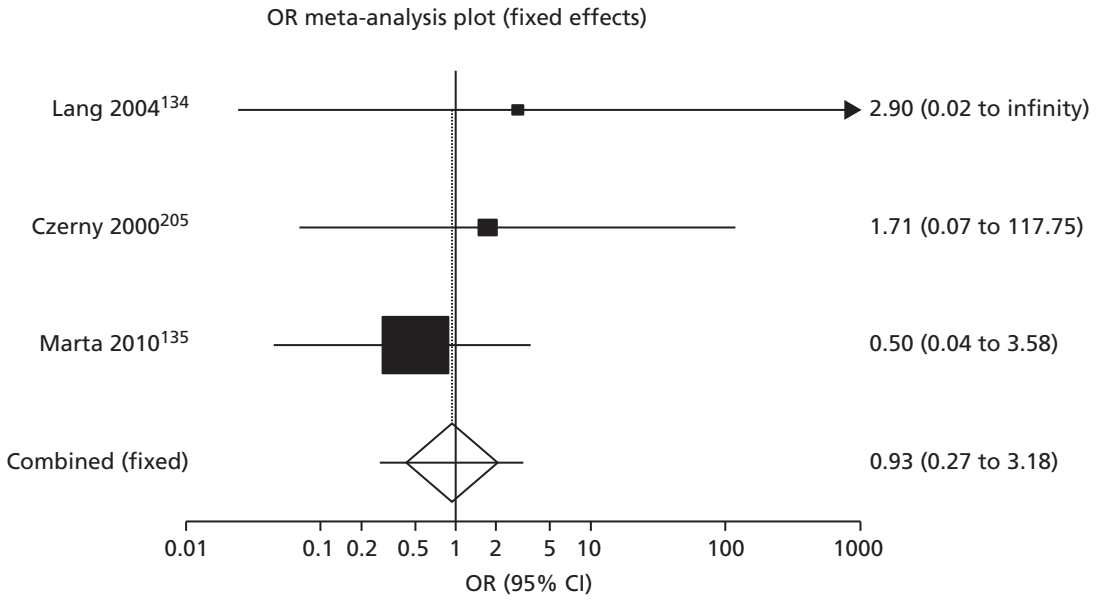

FIGURE 14 Haemorrhage (bleeding) in cardiothoracic lung surgery: fibrin sealant vs. standard care.

statistically significant reduction in risk of haemorrhage when using fibrin sealants compared with standard care within upper GI tract surgery (six RCTs,[62,74,75,84,85,250] $n = 995$, OR 0.39, 95% CI 0.19 to 0.80; $p = 0.01$; $I^2 = 0\%$, fixed-effects model) and no significant difference in the remaining surgical specialties: $p = 0.84$ (three cardiothoracic lung RCTs,[134,135,205] $n = 501$), $p = 0.69$ (two breast RCTs,[99,102] $n = 153$), $p = 0.76$ (two vascular RCTs,[197,199] $n = 339$) and $p = 0.61$ (two eye RCTs,[158,168] $n = 80$). The random-effects models showed similar results (see *Appendix 8*).

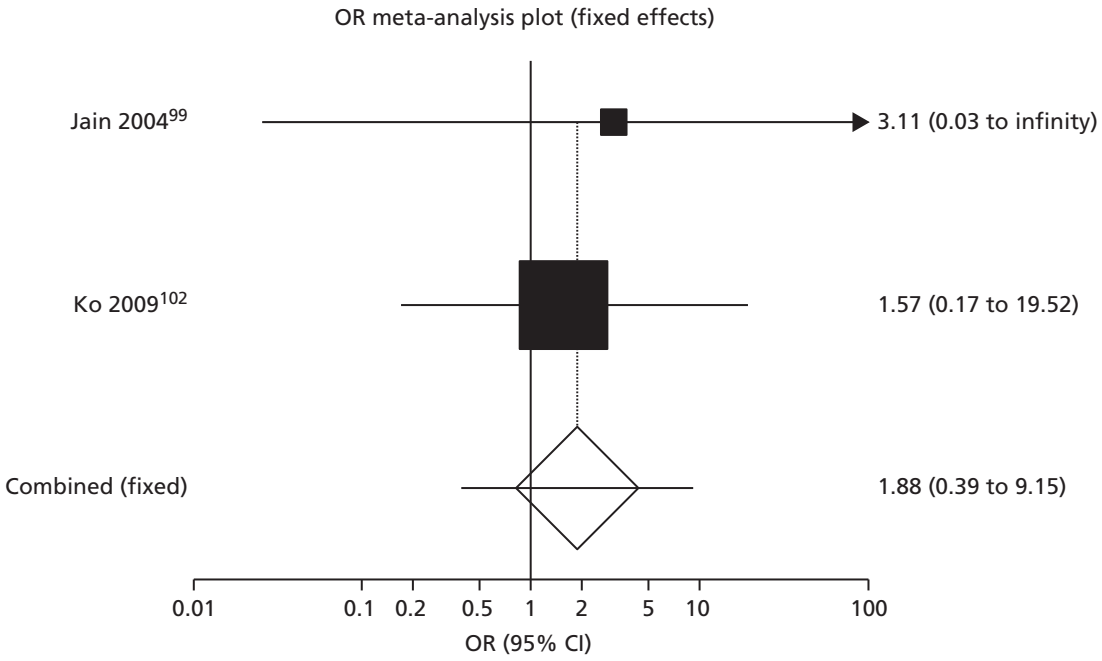

FIGURE 15 Haemorrhage (bleeding) in breast surgery: fibrin sealant vs. standard care.

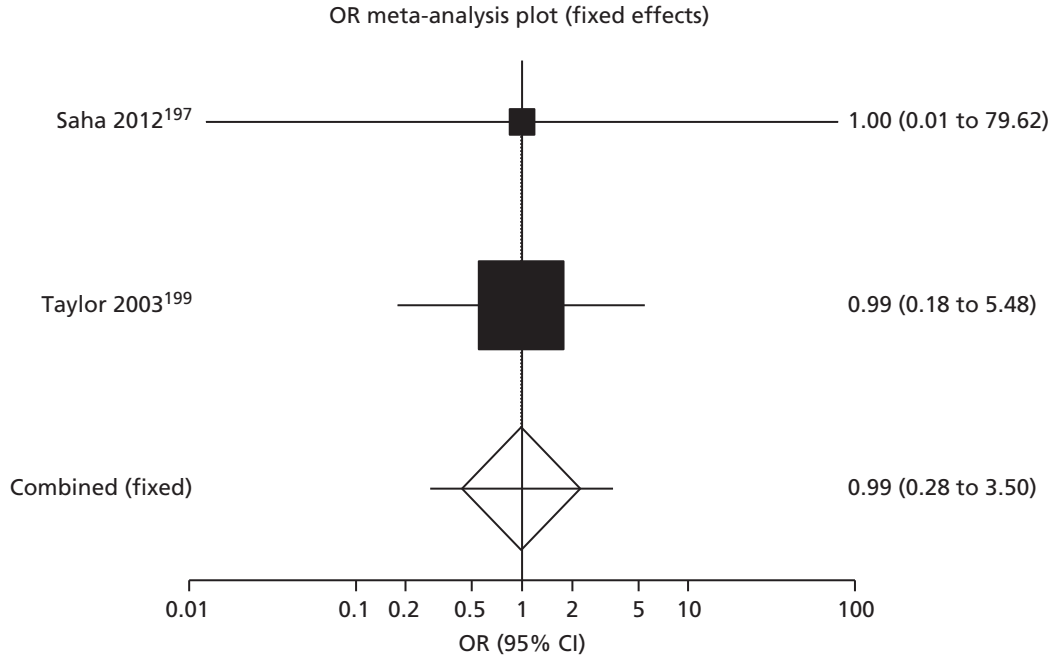

FIGURE 16 Haemorrhage (bleeding) in vascular surgery: fibrin sealant vs. standard care.

Reoperation

A total of 20 RCTs reported reoperation as an outcome, of which 15[60,77,85,86,93,101,107,116,125,135,138,140,143,237,239] were included in the meta-analysis (*Figure 18*). Five RCTs were excluded for the following reasons: Droghetti *et al.*,[124] Milne *et al.*[201] and Dimo *et al.*[80] reported that none of the trial patients had a reoperation; Bulbuller *et al.*[92] reported that the only patients who had a reoperation were in an additional intervention arm and not in the fibrin or standard care arms; and Moser *et al.*[126] did not report any data for the fibrin group.

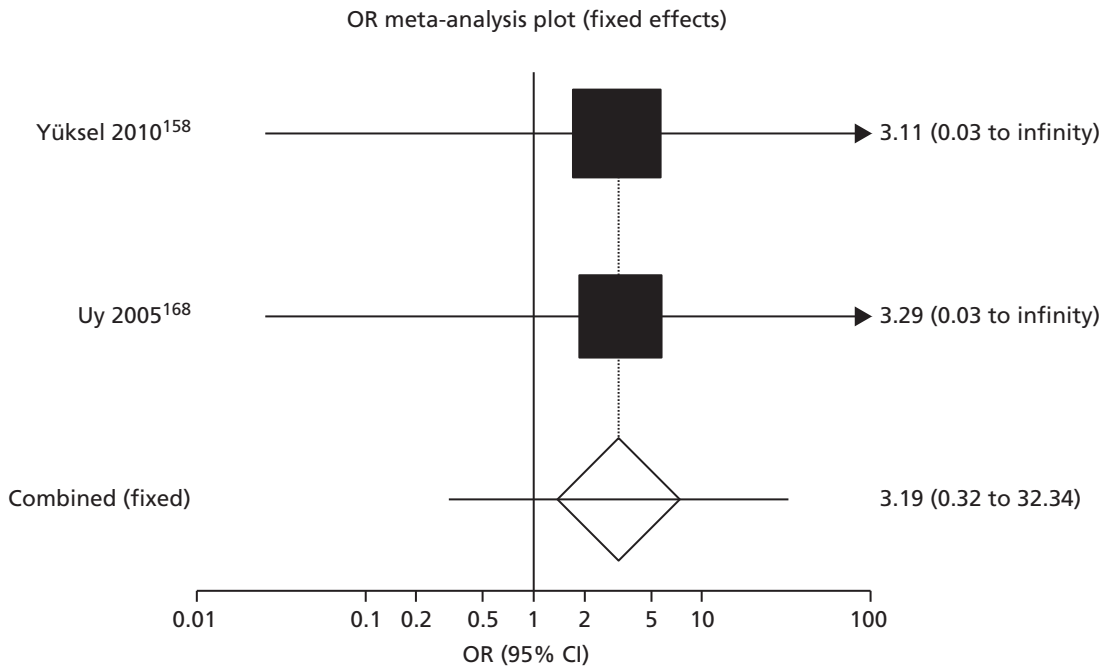

FIGURE 17 Haemorrhage (bleeding) in eye surgery: fibrin sealant vs. standard care.

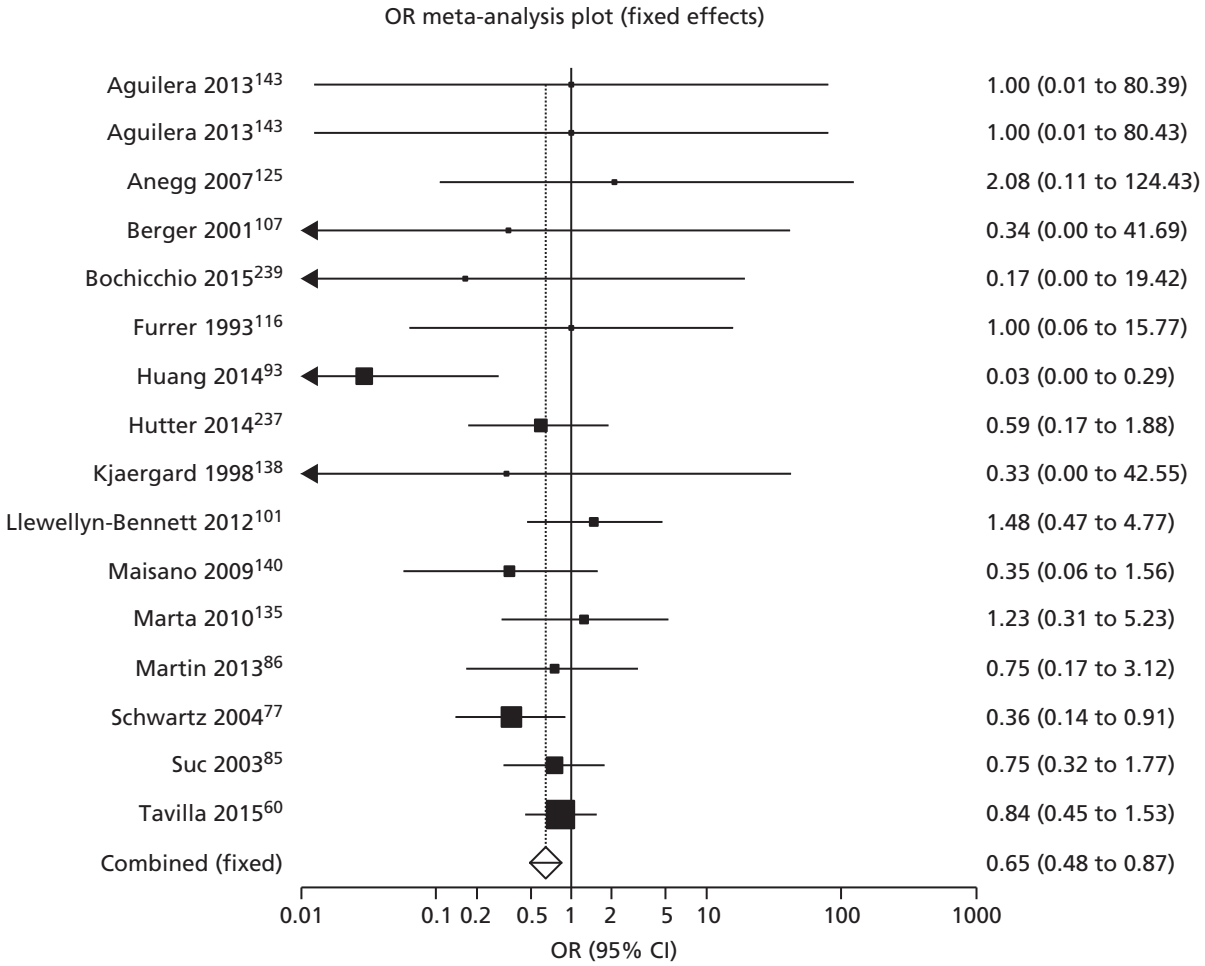

FIGURE 18 Reoperation in all surgical specialties: fibrin sealant vs. standard care.

The RCTs included in the meta-analysis reported fibrin use within four surgical specialties: cardiothoracic lung and heart, breast and axillary/inguinal lymph nodes, orthopaedics and neurosurgery. Patients receiving fibrin sealants had a statistically significant lower risk of reoperation than those in the control group (15 RCTs,[60,77,85,86,93,101,107,116,125,135,138,140,143,237,239] $n = 3789$, OR 0.65, 95% CI 0.48 to 0.87; $p \leq 0.01$; $I^2 = 0\%$, fixed-effects model). The random-effects model showed a similar result (see *Appendix 8*).

A subgroup analysis was conducted for the following surgical specialties: upper GI tract (*Figure 19*), cardiothoracic lung (*Figure 20*), cardiothoracic heart (*Figure 21*) and breast (*Figure 22*). The decrease in reoperations associated with using fibrin sealants was only statistically significant in upper GI tract (four RCTs,[77,85,86,93] $n = 455$, OR 0.43, 95% CI 0.27 to 0.70; $p = 0.0009$; $I^2 = 51.4\%$, fixed-effects model). There was a statistically non-significant decrease in the risk of reoperation in cardiothoracic heart surgery

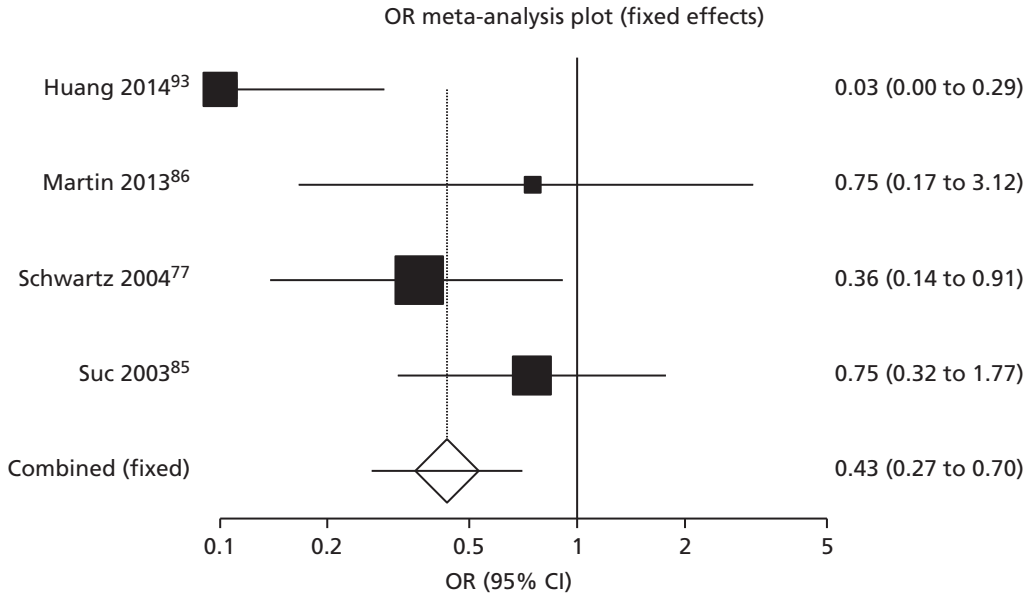

FIGURE 19 Reoperation in upper GI tract surgery: fibrin sealant vs. standard care.

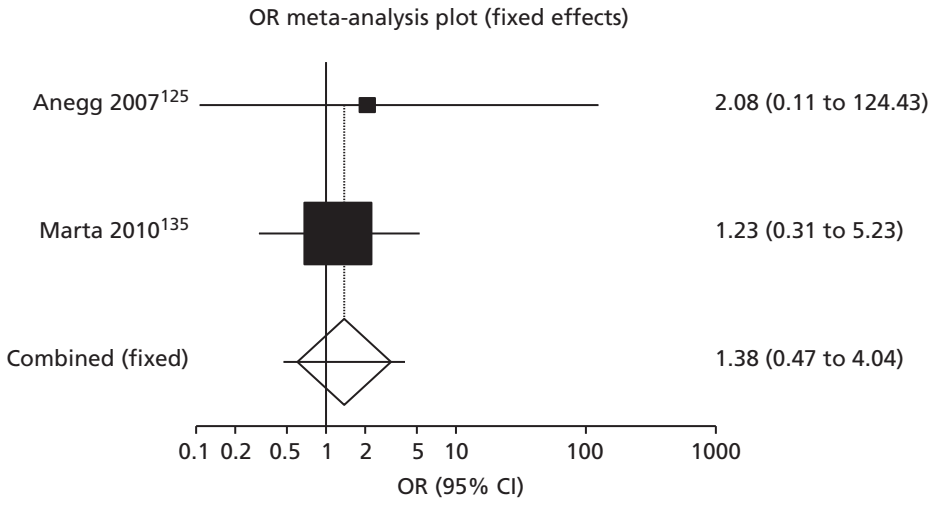

FIGURE 20 Reoperation in cardiothoracic lung surgery: fibrin sealant vs. standard care.

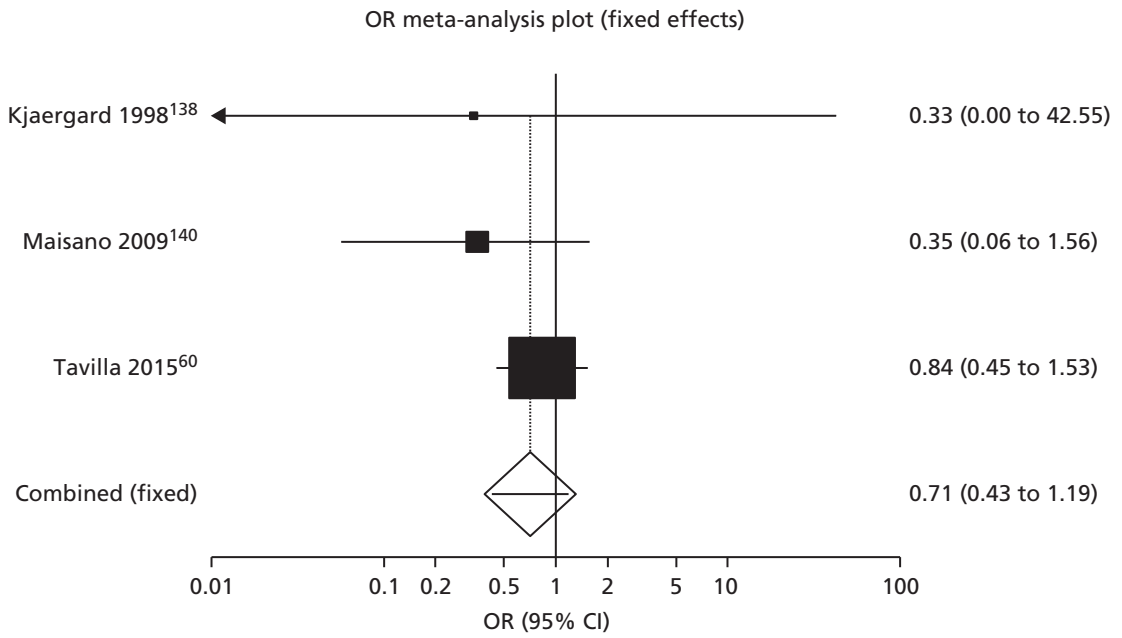

FIGURE 21 Reoperation in cardiothoracic heart surgery: fibrin sealant vs. standard care.

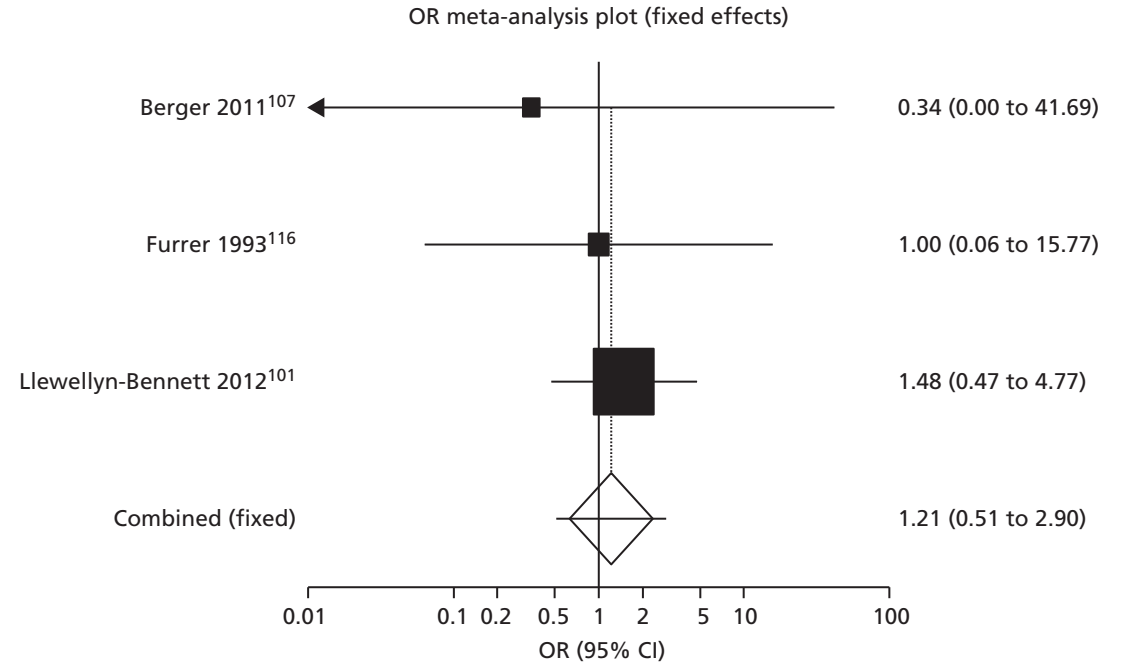

FIGURE 22 Reoperation in breast surgery: fibrin sealant vs. standard care.

(three RCTs,[60,138,140] $n = 1578$; OR 0.71, 95% CI 0.43 to 1.19; $p = 0.24$; $I^2 = 0\%$, fixed-effects model), whereas in cardiothoracic lung surgery (two RCTs,[125,135] $n = 451$; OR 1.38, 95% CI 0.47 to 4.04; $p = 0.76$; no I^2, fixed-effects model) and breast surgery (three RCTs,[101,107,116] $n = 191$; OR 1.21, 95% CI 0.51 to 2.90; $p = 0.83$; $I^2 = 0\%$, fixed-effects model) there was a non-significant increase in risk of reoperation for fibrin sealant compared with standard care.

Infection

Wound infections were reported by 30 RCTs, of which 25[14,59,60,64,72,73,75,83,84,86,96,99,102,111,118,120,122,130,135,143,170,178,198,230,250] were included in meta-analysis (*Figure 23*). The RCTs included in the meta-analysis reported fibrin

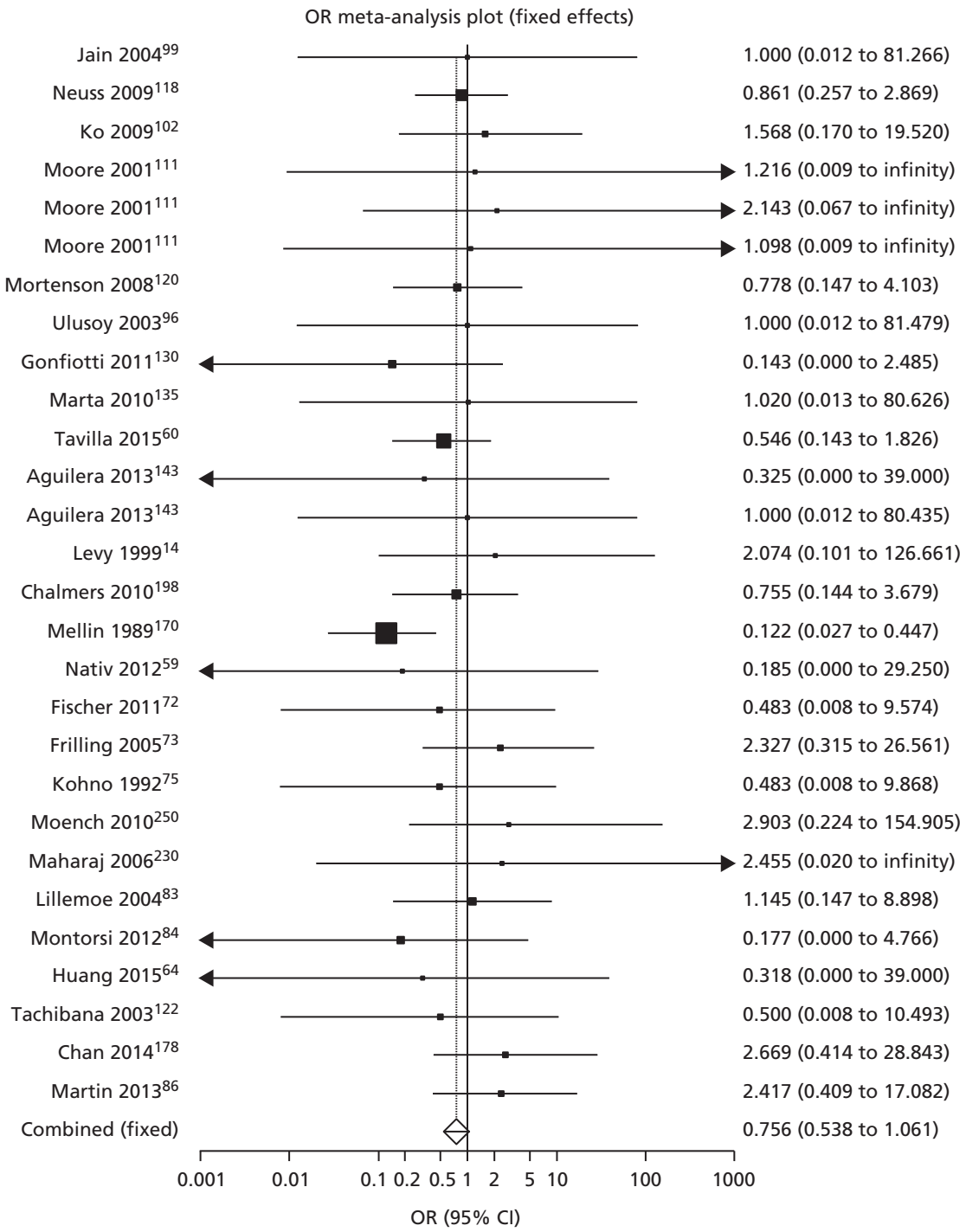

FIGURE 23 Infections in all surgeries: fibrin sealant vs. standard care.

use within four surgical specialties: upper GI tract (eight RCTs),[64,72,73,75,83,84,86,250] breast (seven RCTs),[96,99,102,111,118,120,122] cardiothoracic lung (two RCTs)[130,135] and heart (one RCT),[60] orthopaedic knee (two RCTs),[14,143] vascular (one RCT),[198] eye (one RCT),[170] urology (one RCT),[59] oral (one RCT)[230] and hernia (one RCT).[178] The following five RCTs were excluded because they reported no wound infections in the fibrin sealant and standard care group: Udén *et al.*,[98] Sabatini *et al.*,[148] Danielsen *et al.*,[79] Lovisetto *et al.*[180] and Lau.[172] Patients receiving fibrin sealants did not have a statistically significant lower risk of wound infection than control patients (25 RCTs, $n = 3902$, OR 0.76, 95% CI 0.54 to 1.06; $p = 0.12$; $I^2 = 0\%$, fixed-effects model). The random-effects model showed a similar result (see *Appendix 8*).

A subgroup analysis was conducted for the following surgical specialties: upper GI tract (*Figure 24*), breast (*Figure 25*), cardiothoracic lung (*Figure 26*) and orthopaedic knee (*Figure 27*). The risk of wound infection appeared not to be statistically significantly different in upper GI tract surgery ($n = 917$, OR 1.15, 95% CI 0.59 to 2.27; $p = 0.81$; $I^2 = 0\%$, fixed-effects model), cardiothoracic lung surgery ($n = 484$, OR 0.34, 95% CI 0.05 to 2.16; $p = 0.43$; $I^2 = 0\%$, fixed-effects model), breast surgery ($n = 418$, OR 0.95, 95% CI

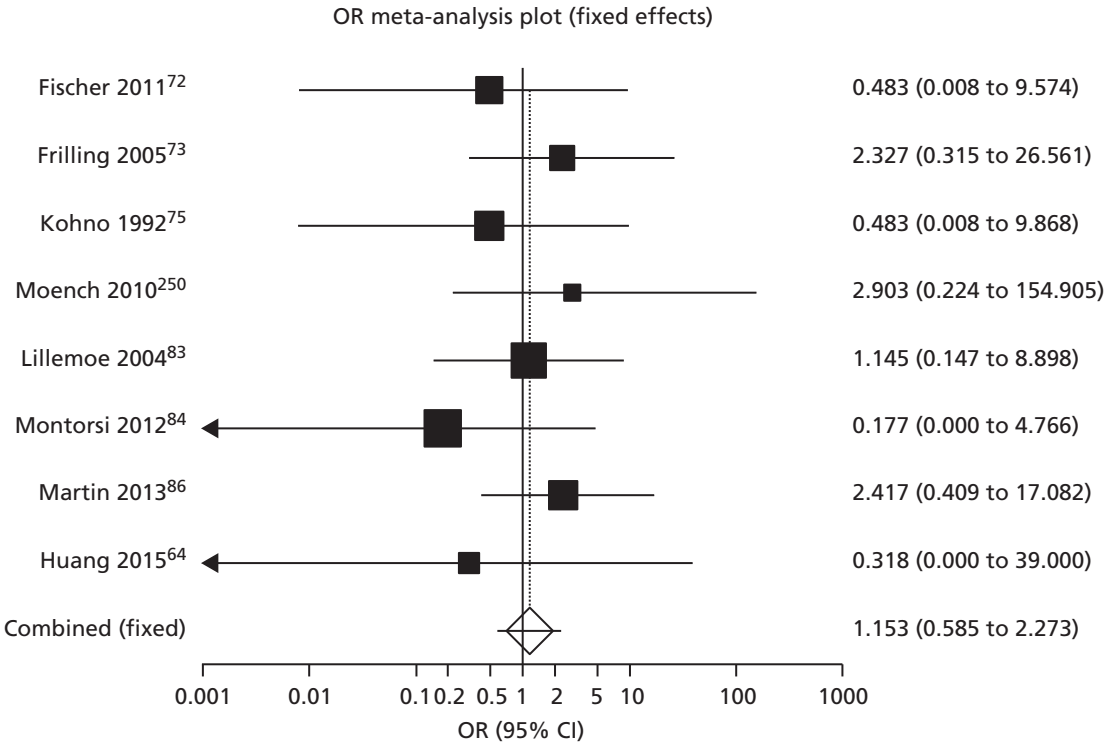

FIGURE 24 Infections in upper GI tract surgery: fibrin sealant vs. standard care.

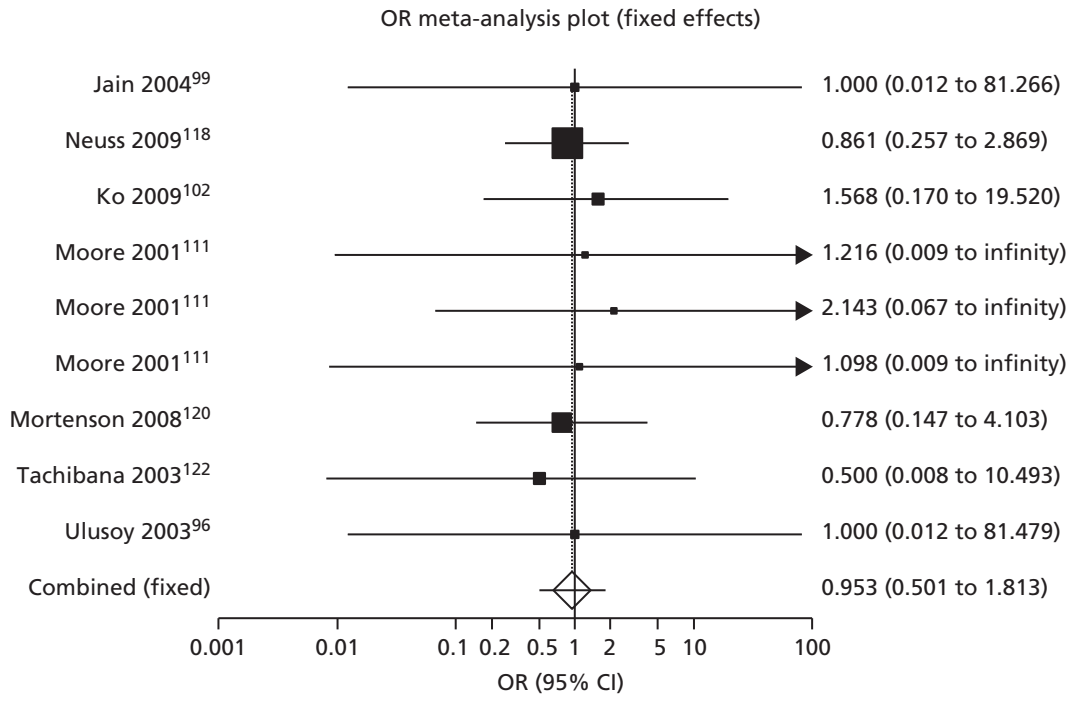

FIGURE 25 Infections in breast surgery: fibrin sealant vs. standard care.

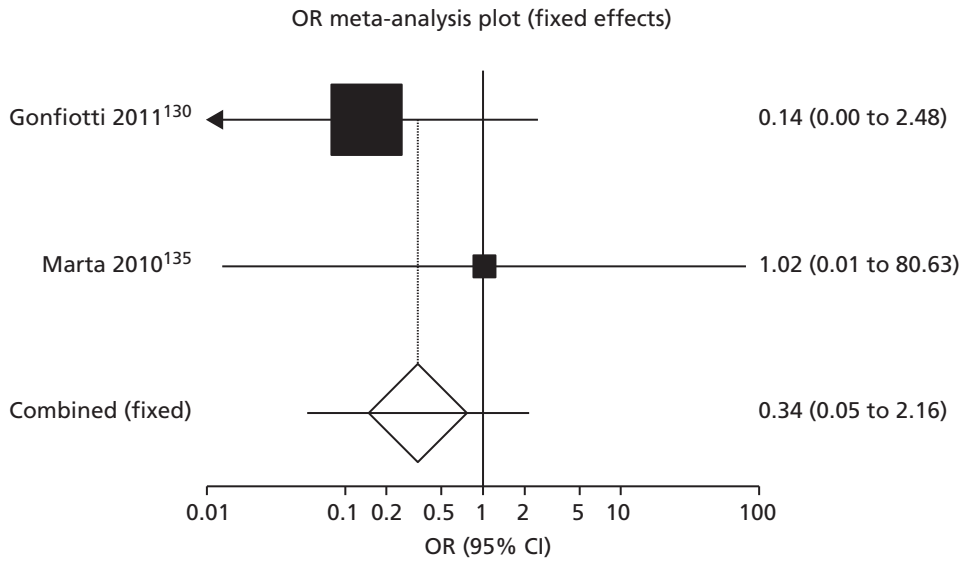

FIGURE 26 Infections in cardiothoracic lung surgery: fibrin sealant vs. standard care.

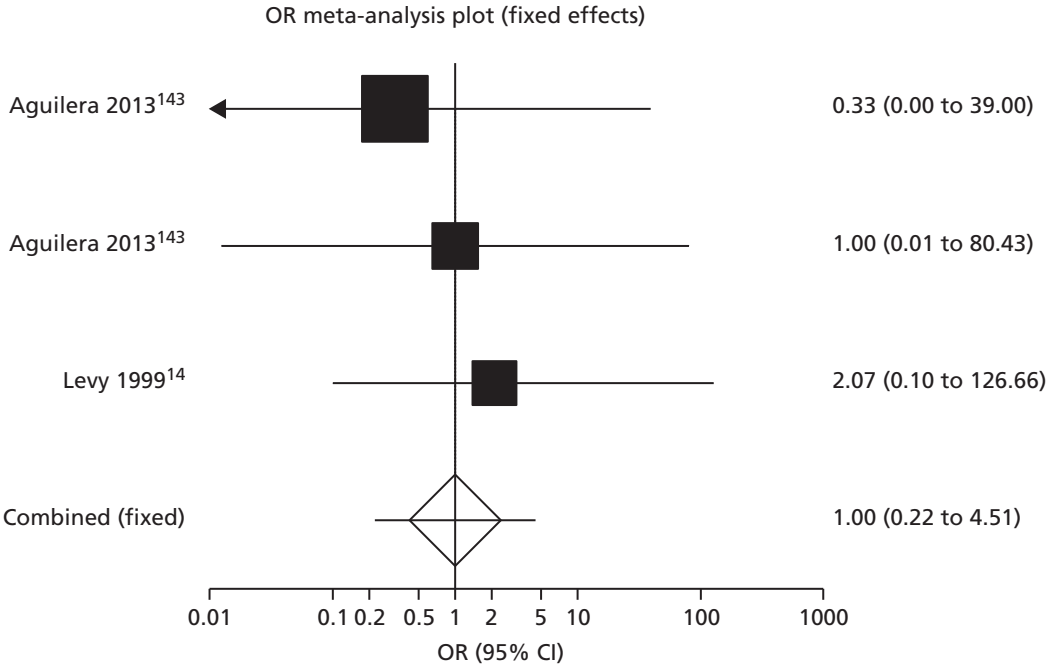

FIGURE 27 Infections in orthopaedic knee surgery: fibrin sealant vs. standard care.

0.50 to 1.81; $p = 0.99$; $I^2 = 0\%$, fixed-effects model) or orthopaedic surgery ($n = 224$, OR 1.00, 95% CI 0.22 to 4.51; $p = 0.70$; $I^2 = 0\%$, fixed-effects model).

Use of analgesics

Three RCTs[133,217,222] reported on use of analgesics, but the data were too heterogeneously reported for meta-analysis. Belboul *et al.*[133] (cardiothoracic lung) reported on the number of days of post-operative thoracic epidural analgesia, which was 2 days in the fibrin group and 3 days in the standard care group. Altomare *et al.*[217] (colorectal) reported that no patients were on analgesics in the fibrin group and almost all patients in the standard care group received analgesics. Cormio *et al.*[222] (kidney) reported on the number of doses of analgesic required during the first 24 hours post operation, which was 1.2 [standard deviation (SD) 1.69] in the fibrin group and 1.17 (SD 1.56) in the control group.

Complications arising from the use of drains

No RCTs reported on complications arising from the use of drains.

Continuous secondary outcomes

Continuous outcomes were analysed separately for each surgical area for RCTs with similar interventions and comparators as the type of intervention (e.g. staples vs. stitches). The following continuous outcomes are reported below: duration of operation, length of hospital stay, duration of drainage, pain levels and health-related quality of life.

Duration of operation (minutes)

Duration of operation was reported in the following surgical specialties: upper GI tract (gastric and liver), eye and hernia.

Upper gastrointestinal surgery

Gastric surgery Mean duration of operation was reported in five gastric surgery RCTs,[62,88–90,92] of which two were included in the meta-analysis[88,90] (*Figure 28*). As operation time was expected to be dictated by the type of surgery and interventions, only Sroka *et al.*[90] and Musella *et al.*,[88] who reported on use of fibrin in laparoscopic sleeve gastrectomies, were comparable. Sroka *et al.*[90] compared sealant application with both sutures and not applying sealant and Musella *et al.*[88] compared fibrin sealant with no sealant. A non-significantly shorter mean time of –2.03 minutes (95% CI –4.12 to 0.14 minutes; $p = 0.07$) was found for fibrin sealant versus no sealant ($n = 198$).

Three RCTs were excluded from the meta-analysis: Pilone *et al.*[89] compared fibrin sealant with no sealant, Silecchia *et al.*[62] compared sealant application with sutures and Bulbuller *et al.*[92] compared sealant application with both sutures and not applying sealant. SDs were reported only by Silecchia *et al.*,[62] who investigated the use of fibrin in laparoscopic gastric bypass and reported no statistically significant difference in operative time. Challenges faced in interpreting these data are that duration of operation was not explicitly defined in the papers and the type of sealant applied may have an effect on the time taken.

Liver surgery Mean duration of surgery was reported by four RCTs[68–71] using fibrin in hepatic resection surgery: Liu and Liu[69] and Noun *et al.*[70] seemed comparable as hepatic resection was carried out without

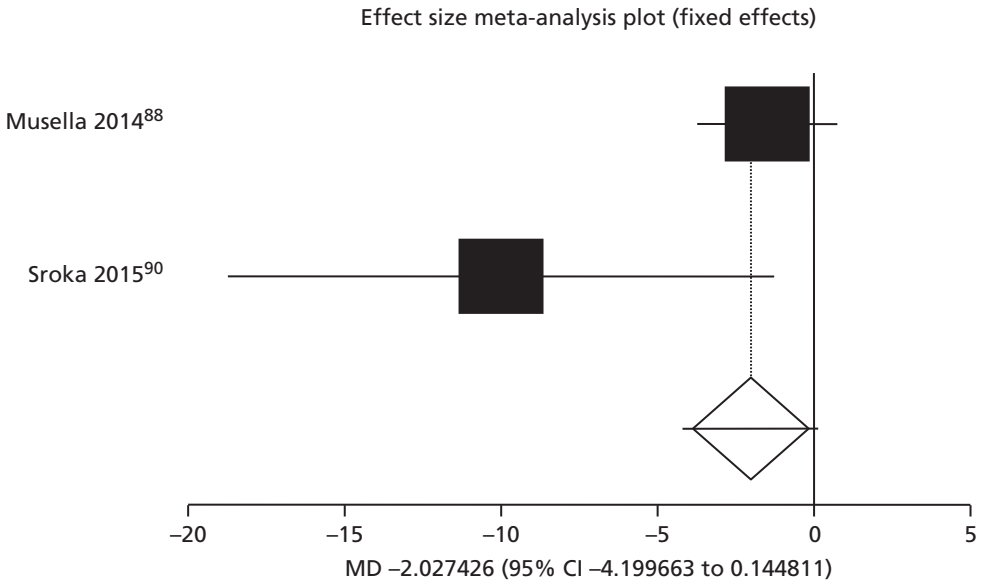

FIGURE 28 Mean duration of gastric surgery in minutes: fibrin sealant vs. no sealant.

liver mobilisation (*Figure 29*). Without liver mobilisation, the MD of the duration of surgery for fibrin sealant compared with standard care is a decrease of 14 minutes (two RCTs,[69,70] $n = 117$, 95% CI –54.2 to 24.3 minutes; $p = 0.46$), but this is not statistically significant.

In Figueras *et al.*,[71] liver mobilisation was carried out in both intervention and comparator groups. Uetsuji *et al.*[68] had three groups: (1) liver mobilisation and no sealant, (2) liver mobilisation with sealant and (3) no liver mobilisation or sealant. Figueras *et al.*[71] and the 'liver mobilisation' groups were combined in a separate meta-analysis. In liver with mobilisation, the MD increased by 19.07 minutes (two RCTs,[68,71] $n = 364$, 95% CI 2.75 to 35.38 minutes; $p = 0.02$) for fibrin sealant compared with standard care (*Figure 30*).

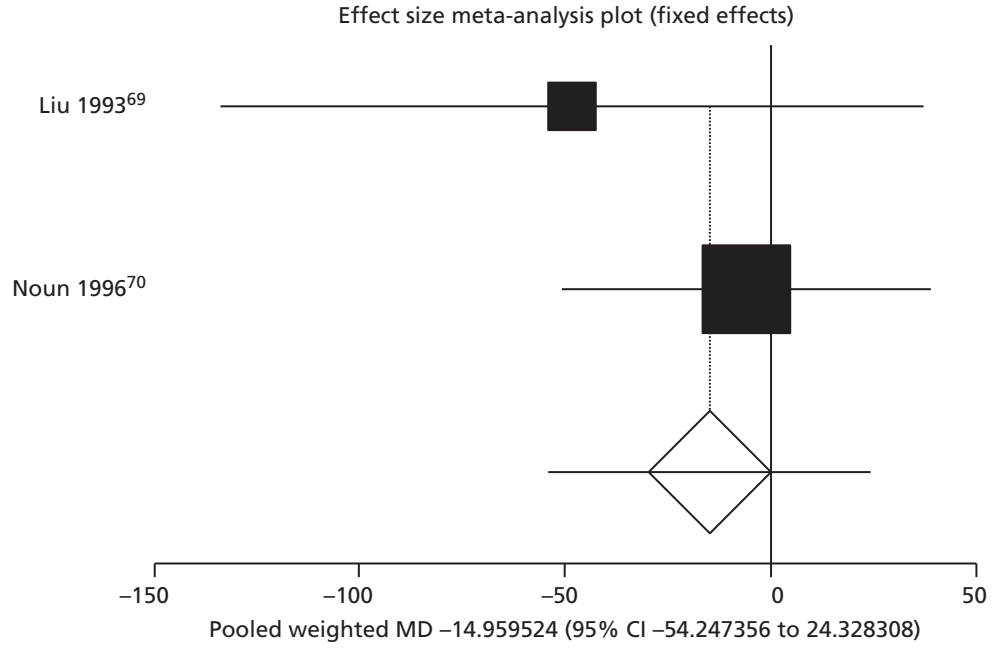

FIGURE 29 Mean duration of hepatic resection without liver mobilisation in minutes: fibrin sealant vs. standard care.

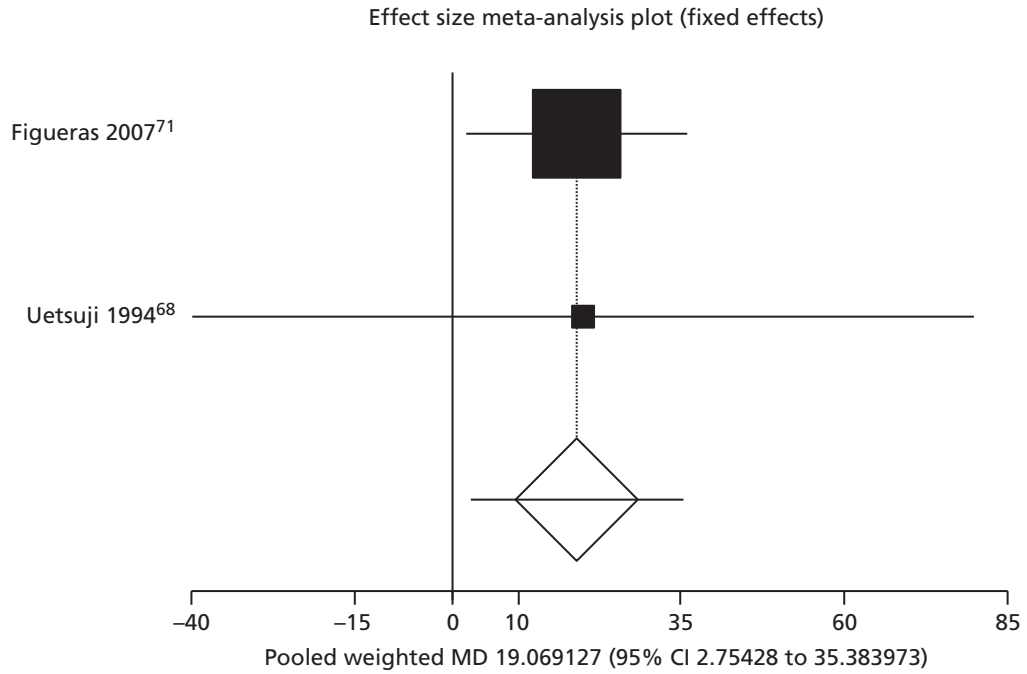

FIGURE 30 Mean duration of hepatic resection with liver mobilisation in minutes: fibrin sealant vs. standard care.

This result indicates a statistically significant increase in surgery time associated with the use of fibrin sealants compared with standard care in hepatic resection with liver mobilisation.

Eye surgery Duration of surgery was reported in 12 RCTs[157–163,165,166,168,169,171] that all compared fibrin sealant with sutures and eight RCTs were included in the meta-analysis (*Figure 31*). Three RCTs[159,160,169] did not report variability around the means and, thus, were excluded from the analysis.

The mean duration was statistically significant shorter in the fibrin group than the sutures group, with a MD of –12.13 minutes (95% CI –12.59 to –11.67 minutes; $p < 0.01$; $I^2 = 99.1\%$, fixed-effects model, eight RCTs,[157,158,161,163,165,166,168,171] $n = 519$). The high level of heterogeneity was explored by sequentially excluding individual RCTs to identify if the potential cause of the heterogeneity was caused by any individual RCT. This was found not to be the case as I^2 always remained > 90%. The random-effects model showed a MD of –17.19 minutes (95% CI –23.35 to –12.50 minutes; $p < 0.0001$; $I^2 = 99.1\%$, see *Appendix 8*). Furthermore, the RCTs excluded from the meta-analysis also reported a shorter mean duration of surgery in the fibrin group than the sutures group: Hall *et al.*[160] (12.04 vs. 26.04 minutes, respectively), Bahar *et al.*[159] (16 vs. 20 minutes, respectively) and Bahar *et al.*[169] (16 vs. 28 minutes, respectively).

Hernia surgery Five RCTs[175,176,178,180,184] reported mean duration of surgery, of which four[176,178,180,184] reported means and SDs and were included in two separate meta-analyses. Campanelli *et al.*[176] and Damiano *et al.*[184] compared fibrin sealant with sutures (*Figure 32*). Surgery time was statistically significantly shorter for fibrin sealant than sutures in the meta-analysis ($n = 784$), with a MD of –2.56 minutes (95% CI –3.57 to –1.56 minutes; $p < 0.01$). Lovisetto *et al.*[180] and Chan *et al.*[178] compared fibrin with staples (*Figure 33*). Surgery time was statistically significantly longer with fibrin than with staples ($n = 326$), with a MD in surgery time of 13.22 minutes (95% CI 11.59 to 15.26 minutes; $p < 0.01$). The excluded RCT[175] reported on a using self-gripping mesh instead of fibrin and, therefore, could not be compared with either intervention.

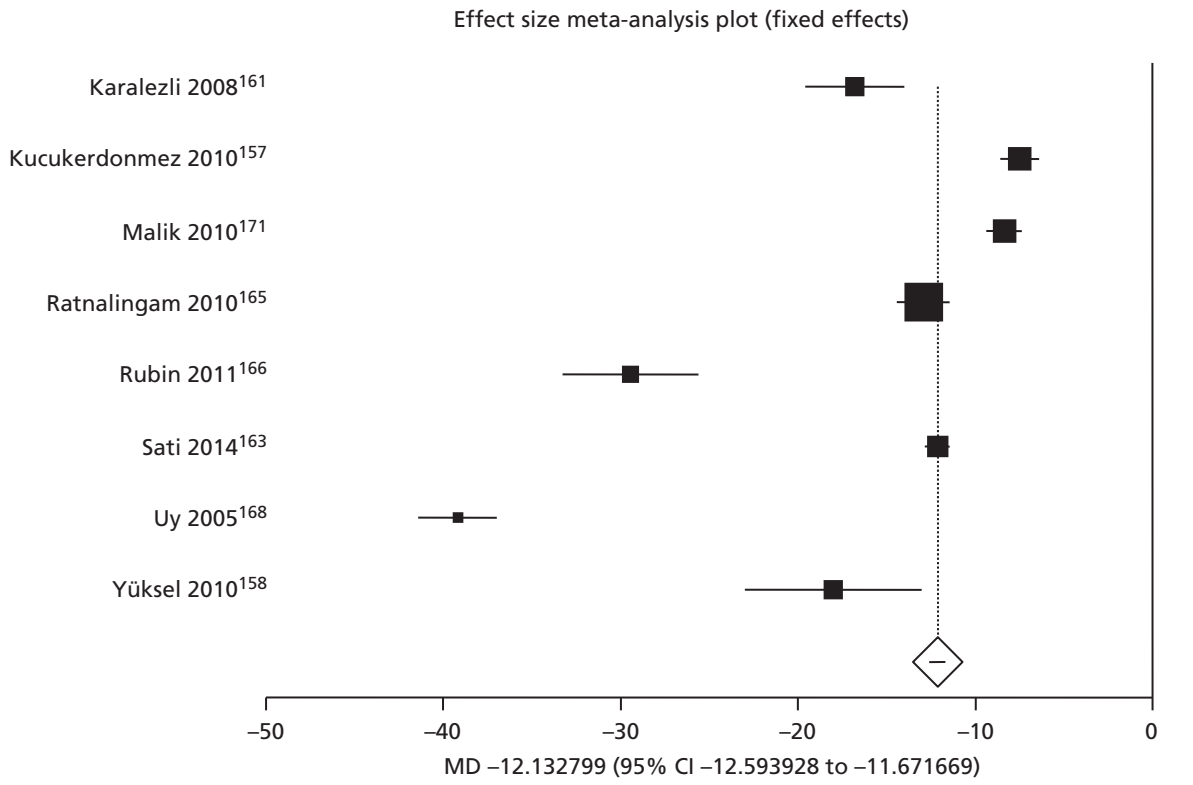

FIGURE 31 Duration of eye surgery in minutes: fibrin sealant vs. sutures.

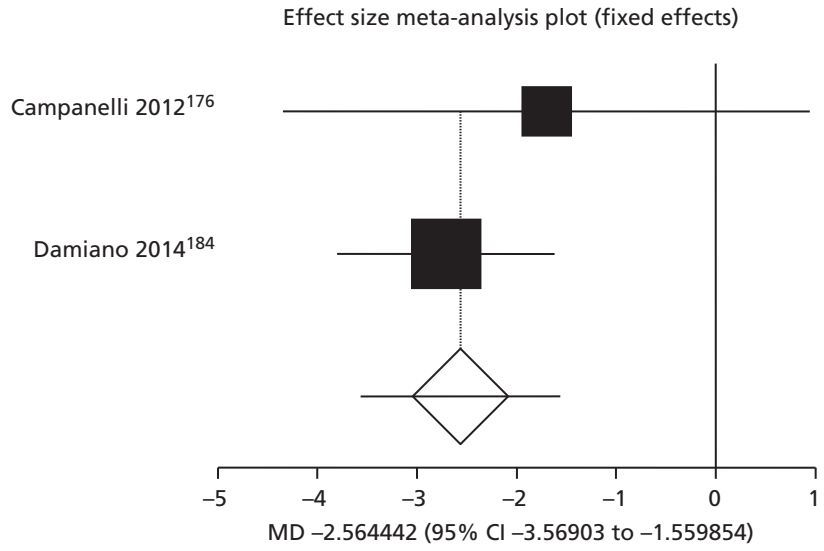

FIGURE 32 Duration of hernia surgery in minutes: fibrin sealant vs. sutures.

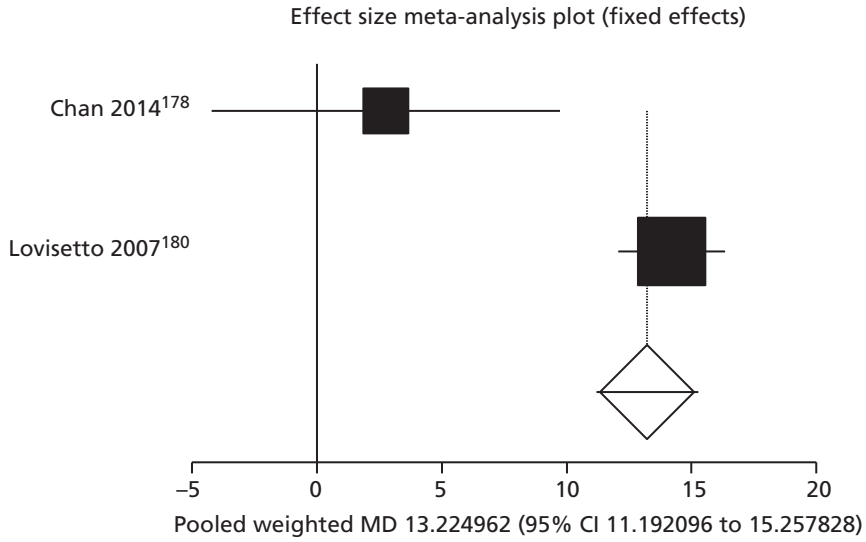

FIGURE 33 Duration of hernia surgery in minutes: fibrin sealant vs. staples.

Length of hospital stay (days)

Length of hospital stay was reported in the following surgical specialties: upper GI tract (pancreas, gastric and bowel), cardiothoracic (lung and heart), breast and joint (knee).

Upper gastrointestinal surgery

Pancreatic surgery Three RCTs[81,83,86] reported mean length of hospital stay for pancreatic surgery when using fibrin sealant and two[83,86] were included in the meta-analysis (*Figure 34*). The study by Carter *et al.*[81] was excluded because the authors did not report variability around the mean. Fibrin sealants statistically significantly decreased hospital stay for fibrin sealant compared with standard care in a meta-analysis ($n = 181$), with a MD of –1.40 days (95% CI –1.72 to –1.09 days; $p < 0.01$). Carter *et al.*[81] reported that mean hospital stay was shorter in the fibrin sealant group (6.4 days) than in the control group (7.3 days), which is consistent with the results of the meta-analysis.

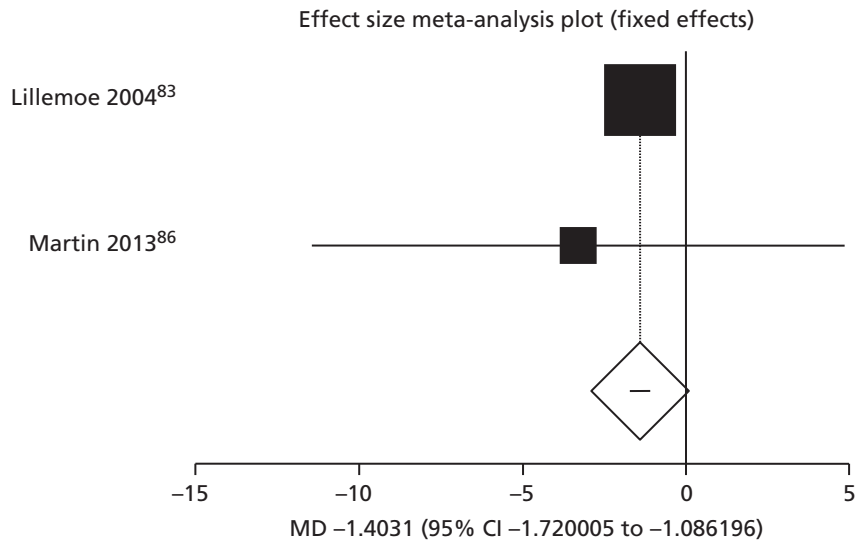

FIGURE 34 Length of hospital stay in days in pancreatic surgery: fibrin sealant vs. standard care.

Gastric and bowel surgery Three RCTs[62,88,89] reported mean length of hospital stay: two for surgery around the gastric region[88,89] and one for stay after bowel surgery,[62] utilising fibrin sealant. The three RCTs were considered sufficiently similar to be analysed together; however, Pilone *et al.*[89] did not report variability around the mean and was therefore excluded. Silecchia *et al.*[62] and Musella *et al.*[88] were combined in meta-analysis (*Figure 35*). There was not a statistically significant increase in hospital stay for fibrin sealant compared with standard care in the meta-analysis ($n = 420$), which had a MD of 0.04 days (95% CI –0.34 to 0.42 days; $p = 0.82$). Pilone *et al.*[89] reported a mean hospital stay of 6.5 days and 7 days for the fibrin sealant and control groups, respectively.

Cardiothoracic surgery

Lung surgery Six RCTs[124,125,127,128,130,136] reported mean hospital stay for lung surgery and were considered similar enough to be included in a meta-analysis. However, only three RCTs[127,130,136] reported variability around the mean and were analysed (*Figure 36*). Mean length of hospital stay was statistically significantly

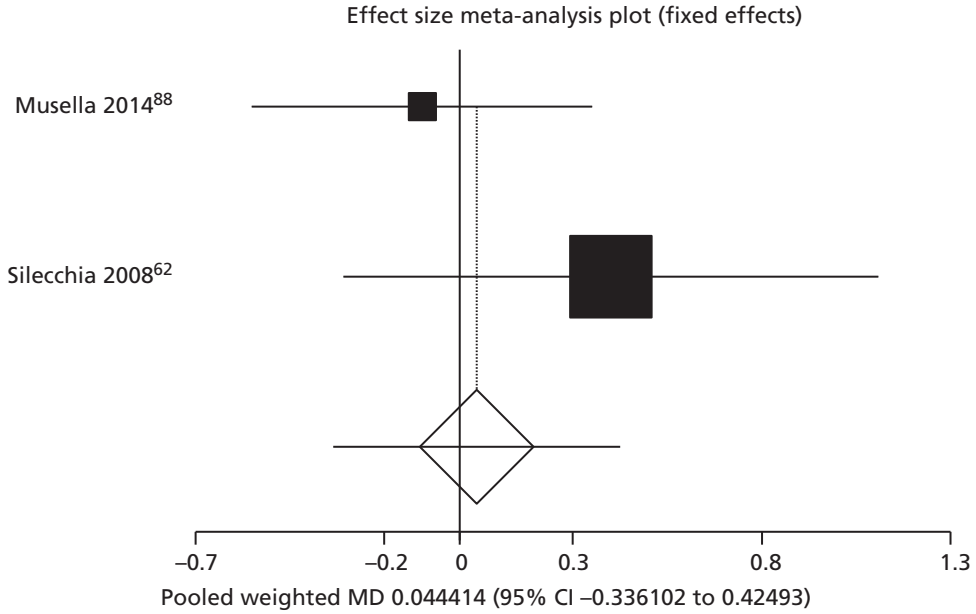

FIGURE 35 Length of hospital stay in days in pancreatic surgery: fibrin sealant vs. standard care.

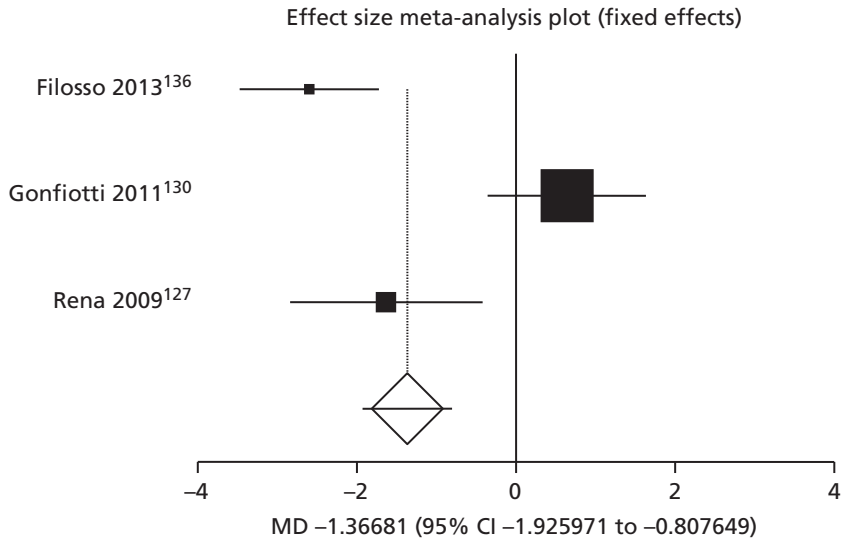

FIGURE 36 Length of hospital stay in days in cardiothoracic lung surgery: fibrin sealant vs. standard care.

reduced for fibrin sealant compared with standard care in the meta-analysis ($n = 269$), with a MD of –1.37 days (95% CI –1.93 to –0.81 days; $p < 0.01$; $I^2 = 91.9\%$). However, there is a high level of heterogeneity between the RCTs, and the significant result becomes non-significant in a random-effects meta-analysis (MD –1.20 days, 95% CI –3.22 to 0.81 days; $p = 0.24$). The studies excluded from the meta-analysis reported a lower mean hospital stay for the fibrin group than the control group: Fabian *et al.*[128] reported 4.6 versus 4.9 days, respectively; Droghetti *et al.*[124] reported 11 versus 14.3 days, respectively; and Anegg *et al.*[125] reported 6.2 versus 7.7 days, respectively.

Heart surgery Tavilla *et al.*[60] ($n = 1436$) reported a mean length of hospital stay of 5.99 days (SD 3.95 days) and 6.07 days (SD 4.21 days) between fibrin and control groups, respectively, and *p*-value of 0.71 indicating no statistically significant difference.

Breast surgery Ten RCTs reported mean hospital stay following breast surgery using fibrin sealants, of which eight[104,106–109,112,115,116] were included in the meta-analysis (*Figure 37*). Two RCTs were excluded for the following reasons: Udén *et al.*[98] did not report variability around the mean and Jain *et al.*[99] did not report mean duration separately for two of the groups. Mean length of hospital stay was statistically significantly reduced in the meta-analysis ($n = 440$), with a MD of –0.73 days (95% CI –0.95 to –0.50 days; $p < 0.01$; $I^2 = 88.7\%$). The high level of heterogeneity was explored by sequentially excluding individual RCTs to identify if the potential cause of the heterogeneity was caused by any individual RCT. This was found not to be the case as I^2 always remained > 80%. However, the statistically significant result became non-significant in a random-effects meta-analysis (MD –0.87 days, 95% CI –1.75 to 0.01 days; $p = 0.05$).

Joint surgery (knee) Four RCTs reported mean hospital stay following knee surgery using fibrin sealants, of which three[143,145,149] were included in the meta-analysis (*Figure 38*). Molloy *et al.*[147] was excluded from the meta-analysis because they did not report variability around the mean. There was no significant effect on the mean duration of hospitalisation for knee surgery for fibrin sealant compared with standard care in the meta-analysis ($n = 251$), giving a MD of 0.07 days (95% CI –0.74 to 0.88 days; $p = 0.87$; $I^2 = 0\%$, fixed-effects model).

Duration of drainage Duration of drainage was reported in the following surgical specialties: breast and axillary lymph nodes, liver and lung surgery.

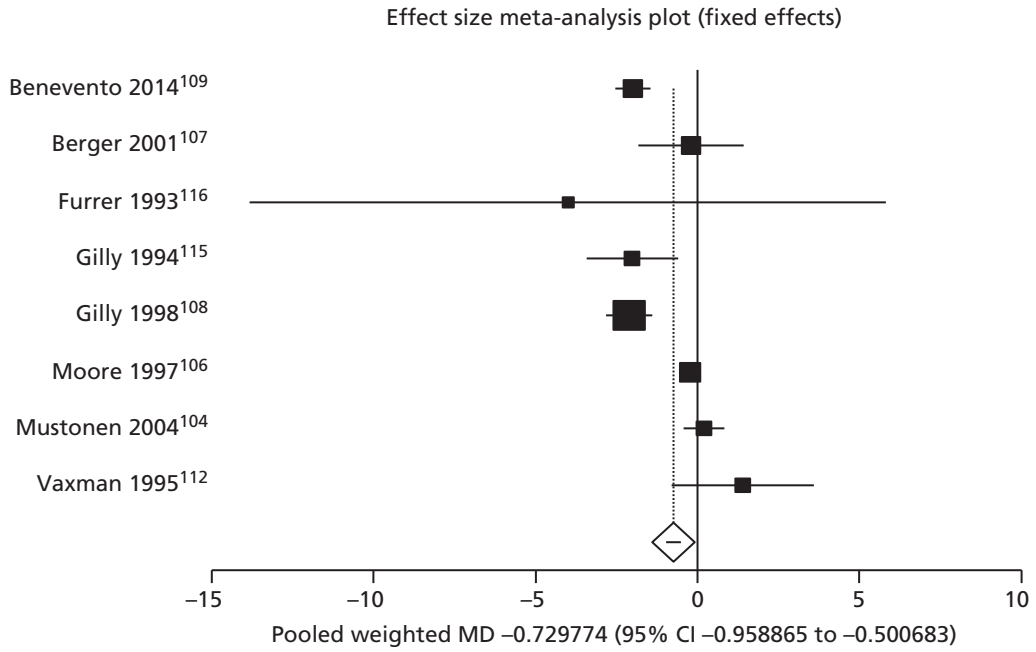

FIGURE 37 Length of hospital stay in days in breast surgery: fibrin sealant vs. standard care.

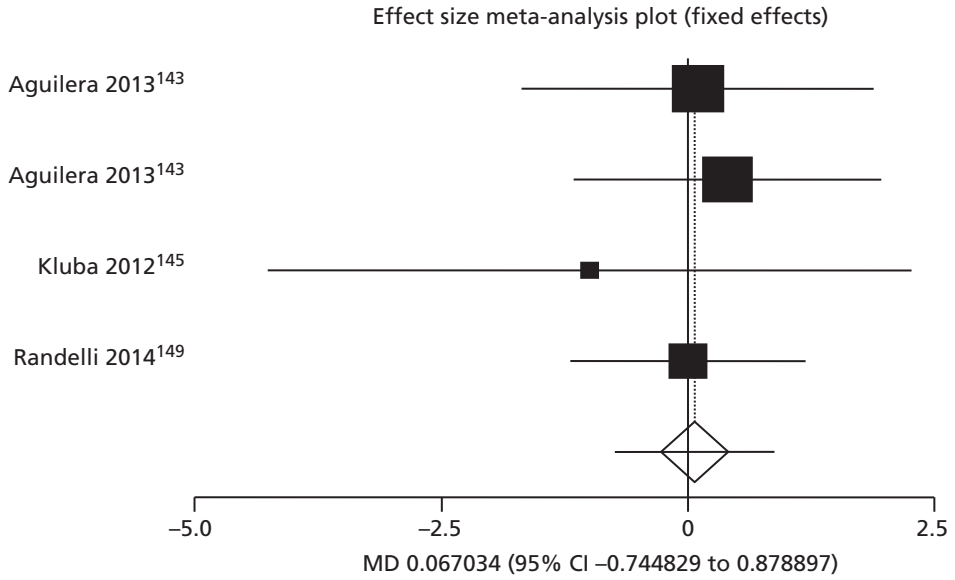

FIGURE 38 Length of hospital stay in days for knee surgery: fibrin sealant vs. standard care.

Breast and axillary lymph nodes A total of 15 RCTs reported mean duration of drainage, of which 13[96,102,104–107,109,110,112,115–117,251] were included in the meta-analysis (*Figure 39*). Two RCTs did not report variability around the means[97,123] and were excluded from the meta-analysis. In the meta-analysis ($n = 953$), there was a statistically significantly lower mean number of days of drainage of –0.50 days (95% CI –0.68 to –0.33 days; $p < 0.01$; $I^2 = 90.6\%$, fixed-effects model) when fibrin sealant was used than standard care. The high level of heterogeneity was explored by sequentially excluding individual RCTs to identify if the potential cause of the heterogeneity was caused by any individual RCT. This was found not to be the case as I^2 always remained > 90%. However, the random-effects model showed an increased MD of –1.06 days (95% CI –1.69 to –0.42 days; $p = 0.01$; see *Appendix 8*).

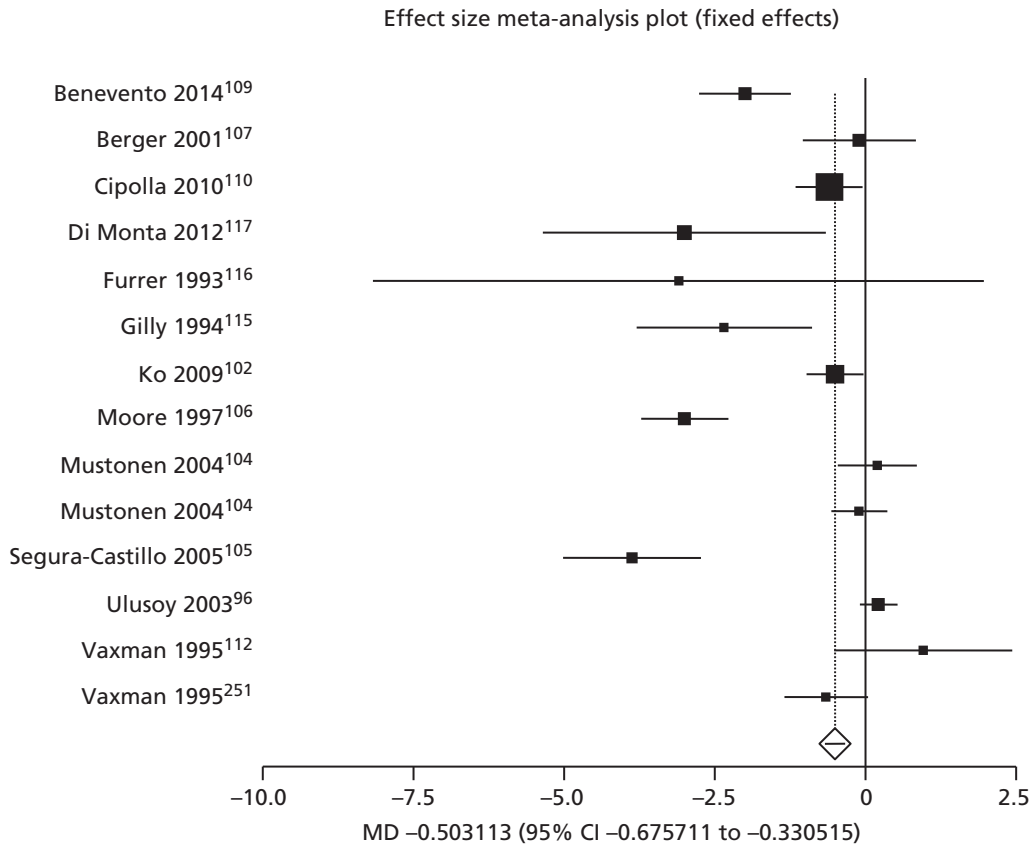

FIGURE 39 Duration of drainage in days in breast and axillary lymph nodes surgery: fibrin sealant vs. standard care.

Liver surgery Mean duration of drainage after liver surgery was reported by four RCTs[65,69,74,75] and combined in a meta-analysis (*Figure 40*). In the meta-analysis ($n = 202$) there was a not a statistically significant difference in the number of drainage days for fibrin sealant compared with standard care, with a MD of –0.27 days (95% CI –0.82 to 0.27 days; $p = 0.33$; $I^2 = 0\%$, fixed-effects model).

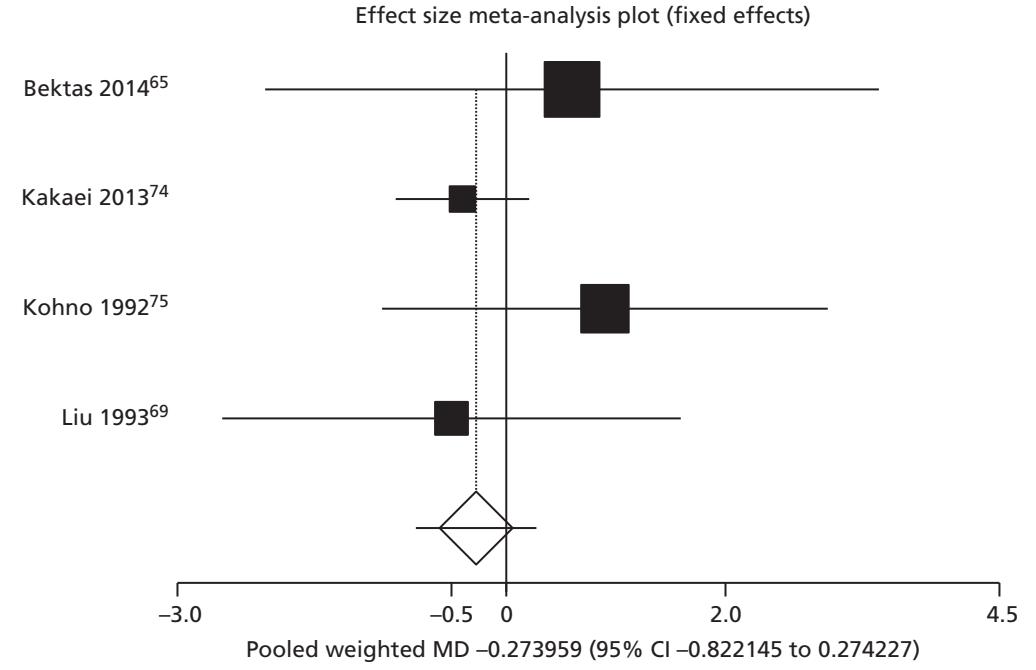

FIGURE 40 Duration of drainage in days for liver surgery: fibrin sealant vs. standard care.

Lung surgery Mean duration of drainage after lung surgery was reported by five RCTs[126,127,130,136,137] that were combined in a meta-analysis (*Figure 41*). In the meta-analysis ($n = 399$) there was a statistically significant lower number of drainage days for fibrin sealant than standard care, with a MD of –0.46 days (95% CI –0.53 to –0.39 days; $p < 0.01$; $I^2 = 91\%$, fixed-effects model). The high level of heterogeneity was explored by sequentially excluding individual RCTs to identify if the potential cause of the heterogeneity was caused by any individual RCT. This was found not to be the case as I^2 always remained > 80%. The random-effects model also showed a statistically significant MD of –2.10 days (95% CI –3.65 to –0.56 days; $p = 0.01$; see *Appendix 8*).

Pain levels

Pain was reported by 20 RCTs in six surgical specialties: breast,[95,99,101] joint,[142,147,150] ENT,[187,190,192] plastic and reconstructive,[209,211] eye[157,159,161,165,166,168,169,171] and urology.[222] The large differences in the different scales used, time points at which assessments took place and lack of variability data did not permit a meta-analysis. When RCTs measured pain at different time intervals, pain is reported for the first mentioned measurement point after surgery (*Table 21*).

No data on pain assessments could be reported for five RCTs for the following reasons: Antuña *et al.*[155] reported values only for the entire group; Mabrouk *et al.*[214] reported only that 'all of the patients suffered from pain, ecchymosis, and oedema postoperatively, but to varying degrees'; Diamond *et al.*[232] reported only that 'the most common adverse event reported was abdominal pain'; Hall *et al.*[160] did not report values; and Pryor *et al.*[186] reported only 'no significance difference for overall rate of pain or recovery ($p = 0.06$)'. Furthermore, eight RCTs[78,107,108,151,153,221,239,250] only reported the number of patients with pain.

Health-related quality of life

No RCTs reported on health-related quality of life.

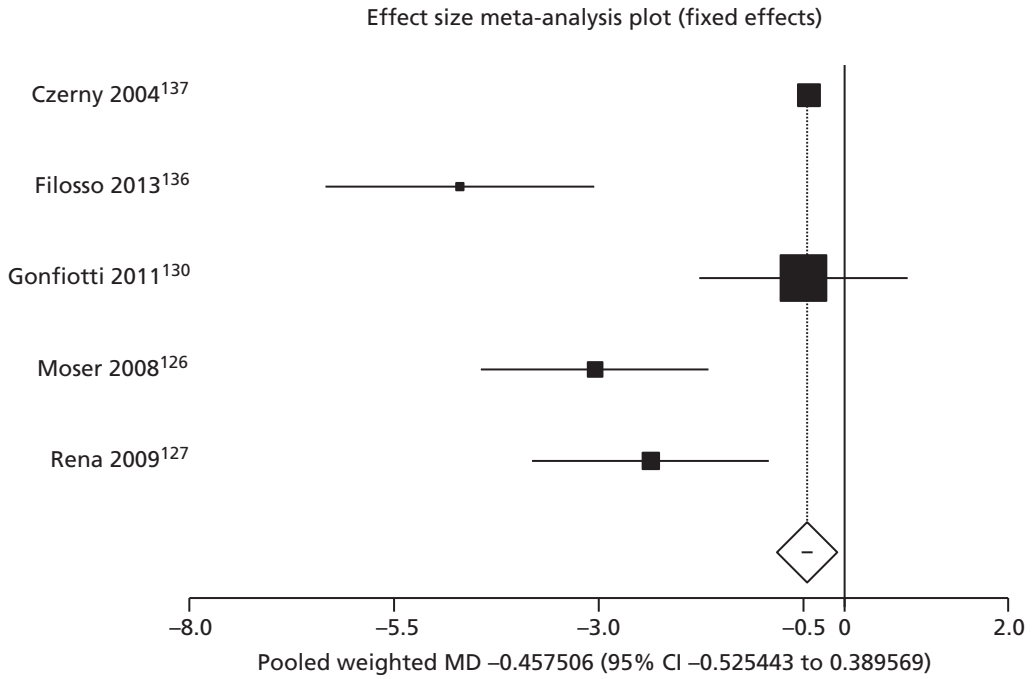

FIGURE 41 Duration of drainage in days for lung surgery: fibrin sealant vs. standard care.

TABLE 21 Pain levels in included RCTs

Study (author, year)	Fibrin sealant and standard care group description	Number of patients	Pain score and variability description	Pain score	Variability around score
Breast					
Jain *et al.*, 2004[99]	Fibrin sealant (Tisseel), no drain	29	Mean post-operative pain at 24 hours (not reported separately for Tisseel, no drain and no glue, no drain groups)	3.2	SD 0.9
	No glue, no drain	29		3.2	SD 0.9
	No glue, drain	58		4.5	SD 1.5
Llewellyn-Bennett *et al.*, 2012[101]	Fibrin sealant (Tisseel)	48	Donor-site pain visual analogue scale score over 15 days	27	Range: 0–89
	Standard closure	53		34	Range: 7–79
Zhibo and Miaobo, 2009[95]	Fibrin sealant and lidocaine	10	Post-operative pain during first week post operation (day 1); self-reported pain recorded on a scale of 0–3, where 0 = no pain, 1 = light pain, 3 = worst pain	1	NR
	Standard care (lidocaine only)	10		9	NR
	Fibrin sealant only	10		10	NR
Joint (knee)					
Skovgaard *et al.*, 2013[150]	Fibrin sealant (EVICEL), spray	24	Visual analogue scale score for rest and flexion at day 1 post surgery	Rest: 22; flexion: 45	Rest: range 8.5–58; flexion: range 22–71
	Standard care (saline)	24		Rest: 26; flexion: 44	Rest: range 12–51; flexion: range 29–67
Molloy *et al.*, 2007[147]	Fibrin sealant (Quixil)	50	Pain scores at 6 hours using a 100-mm visual analogue scale, in which 0 represented no pain and 100 the most severe pain	17.6	15.9
	Tranexamic acid	50		19.4	17.9
	Standard care	50		20.03	20.4
Heyse *et al.*, 2014[142]	Fibrin sealant spray	98	Pain (on visual analogue scale) at 6 weeks	4.3	NR
	Standard care	100		3.9	NR
ENT (nose)					
Vaiman *et al.*, 2006[192]	Fibrin sealant (Quixil)	40	Visual analogue scale pain scores at peak for saliva swallow, normal swallow, drinking and dysphagia severity score	Approximately 6.5–7.0	NR
	Standard care (electrocautery)	40		Approximately 6.8–7.6	NR
Prado *et al.*, 2006[187]	Fibrin sealant (Beriplast)	11	Pain (10-cm visual analogue scale)	4	25% quartile: 3; 75% quartile: 4
	Standard care	11		4	25% quartile: 3; 75% quartile: 5
Yu *et al.*, 2014[190]	Fibrin sealant spray	41	Pain during packing; pain on removal of packing	4.2; 4.5	1.4; 1.0
	Standard care (sponge packing)	Within patient[a]		3.1; 8.3	0.9; 1.1

TABLE 21 Pain levels in included RCTs (*continued*)

Study (author, year)	Fibrin sealant and standard care group description	Number of patients	Pain score and variability description	Pain score	Variability around score
Plastic and reconstructive					
Danielsen *et al.*, 2008[209]	Fibrin sealant (Vivolution)	20/19	Pain score on day 5 post surgery	3	Range: 2.0–5.0
	Standard care (gauze and pressure)	20		4	Range: 3.0–5.0
Healy *et al.*, 2013[211]	Fibrin sealant (Tisseel)	20	Mean daily pain score at 14 days post surgery	0.42	95% CI 0.19 to 0.65
	Mefix self-adhesive fabric dressing	20		1.6	95% CI 1.11 to 2.08
Eye					
Rubin *et al.*, 2011[166]	Fibrin sealant	21	Overall mean post-operative pain as recorded on visual analogue scale	5.1	SD 1.26
	Standard care (sutures)	26		4.77	SD 1.21
Uy *et al.*, 2005[168]	Fibrin sealant (Beriplast)	11	Pain on day 1; using a five-point scale adapted from Lim-Bon-Siong *et al.*:[252] 0 = none, no pain; 1 = very mild, presence of pain but easily tolerated; 2 = mild, pain causing some discomfort; 3 = moderate, pain that partially interferes with usual activity or sleep; 4 = severe, pain that completely interferes with usual activity or sleep[b]	≈2.2	NR
	Standard care (sutures)	11		≈3.1	NR
Bahar *et al.*, 2007[169]	Fibrin sealant (Quixil)	42	Mean pain score on day 1 post surgery; grading symptoms and signs on a scale of 0–4[a]	≈37	NR
	Standard care (sutures)	39		≈66	NR
Malik and Kumar, 2010[171]	Fibrin sealant (Tisseel duo-quick)	25	Pain score, based on Wong Baker FACES® Pain Rating Scale[253]	0.44	SD 0.583
	Standard care (sutures)	25		3.32	SD 0.802
Kucukerdonmez *et al.*, 2010[157]	Fibrin sealant	32	Five-point scale assessment of degree of pain[a]	≈2.4	≈1
	Standard care (Vicryl sutures)	38		≈3.6	≈1
Bahar *et al.*, 2006[159]	Fibrin sealant (Quixil)	39	Mean pain score on day 2 post surgery; grading symptoms and signs on a scale of 0–4[a]	≈48	NR
	Standard care (sutures)	26		≈22	NR

continued

TABLE 21 Pain levels in included RCTs (*continued*)

Study (author, year)	Fibrin sealant and standard care group description	Number of patients	Pain score and variability description	Pain score	Variability around score
Karalezli *et al.*, 2008[161]	Fibrin sealant (Tisseel)	25	Pain on day 1 post surgery using a five-point scale, adapted from Lim-Bon-Siong *et al.*[252]: 0 = none, no pain; 1 = very mild, presence of pain but easily tolerated; 2 = mild, pain causing some discomfort; 3 = moderate, pain that partially interferes with usual activity or sleep; 4 = severe, pain that completely interferes with usual activity or sleep[b]	≈2.5	NR
	Standard care (sutures)	25		≈3.1	NR
Ratnalingam *et al.*, 2010[165]	Fibrin sealant	68	Median pain score day 1 post surgery	1	NR
	Standard care (sutures)	69		2	NR
Urology					
Cormio *et al.*, 2012[222]	Fibrin sealant (TachoSil patch)	49	Visual analogue scale pain score at day 1 post operation	4.24	SD 2.32
	Standard care (nephrostomy tube)	47		4.77	SD 2.28

NR, not reported.
a The patient received the intervention and control on different body areas. Therefore, different body parts were randomised to receive either the intervention or control.
b Absolute values not reported.

Assessment of harms

Randomised controlled trials

Ten RCTs in various surgical specialties (liver, two RCTs;[73,77] kidney, two RCTs;[59,221] mixed, one RCT;[241] oral and maxillofacial, one RCT;[231] hernia, one RCT;[176] plastic and reconstructive, one RCT;[208] vascular, one RCT;[204] and orthopaedic, one RCT[143]) reported adverse events that were thought to be related to the use of fibrin sealants (*Table 22*). Sample sizes varied from 7[59] to 316[176] participants. Only Fischer *et al.*[241] reported a death as possibly related to fibrin sealant application in upper GI tract surgery caused by a large bleed, but bleeding did not occur at the target bleeding site and no further information was provided. Other RCTs reported on various non-severe adverse events: mild cellulitis and mild seroma,[231] anaemia,[73] extravasation of urine,[221] incision site complications[204] and mild generalised skin rash.[143] Severity was unclear for the following: excessive pain, scar pain and testicular pain hydrocele in Campanelli *et al.*,[176] post-procedural haemorrhage in Nativ *et al.*[59] and antibodies to hepatitis B in Schwartz *et al.*[77] It was not reported how adverse events were related to the application of fibrin sealant or how severity was determined. The time when adverse events occurred after surgery was immediately in Aguilera *et al.*,[143] 2 hours later in Nativ *et al.*,[59] 1 and 14 days later in Hester *et al.*[231] and 32 days later in Saha *et al.*,[204] but was not reported in Fischer *et al.*,[241] Campanelli *et al.*,[176] Schwartz *et al.*,[77] Frilling *et al.*[73] and Siemer *et al.*[221] Furthermore, another 21 RCTs explicitly reported that there were no complications or adverse events related to fibrin.[14,62,65,67,88,94,124–127,141,142,193–195,206,207,225,227,232,238]

TABLE 22 Fibrin-related adverse events reported in RCTs

Study (author, year)	Sample size	Surgery	Adverse event
Fischer *et al.*, 2013[241]	90/141	Mixed	Of the patients who received fibrin pads, 2.7% (3/11) experienced a related or possibly related AE, compared with 6.7% (2/30) of patients who received absorbable haemostat. These events include operative haemorrhage, ascites and suspected pulmonary embolism. There was no confirmation to rule out relatedness, therefore these AEs were attributed as related to the assigned treatment Seven serious AEs resulted in death: six (5.4%) in the fibrin group and one (3.3%) in the absorbable haemostat group. One of the deaths in the fibrin pad group was considered possibly related to treatment (massive intraluminal GI bleed, although bleeding did not occur at the target bleeding site)
Hester *et al.*, 2013[231]	75	Oral and maxillofacial	*Two of the non-SAE were considered related to treatment: 1 patient had mild cellulitis on the side of the face treated with FS VH S/D 4 s-apr (14 days postoperatively), and 1 patient had mild seroma on postoperative day 1*
Campanelli *et al.*, 2012[176]	316	Hernia	*Adverse events were attributed to study product in three patients in the fibrin sealant group (1.9%: one excessive pain; one scar pain; one testicular pain hydrocele)*
Schwartz *et al.*, 2004[77]	207	Liver	One patient developed antibodies to hepatitis B after being treated with Crosseal. The patient had also received 16 units of allogeneic blood and, in view of the recognised effectiveness against hepatitis B virus of the viral inactivation techniques used in the manufacture of Crosseal, this event was considered unlikely to be related to the fibrin sealant. No further information was available regarding blood donors
Frilling *et al.*, 2005[73]	148	Liver	*Four adverse events were considered to be possibly related to the test treatment. Three of them were considered to be serious: postoperative haemorrhage (TachoSil), abscess and pleural effusion (argon beamer), while one was considered not to be serious: anaemia (TachoSil)*
Siemer *et al.*, 2007[221]	185	Kidney	*Two severe adverse events were related to treatments in the trial. In a subject who received TachoSil extravasation of urine, a non-serious event was reported. One patient who received standard treatment reported subileus, a serious event. The patient was treated successfully with analgesics, laxatives, and diet. Both patients recovered fully*
Nativ *et al.*, 2012[59]	7	Kidney	One case was haemodynamically instable and post-procedural haemorrhage was observed in the drain 2 hours after surgery. This required the patient to be reoperated, and the source of bleeding was the resection area beneath the fibrin pad. The fibrin pad was removed and haemostasis was achieved using a standard surgical technique. A total of 10 units of blood were administered in the post-operative period and the patient was discharged from the hospital without sequelae
Vanscheidt *et al.*, 2007[208]	225	Plastic or reconstructive	One patient was found to have a 'certain' adverse event (application site disorders) related to the study treatment; this was in the Bio Seed-Ss group. Two AEs (general disorders, $n = 1$; skin and appendages, $n = 1$) reported in the BioSeeds treatment group were 'probably' related to treatment. Six AEs (general disorders, $n = 2$; skin and appendages, $n = 2$; secondary terms, $n = 2$) were 'possibly' related
Saha *et al.*, 2011[204]	73	Vascular	One non-serious AE that was considered possibly related to FS was incision site complications. The complication occurred 32 days after application of FS and raised concerns of possible graft occlusion. An angiogram indicated venous stenosis in the area of the anastomosis. The investigator stated that a causal relationship to FS was unlikely but could not be completely ruled out
Aguilera *et al.*, 2013[143]	166	Orthopaedic (joint)	*A 67-year-old man who received Tissucol developed a mild generalized skin rash in the immediate postoperative period. This rash resolved after the administration of an oral antihistamine and topical corticosteroid treatment*

AE, adverse event; FS, fibrin sealant; SAE, serious adverse event; VH S/D 4 s-apr, ARTISS sealant.

Observational studies

Eight included observational studies reported adverse events that appear to be fibrin related (*Table 23*). There were no reports of death or serious adverse events from the observational studies included in the systematic review. Cagatay *et al.*[242] and Choi *et al.*[244] thought that the application of too much fibrin sealant caused discomfort for patients undergoing eye surgery, but this was expected to be solved by surgeons gaining more expertise with fibrin sealant application. Jiang *et al.*[243] reported a slighter higher proportion of patients with graft oedema in eyes treated with fibrin sealant. In upper GI tract surgery statistically significantly more events were seen in patients treated with fibrin sealants (i.e. inflammation,[245]

TABLE 23 Fibrin-related adverse events reported in observational studies

Study (author, year)	Sample size	Surgery	Adverse event
Cagatay *et al.*, 2014[242]	103	Conjunctival autografting for pterygium surgery (eye)	One patient experienced serious discomfort post operatively as a result of excess glue. The excess was removed from the ocular surface using scissors to trim it under slit lamp biomicroscopy The development of Tenon's cyst was not higher in patients in the fibrin group (5/53) than in the control group (3/53) in a statistically significant manner ($p = 0.71$)
Jiang *et al.*, 2008[243]	40	Conjunctival autografting for pterygium surgery (eye)	A yellowish graft edema was observed in some eyes in the first few days post operatively, which resolved gradually and spontaneously. There were more cases of edema in the fibrin sealant group than in the sutures group (8/20 vs. 3/20, respectively). However, the difference between the two groups in graft edema development was not statistically significant ($p = 0.077$)
Choi *et al.*, 2010[244]	126	Pars plana vitrectomy (eye)	*Three patients reported discomfort, possibly caused by the application of too much glue, and two cases showed wound dehiscence, probably caused by too little solution. However, such problems can be overcome with further experience*
Efthimiou *et al.*, 2010[245]	474	Laparoscopic Roux-en-Y gastric bypass (upper GI tract)	Patients had an increased inflammatory response with the application of fibrin sealant, indicated by statistically significant higher temperature, white blood count and heart rate in the fibrin group compared to the two control groups ($p = 0.001$). There was an increased rate of fever (six patients in fibrin group vs. none in the control group) and abdominal collection (two patients in fibrin group vs. none in the control groups)
Ibele *et al.*, 2014[246]	529	Laparoscopic Roux-en-Y gastric bypass (upper GI tract)	The rate of stricture requiring dilation was a significantly increased in the sealant group (11.3%, compared with 4.8% stricture rate in patients who did not receive sealant; $p = 0.04$) Patients in the fibrin sealant group showed a notable stricture delay with strictures occurring an average of 4.1 weeks following surgery without sealant and 9.2 weeks after surgery ($p = 0.3$), suggesting that the mechanism of stricture formation may have differed between the two groups
Nanashima *et al.*, 2012[247]	341	Hepatobiliary pancreas surgery; hepatectomy and pancreatectomy (upper GI tract)	*In the hepatectomy group, uncontrolled ascites were more frequent in the fibrin glue group (145/228) than in the non-fibrin glue group (6/94) ($p < 0.05$)*
Marchac *et al.*, 1994[248]	200	Rhytidectomy (plastic)	*One complication unique to the fibrin glue treated group was the postoperative finding of trapped pockets of air. These had the appearance of small haematomas and yielded 3–5 cc of air on aspiration*
Sakic *et al.*, 2013[249]	418	Bilateral internal thoracic artery grafting (vascular)	*The use of platelet-enriched-fibrin glue (PRF) sealant, however, was associated with more superficial sternal infections (OR: 3.7, 95% CI: 1.3 to 10.5, p = 0.02)*

strictures requiring dilatation[246] and uncontrolled ascites[247]). In Marchac *et al.*[248] trapped pockets of air were only found in the fibrin group and Sakic *et al.*[249] reported more superficial sternal infections in patients treated with fibrin sealant.

Regulatory body reports

Five reports from the MHRA (one report), EMA (one report) and FDA (three reports) websites reported on deaths associated with the use of fibrin sealants, as either case series or single case reports (*Table 24*).

Medicines and Healthcare products Regulatory Agency

The MHRA notes the findings from the EMA, namely the number of life-threatening or fatal air embolisms. A total of six reports of such events have been reported worldwide according to the EMA – EVICEL (five reports), Tisseel (four reports), Quixil (four reports)[254] – although Quixil is no longer available in the UK. In 2013, the MHRA provided updated guidance for the use of sprayable fibrin sealants. Four sprayable fibrin sealants are authorised for use in the UK:[254]

1. EVICEL
2. Tisseel Lyo
3. Tisseel Ready to use
4. Artiss solution for sealant, deep frozen.

TABLE 24 Serious adverse events (deaths) reported by the MHRA, EMA and FDA

Regulatory body	Fibrin sealant name	Date	Subject	Findings	Source
MHRA[254]	EVICEL, Tisseel and Artiss	February 2013	Drug safety update	The MHRA notes the findings from the EMA	www.gov.uk/drug-safety-update/sprayable-fibrin-sealants-evicel-tisseel-and-artiss-updated-guidance (accessed 11 November 2015)
EMA[255]	Artiss, Beriplast P, EVICEL, Tisseel, Tissucol spray applications	15 March 2013	Questions and answers	Risk of air or gas embolism; recommendations for surgeons	www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/referrals/Fibrinogen-containing_solutions_for_sealant_authorised_for_administration_by_spray_application/human_referral_000332.jsp&mid=WC0b01ac05805c516f (accessed 11 November 2015)
FDA[256]	Artiss and Tisseel	5 October 2009	Important drug warning: fatality reported	Risk of life-threatening air or gas embolism with the use of spray devices employing pressure regulator to administer fibrin sealants	www.fda.gov/biologicsbloodvaccines/safetyavailability/ucm209778.htm (accessed 11 November 2015)
FDA[257]	Tisseel	2014	Fatalities reported	Three deaths thought to have occurred as a result of the use of Tisseel fibrin sealant	www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/pediatricadvisorycommittee/ucm386895.doc (accessed 11 November 2015)
FDA[258]	Tisseel	February 2015	Medical device report analysis	An analysis of nine reports of adverse events involving one death	www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/pediatricadvisorycommittee/ucm388149.pdf (accessed 11 November 2015)

European Medicines Agency

In 2012, the EMA completed a review of the safety and effectiveness of four fibrin sealants (Tisseel, Tissucol, Artiss and Beriplast P) used in spray formation.[254] The agency's CHMP considered the evidence for the development of gas embolisms and concluded that the benefits outweigh the risks. The CHMP recommended that the wording on product information be strengthened; the manufacturers of the products should ensure that they are used with pressure regulators that do not exceed the maximum pressure necessary for the delivery of the fibrin sealant; and labelling with the recommended pressure and distance. Furthermore, the EMA report suggests that the product information should include a warning that the risk of gas embolism appears to be higher when sprayed with air than with carbon dioxide (CO_2). The report also recommends patients to be closely monitored for signs of possible gas embolism (heart rate, blood pressure, oxygen and CO_2 levels in blood) during procedures using sprayable fibrin sealants.

Food and Drug Administration

The FDA website contained reports of five fatalities arising from the use of fibrin sealants.

Artiss and Tisseel, 2009[256] The FDA reported:

> *Air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer fibrin sealants. This event appears to be related to the use of the spray device at higher than recommended pressures and in close proximity to the tissue surface. When applying fibrin sealants using a spray device, be sure to use the pressure within the pressure range recommended by the spray device manufacturer. In the absence of a specific recommendation avoid using pressure above 20–25 psi. Do not spray closer than the distance recommended by the spray device manufacturer. In the absence of a specific recommendation avoid spraying closer than 10–15 cm from the surface of the tissue. When spraying the fibrin sealant, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.*

Recommendations for surgeons are similar those previously mentioned for the EMA:

> *Specifically, the safety update includes the following instructions for sealant application using a spray device to help prevent air or gas embolism:*
>
> - *utilize spray pressure that is within the recommended guidelines by the device manufacturer*
> - *ensure that distance between the spray head and the application bed is within the recommended guidelines of the device manufacturer;*
> - *monitor patients for air or gas embolism.*

EVICEL, 2010[257] The FDA reported a fatal air embolism after the use of an EVICEL spray device. EVICEL was being used to arrest a haemorrhage using a spray device (wall unit) at a higher than recommended pressure. Additionally, the spray head was held at a distance from the bleeding area that was closer than the recommended guidelines suggest. The website also advises the use of fibrin sealant spray at pressures of < 20–25 pounds/inch^2.

Tisseel, 2014[258] A safety review for Tiseel/Tissucol by the Centre for Biologics Evaluation and Research of the FDA identified three adult deaths considered likely to be associated with the use of the fibrin sealant. In one case (reference 9283933) from Columbia, a fatal thrombosis and colon necrosis was observed in a male aged 60 years. Tissucol was sprayed after a right hepatectomy. After the operation the patient underwent a repeat laparotomy and a mesenteric thrombosis was found; after a hepatectomy the patient died. Underlying liver disease is a risk factor for development of mesenteric thrombosis. In a second case

(reference 9540751), from Germany (in 1990), a male experienced a fatal air embolism after gastropic sealing for the closure of a fistula. It is reported that:

> *. . . seconds after the Tissucol immune gas flow, the patient lost consciousness and had a cardiac arrest. Autopsy showed the right ventricle filled with air and death was assumed to be due to air embolism.*

The third death associated with Tissucol (case 8815161) was of a male aged 37 years from the UK who suffered a fatal cardiac arrest during revision laminectomy. The device was held closer than the recommended distance to the tissue, with the tip of the applicator being located within the wound.

Furthermore, the FDA Manufacturer and User Safety Device Experience database reports one death of a patient who lost consciousness and experienced a cardiac arrest:

> *Autopsy showed the right ventricle was filled with air, and death was assumed to be due to an air embolism.*

However, the source is reported to be published literature from 1990 and, as the wording is similar to that of case reference 9540751 from the safety review, the researchers of this report consider it highly likely to be a duplicate report.

Chapter 4 Discussion

Statement of principal findings

This review included 186 RCTs to assess the benefits of fibrin sealants during non-emergency surgery in adults. The RCTs, eight observational studies and five reports from regulatory bodies were used to inform a review of harms caused by the use of fibrin sealants. Studies were found in the following 15 surgical specialties: upper GI tract (digestive system), breast and lymph nodes, orthopaedic (joints), eye, hernia, otolaryngology (ENT), vascular, plastic or reconstructive, colorectal (anus), oral (mouth) and maxillofacial, mixed, gynaecological, urology, neurology and cardiothoracic.

Evidence of effectiveness

A series of meta-analyses carried out over different populations and different formulations of fibrin sealant to assess the effectiveness of fibrin sealants on improving various post-operative outcomes shows that the effectiveness of fibrin sealants does not appear to vary according to surgical procedures, as there was virtually no heterogeneity in the meta-analyses of primary and secondary dichotomous outcomes. The results from the fixed-effects analyses are presented below. However, the results of secondary continuous outcomes should be interpreted with caution because of the uncertain quality of included studies and the large amount of statistical heterogeneity identified in the meta-analyses. Where high levels of heterogeneity were identified, the results from the random-effects analyses are reported (i.e. duration of eye surgery, length of hospital stay for breast surgery and duration of post-operative drainage for breast and lungs surgery).

The primary outcomes of this review were seroma and haematoma development. The most frequently reported indication for fibrin sealant use was the prevention of post-operative seroma (37 RCTs) in surgical procedures for breast and axillary/inguinal, hernia, plastic, liver and otolaryngology. A meta-analysis of data from 3472 patients (32 RCTs) did not identify a significant benefit for fibrin sealant over standard procedures (OR 0.84, 95% CI 0.68 to 1.04; $p = 0.13$; $I^2 = 12.7\%$). Development of haematoma was reported by 26 RCTs in breast and axillary/inguinal lymph nodes, hernia, plastic, orthopaedic, upper GI tract, oral and otolaryngology. A meta-analysis of 24 RCTs ($n = 2403$) demonstrated a statistically significant effect for fibrin sealant compared with standard care (OR 0.62, 95% CI 0.44 to 0.86; $p = 0.01$; $I^2 = 0\%$) that was driven by the results for hernia surgery in four RCTs (OR 0.22 95% CI 0.06 to 0.74; $p = 0.01$; $I^2 = 0\%$). Furthermore, there was a trend of haematoma risk reduction in the remaining surgical specialties that was not statistically significant ($p = 0.87$ for breast, $p = 0.20$ for orthopaedic and $p = 0.88$ for upper GI tract). A post hoc analysis was conducted that combined both seroma and haematoma as it was plausible that these events were broadly similar, and in some studies they were combined in a single outcome. This meta-analysis of 48 RCTs to explore the impact of combining seroma and haematoma showed a statistically significant benefit for fibrin sealant use compared with control (OR 0.77, 95% CI 0.64 to 0.92; $p = 0.01$; $I^2 = 6.7\%$).

Secondary dichotomous outcomes included in this review were haemorrhage (bleeding), reoperation, infections, use of analgesics and complications arising from the use of drains. There was no statistically significant difference in the risk of post-operative bleeding between patients receiving fibrin sealants and standard care (18 RCTs, OR 0.64, 95% CI 0.40 to 1.02; $p = 0.08$; $I^2 = 0\%$) and the risk of developing infections (25 RCTs, OR 0.76, 95% CI 0.54 to 1.06; $p = 0.12$; $I^2 = 0\%$). However, there was a statistically significant reduction in risk of haemorrhage when using fibrin sealants within upper GI tract surgery (six RCTs, OR 0.39, 95% CI 0.19 to 0.80; $p = 0.01$). The risk of reoperation was significantly lower among patients receiving fibrin sealants than among control patients (17 RCTs, OR 0.65, 95% CI 0.48 to 0.87; $p = 0.00$; $I^2 = 0\%$). However, a non-statistically significant higher risk of reoperation was found in breast surgery (three RCTs, OR 1.21, 95% CI 0.51 to 2.90; $p = 0.83$; $I^2 = 0\%$) and lung surgery (two RCTs, OR 1.38, 95% CI 0.47 to 4.04; $p = 0.76$). Use of analgesics was reported by only four RCTs. No RCTs reported on complications arising from the use of drains.

Secondary continuous outcomes included duration of operation, length of hospital stay, use of drains, pain levels and health-related quality of life. There was evidence of statistically significant benefit of fibrin sealants compared with standard care in the mean duration of operation for eye surgery in eight RCTs (fixed-effects model: MD –12.13 minutes, 95% CI –12.59 to –11.67 minutes; $p < 0.01$; $I^2 = 99.1\%$; random-effects model: MD –17.19 minutes, 95% CI –23.35 to –12.50 minutes; $p < 0.0001$; $I^2 = 99.1\%$) and hernia surgery in two RCTs (MD –2.56 minutes, 95% CI –3.57 to –1.56 minutes; $p < 0.01$; no I^2). However, in surgery with liver mobilisation, a meta-analysis of two RCTs showed a statistically significant longer duration of operation when fibrin sealants were used (MD 19.07 minutes, 95% CI 2.75 to 35.38 minutes; $p = 0.02$; no I^2). Fibrin sealants were shown to reduce the length of hospital stay for people undergoing upper GI tract surgery involving the pancreas in two RCTs (MD –1.40 days, 95% CI –1.72 to –1.09 days; $p < 0.01$; no I^2), cardiothoracic lung surgery in two RCTs (MD –1.37 days, 95% CI –1.93 to –0.81 days; $p < 0.01$; no I^2) and breast surgery in eight RCTs (fixed-effects model: MD –0.73 days, 95% CI –0.95 to –0.50 days; $p < 0.01$; $I^2 = 88.7\%$; random-effects model: MD –0.87 days, 95% CI –1.75 to 0.01 days; $p = 0.05$). The duration of post-operative drainage for breast and axillary lymph nodes was slightly reduced (12 RCTs, fixed-effects model: MD –0.50 days, 95% CI –0.68 to –0.33 days; $p < 0.01$; $I^2 = 90.6\%$; random-effects model: MD –1.06 days, 95% CI –1.69 to –0.42 days; $p = 0.01$), as well as the duration of drainage for lung surgery (five RCTs, fixed-effects model: MD –0.46 days, 95% CI –0.53 to –0.39 days; $p < 0.01$; $I^2 = 91.0\%$; random-effects model: MD –2.10 days, 95% CI –3.65 to –0.56 days; $p = 0.01$), for fibrin sealants than standard care. These results were not consistent across surgical specialties, with fibrin sealants showing no beneficial effect when compared to standard care in the following surgical specialties: duration of operation in surgery without liver mobilisation (four RCTs; $p = 0.46$), gastric surgery (two RCTs; $p = 0.07$); length of hospital stay in gastric and bowel surgery (two RCTs; $p = 0.82$), joint surgery (four RCTs; $p = 0.871$) and duration of drainage in liver surgery (four RCTs; $p = 0.33$). However, the high level of heterogeneity warrants caution with interpreting the results of these analyses. This might be expected when the likely duration of different operations conducted is being considered (e.g. a longer duration of upper GI tract surgery than eye surgery). Pain levels were reported in 20 RCTs, but the large differences in the various scales used and time points at which assessments took place, as well as lack of variability data, did not permit a meta-analysis. No RCT reported on health-related quality of life.

Overall, 154 studies were assessed as having an 'unclear risk of bias', eight RCTs as having a 'high risk of bias' and 24 RCTs as having a 'low risk of bias'. The risk-of-bias table (see *Table 37*) shows a high level of uncertainty about the validity of data collected across all parameters, especially regarding the blind collection of patient outcomes.

Evidence of harms

This review considered the evidence that fibrin sealants cause serious adverse events from data contained in reports from the RCTs, observational studies and the regulatory bodies (MHRA, EMA and FDA).

Ten RCTs in various surgical specialties (liver, kidney, mixed, oral and maxillofacial, hernia, plastic and reconstructive, vascular, orthopaedic) reported adverse events that were thought to be related to the use of fibrin sealants by primary study investigators or reviewers. Only one RCT reported a death as possibly related to fibrin sealant application in upper GI tract surgery caused by a large bleed, but bleeding did not occur at the target bleeding site and no further information was provided. Other RCTs reported on various non-severe adverse events including mild cellulitis and mild seroma, anaemia, extravasation of urine, incision site complications and mild generalised skin rash. Severity was unclear for excessive pain, scar pain, testicular pain hydrocele and post-procedural haemorrhage antibodies to hepatitis B. It was not reported how adverse events were related to the application of fibrin sealant or how severity was determined. The time at which adverse events occurred after surgery was immediate,[143] 2 hours,[59] 1 and 14 days[231] or 32 days,[204] but not reported in five RCTs.[73,91,95,110,187] Another 22 RCTs explicitly reported that there were no complications or adverse events related to fibrin.

Eight observational studies reported adverse events that appear to be fibrin related by primary study investigators or reviewers, but there were no reports of death or serious adverse events. In eye surgery,

the application of too much fibrin sealant was thought to cause discomfort for patients, but this was expected to be solved by surgeons gaining more expertise with fibrin sealant application. It was reported that the proportion of eyes that developed graft oedema was higher in the fibrin sealant group (8/20) that in the. in the standard care group (3/20). In upper GI tract surgery more of the following events were seen in patients treated with fibrin sealants: inflammation, strictures requiring dilatation and uncontrolled ascites. In plastic or reconstructive surgery trapped pockets of air were only found in the fibrin group. Furthermore, in vascular surgery more superficial sternal infections were found in patients treated with fibrin sealant. The evidence from observational studies did not produce evidence of causality about fibrin sealants resulting in potentially serious adverse events. The validity of the eight observational studies was compromised by a general failure to report whether or not adverse events were assessed independently, whether or not blinding to the assigned allocation was performed and at which time point the adverse event occurred.

Five MHRA, EMA and FDA reports warned about deaths from air emboli as a result of fibrin sealants, in aerosol form, being held too close to tissues and used at higher than recommended pressures.

Strengths and limitations of the assessment

This research reviewed the evidence on the benefits and harms from the use of fibrin sealants compared with standard care for adults undergoing non-emergency surgery. The large number of RCTs allowed analysis of results for the most common and consistently measured outcomes, and the strength of this systematic review is that the findings are based on increased statistical power from these meta-analyses. It was not possible to provide a detailed evaluation of individual RCTs in their respective contexts because of the limited resources that were available for this research. In addition, the number of RCTs that were identified made it impractical to conduct independent data extraction by two reviewers in the time available. Another consequence of the resource constraints imposed by the identification of such a large number of RCTs was our limited ability to perform a thorough evaluation of the source of heterogeneity in meta-analyses where this was identified at high levels of inconsistency. However, the high level of heterogeneity in continuous secondary outcomes was explored by sequentially excluding individual RCTs to identify if the potential cause of the heterogeneity was caused by any individual RCT. This was often found not to be the case as I^2 remained >80% or >90%. Had additional time been available, analyses to assess the impact of different fibrin glues and delivery mechanisms would have been evaluated. However, all RCTs that met the eligibility criteria were included in order to create a repository for future researchers.

A second strength of the review is the inclusion of evidence regarding harms arising from the use of fibrin sealants, a methodologically challenging approach for those engaged in evidence-based research. However, poor reporting of adverse events in RCTs and observational studies limited our ability to provide a comprehensive overview of harms. The review cites only reported outcomes that are likely to be considered important in clinical practice but were not part of the scope of the review; one example is that the data for the use of fibrin sealant to prevent cerebrospinal fluid leakage in neurology RCTs could not be included in meta-analyses. Although individual RCTs are referenced, their findings are not discussed because of the three RCTs evaluating the effect of fibrin sealants for the prevention of cerebrospinal fluid leakage after neurosurgery,[10,236,237] one measured cerebrospinal fluid in ml,[236] one categorised data into minor, moderate or major cerebrospinal fluid leakage and presented absolute numbers[237] and another RCT presented outcome data as the absolute number of patients with watertight closure of the dura.[10] The findings of these RCTs did not converge and the inconsistencies make any interpretation difficult. Furthermore, cost-effectiveness was not assessed and would be a relevant outcome for policy-makers and budget-holders.

As mentioned in *Chapter 3*, *Methods of analysis/synthesis*, there were changes between the protocol and this review. Systematic reviews were not included and, therefore, the quality of systematic reviews was not assessed, as was mentioned in the protocol.[45] Haematoma is an additional post hoc primary outcome

that was not included in the protocol. As the mechanism of haematoma and seroma formation is similar, and is reported in some studies interchangeably, it was deemed important to include haematoma as a primary outcome. In addition, a post hoc analysis of combined seroma and haematoma development was undertaken. Haemorrhage, pain levels and infections were described in the protocol as adverse events – but have been moved to secondary outcomes as these were found to be adverse events of surgery and not related to fibrin sealant (and fibrin sealants are used to reduce these adverse events related to surgery). The duration of operation was used to reflect the outcome 'nurse or doctor time' instead of the previously mentioned 'dressing or fine-needle aspirations'. Sensitivity analyses were planned to be carried out for aspects of the review that might have an impact on the results, for example, including studies in which there is a high risk of bias.[53] However, most studies were assessed as having an unclear risk of bias and, therefore, these analyses were not deemed to be appropriate. Sensitivity analysis using a random-effects model was conducted, but as a result of the large number of RCTs identified in the review it was not possible to perform additional analyses in the time available. Furthermore, overall risk of bias in included RCTs was deemed to be 'unclear', which may reflect poor reporting of primary studies in published papers rather than potentially flawed methods employed.

The overall results for haematoma development show a significant benefit for using fibrin sealants over standard care, and are supported by the trends in all of the subgroup analyses. However, despite the large number of RCTs included in this systematic review, there remains uncertainty with regard to reducing the risk of post-operative seroma for most of the secondary outcomes considered. In some cases the direction of the non-statistically significant trend suggested that fibrin sealants might be harmful; for example, data from the meta-analyses of RCTs showed a non-statistically significant effect in breast and lung surgery suggestive of an increase in the risk of reoperation.

Clinical opinion noted that most patients are now managed within enhanced recovery programmes and may not stay in hospital with drains, as they did previously. Therefore, data on length-of-stay reduction may not reflect current practice (Mr Kurinchi Gurusamy, UCL and Royal Free NHS Trust, 2016, personal communication).

The researchers were unable to obtain information about the use and costs of fibrin sealants to the NHS in England. NHS England replied to our request indicating that it does not hold this information but that individual hospital trusts may be able to provide these data. It was beyond the scope of the current research to perform a survey of NHS trusts to provide results that would be representative for the NHS in England.

Chapter 5 Conclusions

Implications for service provision

Fibrin sealants statistically significantly reduce the risk of development of haematoma when used in non-emergency surgical procedures compared with standard care, but the reduction in risk of post-operative seroma remains unproven.

We found reports[254] stating that the spraying of fibrin sealants caused the formation of air emboli which resulted in perioperative deaths during elective surgical procedures. Surgeons should follow the detailed safely recommendations when using fibrin sealants and they are advised by regulatory bodies that prior to applying fibrin sealants by spray application, a pressure regulator device should be used and the surface area of the wound should be dried. The patient's blood pressure, heart rate, oxygen saturation and end-tidal CO_2 should be closely monitored when spraying fibrin sealants because of the potential to create an air embolism. The use of air in the spray device is considered more dangerous than CO_2, and warnings to this effect are issued by the regulatory bodies.

Recommendations about how and for which procedures certain products should be used are available. EVICEL spray should be used with CO_2 gas (not pressurised air) and in laparoscopic procedures should be used only when the spray distance is at least 4 cm; it is not recommended for use in any other endoscopic procedures.[37] The recommended spray distance for Tisseel is even shorter, at 2 cm from the tissue.[37] Artiss is recommended for use only in open-wound surgery and not during laparoscopic or any other endoscopic procedures,[37] and there is no risk of gas embolism with Beriplast P when used in accordance with the prescribing advice and with the recommended device, although this product is not used in the UK. Surgeons are advised to utilise spray pressure that is within the recommended guidelines by the device manufacturer; to ensure that the distance between the spray head and the application bed is within the recommended guidelines of the device manufacturer; and to monitor patients for air or gas embolism.

Suggested research priorities

The search carried out for this review (May 2015) identified only a small number of RCTs (< 10) that showed statistically significant differences between fibrin and comparators. No evidence of a statistically significant effect of fibrin sealants compared with standard care was found for the outcomes listed for the following surgical indications:

- all surgical specialties (seroma development)
- neurological, gynaecological, oral and maxillofacial, urology, colorectal and orthopaedics knees or hips (for any outcome)
- breast surgery (haematoma development)
- upper GI tract (haematoma development)
- cardiothoracic heart or lung surgery (reoperation rates).

The most appropriate study type to assess outcomes would be a RCT in which outcome assessors and, potentially, patients, but not surgeons, are blind to intervention. In general, RCTs of fibrin sealants in non-emergency surgery are small and involve fewer than 100 people; an a priori sample size that is adequate to ensure that a statistically significant effect can be detected should be used.

The findings of this review are based on data that show inconsistent effects as a result of the large number of small RCTs that evaluated different outcomes, sometimes for the same surgical area. It is necessary that

those who undertake future RCTs capture all important outcomes in the same population of patients. Researchers should plan RCTs that collect data for biological outcomes, such as seroma, haematoma, duration of drainage and more service-related outcomes, such as length of hospital stay and rates of reoperations, in order to reach a balanced view of the benefits and harms arising from fibrin sealants. A variety of units of analysis were used within the same surgical specialties and this limited the number of studies included in each meta-analysis. The work of other researchers should be evaluated using, for example, this review to inform the design of new RCTs and employ units of analysis that are consistent with those used in previous RCTs to enable the conduct of meta-analyses.

Furthermore, adverse events of the use of fibrin sealants were poorly and infrequently reported in both RCTs and observational studies. Only Fischer *et al.*[241] reported a death as possibly related to fibrin sealant application in upper GI tract surgery caused by a large bleed, but bleeding did not occur at the target bleeding site and no further information was provided. Researchers need to test a biologically plausible hypothesis when testing whether or not adverse events are related to the use of fibrin sealants. Both RCTs and observational studies on the use of fibrin sealants in all surgical specialties need to assess harms relevant to the specific surgical area.

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Steven J Edwards (Head of Clinical and Economic Evidence) was the project lead, supervised the production of the final report, advised on the protocol and the analyses carried out, and was guarantor of the report.

Fay Crawford (Senior Health Technology Assessment Analyst) wrote the protocol and carried out searches, screening, assessment of studies for eligibility and data extraction.

Michelle Helena van Velthoven (Health Technology Assessment Analyst) carried out searches, screening, assessment of studies for eligibility, data extraction, preparation of data for analysis and data analysis.

Andrea Berardi (Health Economist Lead) carried out data extraction and preparation of data for analysis.

George Osei-Assibey (Health Technology Assessment Analyst) carried out screening, assessment of studies for eligibility and data extraction.

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Fatima Salih (Health Economist) carried out screening, assessment of studies for eligibility, data extraction and data analysis.

Victoria Wakefield (Senior Health Technology Assessment Analyst) advised on the protocol and created the search strategies.

All authors read and commented on draft versions of the report.

Publications

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Data sharing statement

This is a systematic review and, therefore, the data used for each analysis are present within the report. Further information and requests for access to the data can be obtained from the corresponding author.

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Appendix 1 Literature search strategies

Randomised controlled trial search MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE search strategy

Date searched: 19 May 2015.

Date range searched: inception to 2015.

Search strategy

1. exp Fibrin tissue adhesive/ (3992)
2. Fibrin Foam/ (155)
3. (fibrin adj2 glu$).tw. (3415)
4. (fibrin adj2 seal$).tw. (1546)
5. (fibrin adj2 adhesi$).tw. (676)
6. fibrin spong$.tw. (38)
7. fibrin bandag$.tw. (7)
8. fibrin aerosol$.tw. (1)
9. (biological adj2 glu$).tw. (541)
10. (biological adj2 seal$).tw. (76)
11. Beriplast.tw. (87)
12. Bolheal.tw. (10)
13. Collaseal.tw. (1)
14. Tissucol.tw. (302)
15. Tisseel.tw. (281)
16. Quixil.tw. (36)
17. Biocol.tw. (6)
18. Omrixil.tw. (1)
19. Vivostat.tw. (36)
20. Hemaseel.tw. (10)
21. Crosseal.tw. (8)
22. Tachocomb.tw. (112)
23. Tachosil.tw. (137)
24. Tissel.tw. (5)
25. Transglutine.tw. (4)
26. or/1-25 (6775)
27. Randomized Controlled Trials as Topic/ (96,124)
28. randomized controlled trial/ (387,346)
29. Random Allocation/ (82,288)
30. Double Blind Method/ (128,148)
31. Single Blind Method/ (19,993)
32. clinical trial/ (490,948)
33. clinical trial, phase i.pt. (14,761)
34. clinical trial, phase ii.pt. (23,777)
35. clinical trial, phase iii.pt. (9622)
36. clinical trial, phase iv.pt. (994)
37. controlled clinical trial.pt. (88,856)
38. randomized controlled trial.pt. (387,346)
39. multicenter study.pt. (181,269)
40. clinical trial.pt. (490,948)

41. exp Clinical Trials as topic/ (285,725)
42. or/27-41 (1,059,020)
43. (clinical adj trial$).tw. (229,125)
44. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (133,359)
45. PLACEBOS/ (32,653)
46. placebo$.tw. (164,245)
47. randomly allocated.tw. (18,131)
48. (allocated adj2 random$).tw. (20,780)
49. or/43-48 (440,148)
50. 42 or 49 (1,217,384)
51. case report.tw. (215,419)
52. letter/ (867,687)
53. historical article/ (311,107)
54. or/51-53 (1,382,196)
55. 50 not 54 (1,186,930)
56. 26 and 55 (788)

Observational study search MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE search strategy

Date searched: 19 May 2015.

Date range searched: inception to 2015.

Search strategy

1. exp Fibrin tissue adhesive/ (3992)
2. Fibrin Foam/ (155)
3. (fibrin adj2 glu$).tw. (3415)
4. (fibrin adj2 seal$).tw. (1546)
5. (fibrin adj2 adhesi$).tw. (676)
6. fibrin spong$.tw. (38)
7. fibrin bandag$.tw. (7)
8. fibrin aerosol$.tw. (1)
9. (biological adj2 glu$).tw. (541)
10. (biological adj2 seal$).tw. (76)
11. Beriplast.tw. (87)
12. Bolheal.tw. (10)
13. Collaseal.tw. (1)
14. Tissucol.tw. (302)
15. Tisseel.tw. (281)
16. Quixil.tw. (36)
17. Biocol.tw. (6)
18. Omrixil.tw. (1)
19. Vivostat.tw. (36)
20. Hemaseel.tw. (10)
21. Crosseal.tw. (8)
22. Tachocomb.tw. (112)
23. Tachosil.tw. (137)
24. Tisseel.tw. (5)
25. Transglutine.tw. (4)
26. or/1-25 (6775)

27. adverse effects.mp. (88,922)
28. contraindications.mp. (15,525)
29. Intraoperative Complications/ or Postoperative Complications/ (312,034)
30. ae.fs. (1,395,438)
31. co.fs. (1,642,251)
32. safe.ti,ab. (235,639)
33. safety.ti,ab. (304,730)
34. side effect$.ti,ab. (184,400)
35. treatment emergent.ti,ab. (2294)
36. undesirable effect$.ti,ab. (2173)
37. adrs.ti,ab. (2252)
38. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab. (267,285)
39. or/27-38 (359,9151)
40. 26 and 39 (2592)

Footnote

'ae' denotes the subheading 'adverse effects'.

'co' denotes the subheading 'complications'.

Appendix 2 Tables of study characteristics and data tables

TABLE 25 Randomised controlled trial characteristics: liver surgery

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Liver					
Bektas *et al.*, 2014[65]	70	Aged ≥ 18 years scheduled for elective resection of at least one anatomical liver segment	Tisseel Spray (applied from a distance of 10–15 cm)	Manual compression	Proportion of subjects with intraoperative haemostasis; failure to achieve haemostasis within 4 minutes; intraoperative rebleeding after 4 minutes
de Boer *et al.*, 2012[66]	310	Aged ≥ 18 years who underwent resection of at least one liver segment or a non-anatomical resection	Quixil (Crosseal in the USA)	Conventional technique such as suture, clip or coagulation	Occurrence of a resection surface-related complication; bleeding or evidence of a haematoma in proximity to the resection surface
Chapman *et al.*, 2000[67]	67	Male or non-pregnant female patients scheduled for hemihepatectomy or segmental resection of the liver by tangential excision	CoStasis Surgical Hemostat (Cohesion Technologies Inc., Palo Alto, CA, USA)	Collagen sponge applied with pressure	Primary end point: haemostatic success; secondary end point: time to bleeding
Uetsuji *et al.*, 1994[68]	87	Not reported	'Spray' manufactured by IMMUNOAG (Vienna, Austria)	Liver mobilisation without fibrin sealant	Presence or absence of liver cirrhosis; operative procedure; time required for operation; duration of anaesthesia; amount of bleeding; amount of blood transfused
Liu and Liu, 1993[69]	40	Patients with diagnoses of benign or malignant disease of the liver scheduled for liver resection	Fibrin adhesive	No fibrin adhesive	Operation time; blood loss; post-operative bloody discharge; removal of drain tube; blood transfusion
Noun *et al.*, 1996[70]	82	Patients undergoing elective hepatic resection. Patients with associated biliary reconstruction/GI procedure were excluded	Glue (Biocol; Bio-transfusion, Lille, France)	No fibrin sealant	Fluid drainage; haemoglobin concentration; bilirubin concentration; complications
Figueras *et al.*, 2007[71]	300	Patients undergoing hepatic resection and patients who required contralateral hepatic resection, concomitant bowel resection or bilioenteric anastomosis	5 ml of Tissucol	No fibrin sealant or collagen	Patients with intraoperative transfusion (%); blood transfusion units; post-operative transfusion; hospital mortality; duration of operation (minutes)

continued

TABLE 25 Randomised controlled trial characteristics: liver surgery (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Frilling *et al.*, 2005[73]	121	Patients undergoing elective hepatic resection. All patients gave their written informed consent before any trial-specific procedures	TachoSil	Argon beamer (argon beam coagulator)	Time to haemostasis was the primary outcome measure
Fischer *et al.*, 2011[72]	119	Aged ≥ 18 years, elective liver resection, at least segmental resection of the liver and only minor (oozing) or moderate haemorrhage persisting after primary procedures	TachoSil	Argon beam coagulation	Primary end point: haemostasis; secondary end points: total drainage volume, post-operative duration of drainage, content of haemoglobin and bilirubin in the drainage
Kakaei *et al.*, 2013[74]	45	All patients with resectable liver lesions of any size during this period were included in this study	TachoSil is an absorbable surgical patch	Glubran 2 (GEM SrI, Viareggio, Italy) is a synthetic surgical glue	The primary objective was to compare time to haemostasis between groups. Secondary outcomes were blood loss calculated; amount of blood substitute administered; sponges used; and total amount of blood in the suction
Kohno *et al.*, 1992[75]	62	Not reported	Beriplast solution	Microcrystalline collagen powder from bovine	Primary end point: (efficacy of the fibrin tissue adhesive). The primary efficacy end point was haemostatic efficacy during surgery, post-operative rebleeding, bile leakage and other complications
Moench *et al.*, 2014[76]	128	Patients aged > 18 years scheduled for an elective, open liver resection (segmental or non-segmental)	Patch (Tachosil)	Collagen hemostat Sangustop fleeces (Aesculap AG, Tuttlingen, Germany)	Haemostasis within 3 minutes after application of haemostat; haemostasis after 5 and 10 minutes of application of haemostat; time to haemostasis; blood transfusions
Schwartz *et al.*, 2004[77]	121	Adult patients (aged > 18 years) were candidates for entry if they required liver resection for any reason except trauma and underwent no major surgical intervention beyond the liver	Spray (Crosseal/ Quixil)	Actifoam (Davol Inc., Cranston, RI, USA), Avitene (CR Bard, Murray Hill, NJ, USA), Gelfoam (Pfizer Inc., New York City, NY, USA), Oxycel (Parke-Davis, Detroit, MI, USA), Surgicel and Surgicel Nu-Knit (Johnson & Johnson, Somerville, NJ, USA), and Thrombinar (King Pharmaceuticals, Bristol, TN, USA)	Time to haemostasis; percentage achieving haemostasis within 10 seconds; volume of blood loss; duration of post-operative bilious drainage; occurrence of abdominal fluid collection

TABLE 25 Randomised controlled trial characteristics: liver surgery (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Pancreas					
Carter *et al.*, 2013[81]	109	Not reported	Fibrin glue was injected	The remnant could be stapled or mattress sutured	Post-operative complications; development of a pancreatic fistula; percutaneous drain placement; drain amylase values
Suzuki *et al.*, 1995[82]	56	Patients undergoing distal pancreatectomy	Tisseel, glue (applied over suture)	No application of fibrin glue	Occurrence of post-operative pancreatic fistula
Lillemoe *et al.*, 2004[83]	124	Patients with pancreatic-enteric anastomosis considered to be at high risk for the development of pancreatic leak	Hemaseel (glue)	No such fibrin application	Pancreatic fistula; complications; length of stay; reoperation; death; cost savings
Montorsi *et al.*, 2012[84]	275	Adults aged ≥ 18 years undergoing elective distal pancreatectomy, with or without spleen preservation, for pancreatic disease other than chronic pancreatitis	Absorbable fibrin sealant patch (TachoSil)	Standard suturing or stapling	Primary end point: occurrence of post-operative pancreatic fistula; number of days until drain removal, volume of fluid drained; and length of hospital stay. Adverse events and post-operative complications were also reported
Suc *et al.*, 2003[85]	182	Patients undergoing pancreatic resection	Tissucol	Resection without ductal occlusion	Post-operative abdominal complications; post-operative mortality; reoperation
Martin and Au, 2013[86]	57	Patients undergoing pancreaticoduodenectomy	Tisseel	No application of Tisseel	Drain lipase levels; anastomotic leak; all complications; length of hospital stay; death
Gall bladder					
Fu *et al.*, 2009[78]	60	All patients whose American Society of Anaesthetists physical status was I or II	Fibrin sealant	Laparoscopic cholecystectomy	Post-operative pain. Secondary efficacy parameters: amount of pethidine hydrochloride used per capita
Danielsen *et al.*, 2010[79]	51	Patients aged ≥ 18 years subjected to elective laparoscopic cholecystectomy	Autologous platelet-rich fibrin (Vivostat)	Human albumin	Wound infection
Dimo *et al.*, 1989[80]	80	Patients admitted to the surgical department for elective simple cholecystectomy	Beriplast, spray	No application of Beriplast	Secretion volume and total at day 1 post surgery; number of days until drain removal

continued

TABLE 25 Randomised controlled trial characteristics: liver surgery (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Mixed GI					
Hwang and Chen, 1996[61]	13	Patients with low output (< 20 ml/day) enterocutaneous fistulas that had been present for 2–4 weeks	Fibrin tissue glue, infused	Conservative treatment with total parenteral nutrition	Fistula closure time; time to discharge; recurrence; adverse reactions
Huang *et al.*, 2015[64]	42	Aged 16–70 years with locally advanced gastric cancer confirmed by pathological testing and confined to the abdominal cavity	Cisplatin loaded into a syringe and sprayed	Standard care	Disease-specific overall survival; local and/or systemic infections; abdominal leakage; death as a result of the procedure; biochemical differences over time
Oliver *et al.*, 2012[87]	61	Patients undergoing high-risk anastomosis of the digestive tract with or without GI surgery, intestinal anastomosis	Tissucol Duo	No fibrin adhesive in the suture line	Incidence of anastomotic leakage; incidence of further surgical intervention and mortality
Bulbuller *et al.*, 2013[92]	65	Adult patients aged 18–60 years undergoing classical laparoscopic sleeve gastrectomy	4 ml of Tisseel fibrin sealant	Without suture or with suture	Post-operative complications: bleeding; anastomosis leakage; wound site infection; abscess formation; duration of hospital stay; reoperation
Fernandez Fernandez *et al.*, 1996[63]	86	Patients undergoing total gastrectomy for gastric adenocarcinoma	Tissucol	Curative resection without fibrin glue	Number of fistulas; post-operative complications; length of hospital stay; death
Musella *et al.*, 2014[88]	100	Men and women aged 18–65 years with a BMI ranging from 40 to 55 kg/m^2	Spray (Tisseel)	No fibrin sealant	Occurrence of complications; operative time; length of hospital stay; time to oral diet initiation
Silecchia *et al.*, 2008[62]	320	Aged 21–65 years, morbidly obese (BMI 40–59 kg/m^2), undergoing laparoscopic gastric bypass	Tissucol/Tisseel fibrin sealant	Closure of the mesentery defects and the Petersen space was carried out using stitches	Proportion of complication-free patients; length of hospital stay; occurrence of anastomotic stenosis; weight loss; occurrence of early complications; adverse effects directly related to fibrin sealant
Pilone *et al.*, 2012[89]	30	Candidates for sleeve gastrectomy	Tachosil	Spray (Tachosil)	Operation time; length of hospital stay (time of discharge); complications; change in haemoglobin and red blood cells
Sroka *et al.*, 2015[90]	165	Aged > 18 years and had clear indication for bariatric surgery	EVICEL	Suture	Operating time; change in haemoglobin level; drain amount; patients receiving packed cells; late, infected haematoma

TABLE 25 Randomised controlled trial characteristics: liver surgery (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Fékété *et al.*, 1992[91]	100	Patients undergoing surgery and requiring oesophageal anastomosis	Quick-setting fibrin glue	No application of fibrin glue	Operative mortality rate; fistulas incidence rate and severity; anastomotic stenosis
Huang and Qian, 2014[93]	95	Patients diagnosed with gastric carcinoma by preoperative gastric endoscopy and pathological examination	Fibrin glue	Standard surgery procedure	Operative time; intraoperative blood loss; post-operative drainage volume; complications; wound healing conditions

BMI, body mass index.

TABLE 26 Randomised controlled trial characteristics: mixed orthopaedic surgery

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Antuña *et al.*, 2013[155]	28	Patients with a diagnosis of a massive rotator cuff tear of the posterosuperior rotator cuff (two tendons, > 5 cm) made by clinical examination and magnetic resonance imaging	Platelet-rich fibrin	No additional treatment was applied	Primary end point: shoulder function; secondary end points: self-report scale to evaluate the upper-extremity of disability, pain and degree of satisfaction
Aguilera *et al.*, 2013[143]	172	Adult patients (aged ≥ 18 years) scheduled for elective primary total knee arthroplasty	Tissucol	Tranexamic acid or routine haemostasis	Post-operative drain blood; total blood loss; rate of perioperative blood transfusion; haemoglobin; rate of surgical infections; length of hospital stay; rate of venous thrombosis; mortality
Wang *et al.*, 2003[153]	71	Aged > 18 years with diagnosis of osteoarthritis of the hip, scheduled for primary unilateral total hip replacement	Omrixil, spray	Standard haemostatic techniques	Intraoperative blood loss; blood loss for the post-operative period; volume of blood in the drains
Lassen *et al.*, 2006[141]	69	Patients (aged > 18 years) undergoing elective primary hip arthroplasty surgery in one Danish hospital	Vivostat (spray)	No topical haemostatic treatment	Intraoperative blood loss; drain volume; auto-transfusion; hospitalisation times; oozing; haematoma
Levy *et al.*, 1999[14]	46	Patients who had osteoarthritis of the knee scheduled to have unilateral total knee arthroplasty with cement (cruciate-sparing implants)	Octacol F15 (Quixil); spray	No fibrin adhesive	Reduction in blood loss; reduction in haemoglobin levels; reduction in blood transfusion; development of haematoma; functional recovery; range of motion
Skovgaard *et al.*, 2013[150]	24	Adults aged > 18 years with symptomatic and radiographic bilateral knee osteoarthritis	EVICEL, spray	Saline as placebo	Blood loss; pain; range of movement; swelling; readmission within 90 days from the operation

continued

TABLE 26 Randomised controlled trial characteristics: mixed orthopaedic surgery (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Falez *et al.*, 2013[154]	57	Aged between 45 and 75 years; pre-operative haemoglobin levels equal to 11 g/dl and fibrinogen levels within normal range	Fibrin spray	Standard care: electrocautery to seal the vessels	Blood loss (ml) at 6, 24, 48 and 72 hours; measured using autologous blood transfusion device (Bellovac™, Astra Tech Ltd, Gloucestershire, UK)
Kluba *et al.*, 2012[145]	24	Patients diagnosed with primary osteoarthritis of the knee and scheduled for primary bicondylar knee arthroplasty with cement	Quixil (topical spraying)	Standardised general anaesthesia and fluid regiment control	Post-operative fluid loss; maximum flexion; length of stay; complications
McConnell *et al.*, 2011[156]	66	Patients were eligible if they were scheduled to undergo elective primary unilateral cemented hip arthroplasty	Fibrin spray	Tranexamic acid	Median intraoperative blood loss
Molloy *et al.*, 2007[147]	100	Pre-operative haemoglobin level ≤ 13.0 g/dl prior to total knee replacement	Quixil spray	Tranexamic acid intravenously	Post-operative pain scores; total blood loss; post-operative haemoglobin level; length of hospital stay; complications
Sabatini *et al.*, 2012[148]	70	Patients treated for osteoarthritis of the knee with total knee cement-less arthroplasty	Quixil	Blood recovery device	Blood loss; haemoglobin decrease; surgical time; transfusions; complications
Randelli *et al.*, 2014[149]	114	Patients with a diagnosis of osteoarthritis of the knee scheduled for primary total knee arthroplasty	EVICEL	Electrocautery after the release of the tourniquet	Total blood loss; time to drain removal; changes in haemoglobin levels; mean haemoglobin level and haemoglobin loss; drained blood loss; length of hospital stay
Wang *et al.*, 2001[144]	53	Patients with osteoarthritis and a baseline haemoglobin level of ≤ 110 g/l and evidence of a bleeding or metabolic-based haemolytic disorder were excluded from the study	Spray	No placebo was used in the control group	Amount of post-operative drainage in 12 hours; haemoglobin level on the first post-operative day; transfusion requirements; adverse events; hematoma; seroconversion
Choufani *et al.*, 2015[151]	60	Patients undergoing elective total knee replacement	EVICEL, spray	No fibrin sealant	Post-operative blood transfusion, difference in haemoglobin levels between pre and post operation; total blood loss at third post-operative day; adverse events
Heyse *et al.*, 2014[142]	198	Patients aged > 18 years who were able and willing to give informed consent	Spray applicator	Standard care – no fibrin sealant	Drain output 24 hours after surgery; transfusions; haemoglobin levels; haematocrit levels; range of motion; pain scores

TABLE 26 Randomised controlled trial characteristics: mixed orthopaedic surgery (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Mawatari *et al.*, 2006[152]	100	Total hip arthroplasty patients	Autologous fibrin tissue adhesive, spray	No application of fibrin sealant	Intra- and post-operative blood loss; complications such as infection, deep-vein thrombosis, pulmonary embolism

TABLE 27 Randomised controlled trial characteristics: vascular surgery

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Bajardi *et al.*, 2009[194]	20	Patients with intact infrarenal abdominal aortic aneurysm	TachoSil haemostatic surgical patch	Compression	Primary outcome: time to achieve haemostasis; secondary outcomes: blood loss, duration of the operation, drain volume, requirement for blood transfusion
Schenk *et al.*, 2003[195]	38	Patients who were undergoing PTFE graft placement for dialysis access	Glue (Bioplasma)	Cellulose (surgical)	Time to haemostasis; occurrence of haemostasis; time of application plus time to haemostasis; duration of graft implant procedure
Jackson *et al.*, 1999[193]	47	Patients undergoing elective carotid endarterectomy with expanded PTFE patch closure	Human fibrin sealant, applied as a liquid	Thrombin-soaked gelatine sponge	Haemostasis within 15 minutes; amount of blood loss; time to haemostasis
Milne *et al.*, 1995[201]	16	Patients undergoing a carotid endocardectomy	Spray	Nothing was applied to the suture line	Operative blood loss; time to achieve haemostasis; total operative time; drop in haemoglobin level; post-operative cerebrovascular accident
Milne *et al.*, 1996[203]	39	Patients undergoing either arterial bypass surgery with a PTFE bypass graft or aortic aneurysm repair with a woven Dacron graft	Injection (applied using a syringe)	Nothing was applied to the suture line	Time to achieve haemostasis; operation time; intraoperative blood loss; proportion achieving haemostasis; post-operative virology/ infection
Saha *et al.*, 2012[197]	140	Patients scheduled for arterio-arterial bypasses with expanded PTFE grafts. Patients with moderate or severe anastomotic suture-hole bleeding that could not be controlled with additional suturing	A soluble mixture that transforms to form a matrix	Continuous manual compression with surgical gauze pads	Proportion of patients who achieved haemostasis at the study suture line of the graft; incidence of intraoperative rebleeding; incidence of post-operative rebleeding

continued

TABLE 27 Randomised controlled trial characteristics: vascular surgery (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Joseph *et al.*, 2004[200]	24	Patients undergoing femoral anastomosis and femoral or carotid patch angioplasty with PTFE grafts	TachoComb, moistened patches	Compression with 10 × 10 cm^2 surgical swabs	Time to haemostasis; blood loss during the operation; duration of operation; drain volume; requirement for blood transfusion; surgeons rating of efficacy; coagulation parameters
Sintler *et al.*, 2005[202]	20	Primary procedure, normal clotting profile and on aspirin (75 mg) for at least 2 weeks prior to surgery	Quixil	Kaltostat	Time to achieve haemostasis; blood loss; adverse events
Taylor *et al.*, 2003[199]	128	Male or non-pregnant, non-lactating females, aged > 18 years, scheduled for elective extruded PTFE grafting	Beriplast P gel	Thrombin-soaked gelatin sponge	Haemostasis at 4 minutes post randomisation; volume of blood loss at the anastomosis; incidence of repeat bleeding; duration of intensive care unit stay; length of hospital stay; mortality
Chalmers *et al.*, 2010[198]	70	Aged ≥ 18 years, scheduled for vascular procedure using uncoated or heparin-coated PTFE prosthetic graft material with at least one end-to-side anastomosis to a femoral or upper-extremity artery	EVICEL	Manual compression	Primary end point: absence of bleeding at the anastomosis at 4 minutes after randomisation; secondary end point: absence of bleeding at the anastomosis
Czerny *et al.*, 2000[205]	60	Vascular reconstruction surgery with PTFE prosthesis, aged ≥ 18 years	TachoComb H patch	Surgical compresses only to control suture hole bleedings	Time to haemostasis; intraoperative blood loss; intraoperative blood substitutes; duration of the operation
Saha *et al.*, 2011[204]	73	Patients undergoing PTFE graft placement surgery, including arterio-arterial bypasses and arteriovenous dialysis access shunts	Fibrin sealant (Tisseel)	Manual compression	Proportion of patients achieving haemostasis; incidence of intraoperative rebleeding after achievement of haemostasis; incidence of post-operative rebleeding that required surgical exploration; transfusion requirements
Schenk *et al.*, 2002[196]	28	Aged ≥ 18 years who required placement of a PTFE graft with arterial and venous anastomoses using non-filament non-absorbable suture to obtain an arteriovenous fistula for renal dialysis access	Hemaseel	Commercial topical bovine thrombin (thrombogen), oxidised cellulose (Surgicel)	Time to haemostasis

PTFE, poly(1,1,2,2-tetrafluoroethylene).

TABLE 28 Randomised controlled trial characteristics: breast

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Berger *et al.*, 2001[107]	61	Primary breast cancer, no previous breast surgery or neo-adjuvant chemotherapy or prior locoregional radiotherapy	TachoComb	Standard closure (not described)	Duration of axillary drainage; length of post-operative hospital stay; drainage volume; presence of local infection; use of antibiotics; use of local wound treatments; seroma formation at discharge
Udén *et al.*, 1993[98]	68	Women undergoing modified radical mastectomy with axillary clearance for breast cancer	Tisseel	Control group had no glue applied	Seroma formation; wound infection; necrosis of skin flaps
Benevento *et al.*, 2014[109]	60	Female sex, aged ≥ 25 years, absences of anticoagulopathy, and/or liver disease, BMI ≤ 35 kg/m^2, indication to axillary lymph node dissection	Artiss	All patients received a percutaneous vacuum drain	Volume of serous fluid; time to remove drain (days); length of post-operative hospital stay (hours); seroma; number of patients with lymphoedema
Jain *et al.*, 2004[99]	116	Patients presenting with newly diagnosed carcinoma of the breast who required primary excision and axillary lymphadenectomy	Tisseel spray	Suction drain, and no drain and no fibrin	Frequency and volume of seroma; post-operative length of hospital stay; post-operative pain and wound infection; bleeding complication
Johnson *et al.*, 2005[100]	82	Females aged ≥ 18 years scheduled for elective breast procedure	Hemaseel	Placement of one or two Jackson–Pratt drains in their wound and/or axilla	Incidence of seroma formation and volume; blood loss; length of hospital stay; complications; interval to seroma resolution; number of post-operative visits
Llewellyn-Bennett *et al.*, 2012[101]	101	Women with newly diagnosed invasive or non-invasive breast cancer who required mastectomy and axillary staging	Tisseel	Standard closure of the back skin wound	Total seroma volume; total back seroma volumes aspirated after drain removal over 3 months; volume of donor-site seromas; number of seroma aspirations after drain removal; post-operative complications
Nielsen *et al.*, 1985[123]	38	NR	2 ml of Tisseel vs. 4 ml of Tisseel	Standard/control group not defined	Wound secretion
Ko *et al.*, 2009[102]	95	Newly diagnosed breast cancer, female sex, scheduled for elective breast lumpectomy and axillary dissection	Greenplast kit (Green Cross Corp., Seoul, Korea) (spray)	Control group (non-fibrin glue)	Duration of drainage; overall drain output; incidence of seroma formation; wound-related complications

continued

TABLE 28 Randomised controlled trial characteristics: breast (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Di Monta *et al.*, 2012[117]	70	Candidates for surgical treatment of metastatic melanoma stage III by axillary or ilioinguinal radical lymph node dissection	Tachosil	Standard treatment alone	Post-operative duration of drainage; incidence of drainage removal; daily drainage volume
Miri Bonjar *et al.*, 2012[103]	60	Female aged > 18 years scheduled for elective breast procedure, had platelet counts ≥ 100,000/ml, no diabetes or advanced liver disease, not severely obese, not had axillary lymph surgery	Hemaseel	Conventional drain placement (Jackson–Pratt drain)	Estimated blood loss; length of hospital stay; post-operative day drain removal; complications; incidence of seroma; interval to seroma resolution; seroma aspirate volume; number of post-operative visits
Moore *et al.*, 2001[111]	80	Patients who were about to undergo axillary node dissection with either a lumpectomy or a modified radical mastectomy procedure	4, 8 or 16 ml of fibrin	Use of no therapeutic agent	Time of wound drainage; volume of drainage after treatment; adverse events; serological presence of hepatitis A, B or C virus
Mortenson *et al.*, 2008[120]	30	Patients scheduled to undergo a superficial inguinofemoral lymph node dissection	Tisseel	One or two closed suction drains are inserted	Time to drain removal (days); estimated blood loss; operative time (minutes); complications
Mustonen *et al.*, 2004[104]	40	Patients undergoing modified radical mastectomy (including axillary evacuation) for breast cancer	Tisseel	Non-fibrin sealant group	Axillary drain volume and time; breast drain volume and time; length of hospital stay; seroma incidence; number of aspirations
Segura-Castillo *et al.*, 2005[105]	45	Women diagnosed with breast cancer who underwent modified radical mastectomy	Quixil	Standard mastectomy using electrocauterisation and sutures	Time to drain removal; volume of lymphatic fluid days 1–6 post surgery; seroma formation
Vaxman *et al.*, 1995[112]	20	Patients with breast cancer requiring axillary lymph node dissection with lumpectomy or a modified radical mastectomy	Tisseel	Standard mastectomy technique (cutaneous suture)	Total drainage fluid volume and duration of axillary drainage fluid; mastectomy drainage fluid and duration; hospital stays; complications
Zhibo and Miaobo, 2009[95]	30	Women undergoing surgical breast augmentation procedures	Fibrin glue only	Fibrin glue and lidocaine, or lidocaine only	Self-reported pain
Swan *et al.*, 2011[113]	74	Patients aged ≥ 18 years or who required elective lymph node dissection	Tisseel	No fibrin sealant	Total volume of wound drainage before drain removal; duration of drainage; seroma formation; total number of aspirations and volume; wound cellulitis; locoregional recurrence; survival

TABLE 28 Randomised controlled trial characteristics: breast (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Ulusoy *et al.*, 2003[96]	54	Patients who underwent modified radical mastectomy because of breast cancer	Fibrin glue	Siliconised suction drain	Drainage volumes; drain removal times; seroma formation frequency; seroma formation volume
Cipolla *et al.*, 2010[110]	160	Diagnosis of N1 breast carcinoma, and aged ≥ 18 years	Fibrin sealant	Placement of a Jackson–Pratt suction drain only	Post-operative day of drainage removal; total volume of drained serum; total volume of evacuated seroma; number of seroma aspirations needed
Dinsmore *et al.*, 2000[97]	27	Women diagnosed with breast cancer who had selected radical mastectomy for treatment	Fibrin glue	Standard closure of wound	Drain output
Gilly *et al.*, 1994[115]	40	Patients undergoing inguinal or axillary lymphadenectomy	Tissucol	Same surgical procedure without the application of fibrin glue	Drainage volume; number of drainage days; number of hospitalisation days; occurrence of parietal suppuration; occurrence of post-operative seroma; post-operative comfort of the patient; skin state 1 month after the operation
Gilly *et al.*, 1998[108]	108	Patients scheduled for axillary lymphadenectomy for breast cancer, with no previous irradiation or chemotherapy	Tissucol	Same intervention without application of fibrin glue	Daily and cumulative drainage volume over the first 6 post-operative days; time to hospital discharge
Moore *et al.*, 1997[106]	21	Women who elected modified radical mastectomy for carcinoma, with level I and II axillary node dissections for an infiltrating ductal or lobular breast carcinoma	Autologous fibrin sealant	No fibrin sealant	Cumulative drainage; number of days to the first drainage reading of ≤ 40 ml (length of time the patient needed to retain a wound drain)

BMI, body mass index; NR, not reported.

TABLE 29 Randomised controlled trial characteristics: hernia surgery

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Lau, 2005[172]	93	People aged ≥ 18 years with bilateral inguinal hernia	Tisseel	Endoscopic stapler	Post-operative pain; analgesic requirement; incidence of seroma; operative time; length of hospital stay; number of days required to resume normal activities; recurrence rate; pain
Boldo, 2008[173]	27	Patients with bilateral hernia	Autologous fibrin sealant, Vivostat	Staples	Post-operative seroma; post-operative haematoma; hernia recurrence
Bracale *et al.*, 2014[174]	102	Adult aged ≥ 18 years primary uncomplicated inguinal hernia	Quixil	Conventional Lichtenstein technique	Operative time; inguinal pain recurrence; numbness
Cambal *et al.*, 2012[175]	100	Patients with unilateral inguinal hernia	Fibrin glue	Self-gripping mesh	Operative time; local complications; recurrence; ease of product use
Campanelli *et al.*, 2012[176]	315	Men aged 18–60 years	Tissucol/Tisseel drops and spray	Lichtenstein technique	Prevalence of moderate to severe pain or numbness and groin discomfort
Canonico *et al.*, 1999[177]	50	Patients with coagulation disorders	Tissucol	Lichtenstein technique	Haemorrhagic complications
Eriksen *et al.*, 2011[260]	40	Patients with umbilical hernia defects aged 18–85 years	Tisseel	Tack fixation	Acute post-operative pain
Lionetti *et al.*, 2012[179]	148	Aged > 18 years, male and with groin hernia	Quixil	Lichtenstein technique	Post-operative pain score; recurrences; proportion of patients with chronic pain
Lovisetto *et al.*, 2007[180]	197	Aged > 18 years with a diagnosis of inguinal or femoral hernia	Tissucol/Tisseel	Endopath multifeed stapler	Post-operative neuralgia
Chan *et al.*, 2014[178]	130	Male patients aged 18–70 years	Tisseel spray	Staples	Incidence of chronic pain
Tolver *et al.*, 2013[181]	112	Mean aged 18–80 years with unilateral inguinal or femoral hernia	Tisseel spray	Protacks fixation devices	Pain, discomfort, fatigue, nausea or vomiting; seroma formation; haematoma formation; hernia recurrence
Wong *et al.*, 2011[182]	56	Primary inguinal hernia, aged > 20 years	Glue (Tissucol, Tisseel)	Sutures	Post-operative pain; seroma or haematoma formation; infection; mortality
Damiano *et al.*, 2014[184]	468	Patients with primary unilateral inguinal hernia	Tisscol fibrin glue	Sutures	Operating time; intra- and post-operative complications
Olmi *et al.*, 2007[259]	600	Patients undergoing laparoscopic hernia repair	Tissucol/Tisseel	Endopath multifeed stapler	Operating time; time to return to work; rates of conversion; morbidity; mortality; recurrence

TABLE 30 Randomised controlled trial characteristics: lymph node surgery

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Carlson *et al.*, 2008[94]	137	Female patients with a vulvar malignancy undergoing a radical vulvectomy or hemivulvectomy	Tisseel, spray	No fibrin sealant	Incidence of grade 2 and 3; incidence of wound complications; infections; number of days of drainage; discontinuation; incidence of wound separation
Furrer *et al.*, 1993[116]	30	Patients undergoing inguinal or axillary radical lymph node dissection. Lymphadenectomy-relapsed interventions, however, were excluded	Tissucol spray	Radical lymph node dissection	Drainage volume and time; lymphocele volume; hospitalisation; wound healing (clinical follow-up)
Siim *et al.*, 1994[114]	30	Patients with malignant melanoma lymph node metastases	Fibrin adhesive glue	Standard lymphadenectomy	Daily amount of wound secretion; total amount of wound secretion; number of days with drains; duration of hospital stay; post-operative, complications (i.e. hematomas, seromas, infections and flap necrosis)
Neuss *et al.*, 2009[118]	58	Patients with malignant melanoma with stage III or IV disease with lymph node metastases of the groin	Tissomat spray	Low-molecular-weight heparin	Amount and quality of the drained fluids were recorded every 24 hours; duration of drain placement
Simonato *et al.*, 2009[119]	60	The only exclusion criterion was any evidence of coagulation disorders and such cases were, in fact, excluded from study	TachoSil patch	Standard technique only	Development of symptomatic or asymptomatic lymphoceles; drainage volume and duration; all complications; need for further surgical intervention
Tachibana *et al.*, 2003[122]	43	Patients with primary carcinoma of the thoracic oesophagus undergoing one-stage transthoracic oesophagectomy	Bohleal (Kaketsuken Pharmaceuticals, Kumamoto, Japan), spray	Same surgical procedure without the application of the fibrin sealant	Reduction in the interval until the thoracic drain can be removed; incidence of post-operative complications and viral infectious diseases
Scholz *et al.*, 2002[121]	93	Patients with gynaecological malignancies undergoing surgery including pelvic or pelvic and para-aortic lymphadenectomy	Tissucol spray	Sutures	Incidence of lymphocysts; incidence of lymphoedema; incidence of deep-vein thrombosis; time to diagnosis of lymphocysts; time to regression of lymphocysts; time to diagnosis of lymphoedema; time to thrombosis

TABLE 31 Randomised controlled trial characteristics: mixed surgery

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Nose					
Prado *et al.*, 2006[187]	22	Patients undergoing primary open rhinoplasty	Fibrin sealant glue (Beriplast)	No fibrin sealant glue	Post-operative pain; oedema; ecchymosis; skin adherence; average operating time; patient satisfaction
Pryor *et al.*, 2008[186]	10	Patients undergoing rhinoplasty involving lateral osteotomy	EVICEL	Gentle manual compression	Swelling, bruising and pain
Vaiman *et al.*, 2002[188]	204	Patients undergoing septoplasty	Fibrin aerosol glue (Quixil)	Merocel foam packing (Medtronic Inc., Minneapolis, MN, USA)	Number of post-operative bleeds
Vaiman *et al.*, 2005[189]	64	Patients with excessive intraoperative or immediate bleeding	Aerosol spray (Quixil/Crosseal)	Nasal packing	Bleeding
Yu *et al.*, 2014[190]	82	Patients aged > 18 years undergoing bilateral functional endoscopic sinus surgery	Fibrin sealant aerosol spray	Polyvinyl acetyl sponge packing	Severity of symptoms
Tonsils					
Vaiman *et al.*, 2005[191]	513	Patients undergoing endonasal surgeries	Fibrin glue (Quixil)	Merocel nasal packing	Unclear
Vaiman *et al.*, 2006[192]	102	Patients undergoing tonsillectomy	Spray (Quixil)	Electrocautery	Pain; dysphagia
Skin					
Drake and Wong, 2003[207]	46	Patients requiring harvest of a split thickness skin graft	Spray pen	Thrombin solution and manual pressure	Time to haemostasis; differences of rates; safety of Vivostat sealant
Vanscheidt *et al.*, 2007[208]	215	Patients aged 18–90 years with a history of leg ulceration of at least 3 months	Bioseed	Compression bandage	Time to complete healing; number of patients achieving healing
Danielson *et al.*, 2008[209]	40	Patients aged > 18 years and scheduled for surgical debridement of ulcer	Autologous platelet-rich fibrin	Epithelial resurfacing; pain scores	Venous insufficiency
Erba *et al.*, 2010[210]	10	Patients with paraplegia and decubitus ulcers stage IV (Daniel's classification)	Fibrin glue	No fibrin glue	Drainage volume; time of drain removal
Healy *et al.*, 2013[211]	50	Patients aged > 18 years undergoing split skin grafting from a lateral thigh donor site	Fibrin sealant (spray)	Self adhesive fabric dressing (Mefix)	Pain; incapacity
Colorectal					
Ellis and Clark, 2006[216]	58	Patients with trans-sphincteric anal fistulas	Tisseel	Sutures	Fistula recurrence
Altomare *et al.*, 2011[217]	101	Patients with trans-sphincteric anal fistulas	Tissucol	No fibrin sealant	Healing rate; hospital stay; healing time; faecal incontinence

TABLE 31 Randomised controlled trial characteristics: mixed surgery (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Lindsey *et al.*, 2002[218]	42	Patients aged ≥ 18 years with cryptoglandular or Crohn's anal fistulas	Beriplast	Current standard fistula practice	Pain score; time to return to work; satisfaction
Hammond *et al.*, 2011[219]	29	Patients with anal fistulas	Tisseel glue	Permacol, collagen sheet	Wound healing time; return to work; patient satisfaction; continence disturbance; recurrence; proportion of symptoms
van der Hagen *et al.*, 2011[220]	30	Patients with perianal fistulas	Fibrin glue	No fibrin	Treatment failure; recurrent fistulas; soiling after treatment; quality of life; incontinence score
Prostate					
Luke *et al.*, 1986[223]	30	Patients undergoing transurethral prostatectomy	Beriplast fibrin glue	No fibrin glue	Blood loss; urine volume; concentration of haemoglobin
Schultz and Christiansen, 1985[224]	16	Patients with obstruction caused by a ureteral stone	Tisseel adhesive	Interrupted sutures	Median drainage of urine postoperatively
Facelift					
Marchac and Greensmith, 2005[226]	29	Patients undergoing rhytidectomy	Tisseel aerosol spray	No fibrin glue	Post-operative drainage; haematoma; degree of ecchymosis; degree of oedema
Lee *et al.*, 2009[227]	9	Patients undergoing rhytidectomy	Crosseal	No Crosseal treatment	Seroma formation; ecchymosis score
Oliver *et al.*, 2001[228]	40	Rhytidectomy procedures	Beriplast fibrin spray	No fibrin glue	Median drainage; post-operative haematoma
Thyroid					
Uweria *et al.*, 2005[225]	56	Patients with anterior neck dissection in conjunction with thyroid surgery	Tisseel	No Tisseel treatment	Drainage from surgical site; wound drainage; drain removal
Carter *et al.*, 2003[229]	49	Patients undergoing dental extractions who were therapeutically anticoagulated for comorbidities	Autologous fibrin glue	Tranexamic acid solution	Pain; discomfort haematoma; oedema
Maharaj *et al.*, 2006[230]	60	Patients aged > 18 years planned to receive superficial or total parotidectomy	Tisseel fibrin glue	Sutures	Wound drainage; duration of percutaneous drainage; length of hospital stay; frequency of complications
Hester *et al.*, 2013[231]	75	Healthy patients aged 18–75 years undergoing full rhytidectomy	Artiss sealant	No fibrin glue	Total drainage volume; incidence of adverse events

continued

TABLE 31 Randomised controlled trial characteristics: mixed surgery (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Mixed					
Bochicchio *et al.*, 2015[239]	721	Patients undergoing spinal vascular, hepatic and soft tissue procedures	Fibrocaps (Raplixa, The Medicines Company, Leiden, the Netherlands)	No fibrin glue	Gelatin sponge
Fischer *et al.*, 2013[241]	90	Patients aged > 18 years requiring non-emergency surgical procedures	Fibrin pad	Surgical original absorbable hemostat	Haemostasis
Verhoef *et al.*, 2015[240]	126	Patients with mild or moderate bleeding during a surgical procedure	Fibrocaps	Gelatin sponge	Haemostasis
Hanks *et al.*, 2003[238]	73	Patients aged 18–75 years undergoing elective surgery	Spray pen	Dry surgical sponge	Time to haemostasis; success of treatment
Oliver *et al.*, 2002[215]	50	Patients undergoing mixed surgical procedures	Beriplast	No fibrin sealant	Average drainage
Gynaecology (uterus)					
Diamond *et al.*, 2011[232]	34	Patients with bilaterally documented ovarian disease scheduled for laparoscopy	Adhexil (Johnson & Johnson, Somerville, NJ, USA) sprayed or dipped	No fibrin sealant	Incidence of adhesions; serious adverse events
Maggiore *et al.*, 2011[233]	70	Patients with intraurine uterine fibroma	Tachosil fibrin-coated sponge	No haemostatic agent used	Surgery duration; intraoperative blood loss; post-operative drainage; length of hospital stay
Takeuchi *et al.*, 2005[234]	83	Women with symptomatic uterine myomas	Beriplast spray	No application of fibrin sealant	Occurrence of post-operative adhesions
Safan *et al.*, 2009[235]	40	Patients with vesicovaginal fistulas	Autologous fibrin preparation	No fibrin preparation	Fistula size and location; fibrosis; dryness
Neurosurgery					
Nakamura *et al.*, 2005[236]	39	Patients with spinal cord tumours	Beripast-P autologous fibrin sealant	No fibrin sealant	Volume of drainage; coagulation; mean post-operative cerebrospinal fluid leakage
Hutter *et al.*, 2014[237]	229	Patients scheduled for elective cranial surgery, aged > 18 years	Collagen sponge coated with a dry layer of fibrinogen and thrombin	Standard care	Incidence of cerebrospinal fluid leakage; incidence of meningitis
Green *et al.*, 2015[10]	139	Patients undergoing elective craniotomy in the supraentorial region or the processes in the posterior fossa, aged > 18 years	EVICEL	Closure with sutures	Watertight closure of the dura

TABLE 32 Randomised controlled trial characteristics: cardiothoracic surgery

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Heart					
Kjaergard and Trumbull, 1998[138]	24	Aged 18–80 years with coronary artery disease demonstrated by arteriogram and suitable candidate for coronary artery bypass grafting	Vivostat	Traditional methods of haemostasis alone (sutures, clips and electrocautery)	Survival (death); atrial fibrillation; anaemia; pleural effusion; pneumothoraxes; post-operative transfusions; chest tube drainage; reoperations
Kjaergard and Trumbull, 2000[139]	30	Aged > 18 years admitted for elective cardiac operation requiring median sternotomy	Vivostat	No application of fibrin sealant	Time to haemostasis
Maisano *et al.*, 2009[140]	119	Aged ≥ 18 years with planned elective heart surgery, ascending aorta or arch requiring a cardiopulmonary bypass procedure	TachoSil	Standard haemostatic fleece material	Haemostasis; duration of surgery; need for intraoperative transfusions; duration of drainage; post-operative drainage volume; incidence of reoperation; post-operative transfusion and other post-operative complications
Shiono *et al.*, 1998[261]	32	Adult patients undergoing elective cardiac surgery	Fibrin glue	Cryoprecipitate from patients' own fresh-frozen plasma	Post-operative haemoglobin concentration; platelet levels; cardiac index; rate of homologous transfusion; homologous transfusion volume
Tavilla *et al.*, 2015[60]	1445	Patients undergoing elective isolated coronary artery bypass graft (either on pump or off pump)	CryoSeal	No CryoSeal treatment	Number of transfused blood products; duration of stay in intensive care unit; amount of blood loss within 48 hours post surgery; reoperations; 30-day mortality; duration of hospital stay
Lung					
Fabian *et al.*, 2003[128]	100	Patients undergoing planned open anatomic pulmonary resection or wedge resection	HemaMyst system (Haemacure Corp., Sarasota, FL, USA)	Stapling techniques	Mean duration of AAL; mean time to chest tube removal; incidence of prolonged AAL; mean first 24-hour drainage; percentage of patients discharged with valve; mean post-operative length of stay
Droghetti *et al.*, 2008[124]	40	Early stage non-small-cell lung cancer patients scheduled for elective pulmonary lobectomy	TachoSil	Routine surgical procedure with staplers	Intraoperative alveolar air leaks; percentage of patients free of air leaks throughout hospitalisation; last post-operative day when an air leak was observed; costs of procedure and hospitalisation

continued

TABLE 32 Randomised controlled trial characteristics: cardiothoracic surgery (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Lang *et al.*, 2004[134]	186	Lung cancer patients undergoing elective standard lobectomy with or without mediastinal lymphadenectomy	TachoComb	Single or continuous running sutures	Incidence of air leakage 48 hours after lobectomy; post-operative mortality and morbidity pattern was recorded in all patients
Anegg *et al.*, 2007[125]	152	Patients undergoing lobectomy or segmentectomy for non-small-cell lung cancer	TachoSil	Standard treatment	Post-operative mean air leakage (volume in ml/min); efficacy outcome; incidence of post-operative air leakage; rate of complications
Belboul *et al.*, 2004[133]	40	Adult patients with lung tumour limited to one lobe, undergoing elective lobectomy	Vivostat system	Patients assigned to the control group underwent no additional interventions (after randomisation)	Time to chest tube removal; volume at removal of chest tube; duration of thoracic epidural analgesia treatment; post-operative length of hospital stay; post-operative haemorrhage; post-operative leucocyte counts; adverse events
Belcher *et al.*, 2010[131]	113	Patients undergoing elective open thoracic procedures likely to result in a post-operative air leak	Vivostat	Reducing AAL after pulmonary resection	Duration of air leak; time to drain removal; length of hospital stay; post-operative complications
Lopez *et al.*, 2013[129]	346	Aged ≥ 18 years; patients undergoing pulmonary resection (anatomical segmental resection for lung cancer)	TachoSil	Manual suturing	Intraoperative air leakage; duration of post-operative air leakage: time to removal of last chest drain; duration of surgery; volume of drained pleural effusion; hospital length; adverse events; post-operative complications
Filosso *et al.*, 2013[136]	24	Aged ≥ 18 years who had previously undergone pulmonary resection for a thoracic malignancy	TachoSil	Stapling/suturing	Duration of air leaks; time to first and second chest tube removal; possible post-operative complications; duration of hospital stay
Gonfiotti *et al.*, 2011[130]	185	Aged 18–75 years; lung resection; primitive/ secondary neoplastic pulmonary pathology	Fibrin sealant used is obtained from human plasma	The standard treatment	Mean duration of AAL from the wound closure; mean duration of drainage; percentage of patients without AALs for the entire hospitalisation time; duration of post-operative hospitalisation
Moser *et al.*, 2008[126]	25	Patients with severe airflow obstruction	Vivostat	No additional treatment	Incidence and intensity of air leaks
Mouritzen *et al.*, 1993[132]	114	Patients undergoing pulmonary resections	Spray (Beriplast P)	Suture alone	Airway tolerance pressure; rate of post-operative air leakages; duration of post-operative air leakages; length of hospital stay

TABLE 32 Randomised controlled trial characteristics: cardiothoracic surgery (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Rena *et al.*, 2009[127]	60	Patients requiring a lobotomy	Fibrin patch	Suture	Intraoperative air leak
Czerny *et al.*, 2004[137]	40	Patients with clinical stage I	TachoComb	Conventional surgical haemostasis	Cumulative chest drain volume; duration of test tubes
Marta *et al.*, 2010[135]	299	Patients aged ≥ 18 years with lung cancer	TachoSil	Resuturing, stapling or no treatment	Number of patches used; success of lung inflation; need for rescue treatment; air leakage; atrial fibrillation; deaths

AAL, alveolar air leak.

TABLE 33 Randomised controlled trial characteristics: eye surgery

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Kucukerdonmez *et al.*, 2010[157]	70	Patients with primary nasal pterygium who underwent pterygium excision	Tisseel (two-component fibrin glue)	8–0 Vicryl sutures (8–10 sutures)	Procedure outcome (photographic images, graded); post-operative symptoms; operative time; recurrence
Yüksel *et al.*, 2010[158]	61	Patients with primary nasal pterygium	Beriplast P/Combi-set Aventis 1 ml	Silk (Surgisilk, Sutures Ltd, Wrexham, UK)	Complications; haemorrhage under graft; conjunctival cyst; granuloma; recurrence; surgery time; mean surgery cost; objective signs; hyperaemia
Bahar *et al.*, 2006[159]	65	Patients undergoing primary pterygium removal	Quixil	Interrupted 8–0 Vicryl sutures	Best corrected visual acuity; intraocular pressure; pain; photophobia; foreign body sensation; irritation; epiphora; local hyperaemia; conjunctival chemosis; dry-eye sensation; operative time; recurrence
Hall *et al.*, 2009[160]	50	Patients with primary nasal pterygia booked for surgery with conjunctival autograft	Tisseel (glue)	Standard sutured interrupted (Vicryl)	Surgical time; patient discomfort; recurrence; complications; post-operative pain
Karalezli *et al.*, 2008[161]	50	Patients with primary nasal pterygium	Tisseel (glue)	Vicryl 8–10 sutures	Operation time; recurrence; intensity of post-operative complaints (pain, irritation, foreign body, epiphora)
Koranyi *et al.*, 2005[162]	43	Patients with nasal primary pterygium and if informed consent was obtained	Tisseel (glue/spray)	Absorbable sutures	Post-operative pain; surgical times; recurrences

continued

TABLE 33 Randomised controlled trial characteristics: eye surgery (*continued*)

Study (author, year)	Sample size (*n*)	Population (inclusion criteria)	Intervention	Comparator	Outcomes
Sati *et al.*, 2014[163]	60	Eyes with ocular pterygia of grade 1, 2 and 3, and at least 2-mm extension from the limbus	Spray (Tisseel)	Vicryl suture group: I, 8/0 Vicryl	Rate of recurrence; surgical time; post-operative discomfort
Sharma *et al.*, 2003[164]	40	Patients (eyes) treated for corneal perforation	Glue	Cyanoacrylate tissue adhesive	Anterior chamber depth; inflammatory reaction; glue adherence
Ratnalingam *et al.*, 2010[165]	113	Patients with pterygium	Adhesive	Vicryl 8/0	Duration of surgery; recurrence rate; pain scores; complications (displaced graft, conjunctival cysts)
Rubin *et al.*, 2011[166]	47	Aged 18–70 years, patients diagnosed with primary medial located pterygium	Quixil	Mononylon 10–0 (Ethicon) suture	Efficacy of the fibrin tissue adhesive; mean surgery time; ocular discomfort measured with the visual analogue scale; ocular hyperaemia was also measured
Srinivasan *et al.*, 2009[167]	40	Patients with primary pterygium	Tisseel, dripped on the graft	Polygactin sutures	Grading of Adobe Photoshop-edited eye pictures (version 7.0, Adobe Systems Inc., San Jose, CA, USA) on the degree of graft inflammation, subconjunctival haemorrhage and stability
Uy *et al.*, 2005[168]	22	Patients with primary pterygia undergoing primary pterygium excision at the Philippine General Hospital, Manila	Fibrin glue	Nylon sutures	Graft success; recurrence; subjective sensations of pain; foreign body sensation; tearing; discomfort
Bahar *et al.*, 2007[169]	81	Patients undergoing primary pterygium removal	Quixil	For excessive bleeding, one drop of adrenaline 10% solution or small amounts of sodium hyaluronate 10 mg/ml	Mean operative time (minutes); intraocular pressure; post-operative signs and symptoms (mean score); overall patient satisfaction (mean score); complications (incidence); recurrence (number of eyes)
Mellin and Kondler, 1989[170]	100	Aged > 70 years, without other eye diseases such as cataract, or maculopathy	Fibrin glue	2 8/0 silk sutures from the limbus, nasally	Foreign body sensation; wound closure
Malik and Kumar, 2010[171]	50	Patients with recurrent pterygium	Tisseel Duo Quick	Three interrupted 8–0 Vicryl sutures	Pterygium recurrence; surgical time; post-operative discomfort

Appendix 3 Tables of excluded randomised controlled trials

TABLE 34 Excluded randomised controlled trials

Study excluded	Reason for exclusion
Agresta F, Tordin C. Laparoscopic transabdominal inguinal hernia repair: a randomized study of fibrin sealant versus absorbable tack to fix the mesh. *Surg Endosc* 2015;**29**:S35	Abstract/full text unavailable
Ak G, Alpkılıç Başkırt E, Kürklü E, Koray M, Tanyeri H, Zülfikar B. The evaluation of fibrin sealants and tissue adhesives in oral surgery among patients with bleeding disorders. *Turk J Haematol* 2012;**29**:40–7	Did not meet population/ intervention criteria
Albala DM, Wood C, Fischer C, Hart J, Batiller J, Shen J. A randomized trial of aprotinin free fibrin sealant versus absorbable hemostat. *J Endourol* 2011;**25**:A95	Abstract/full text unavailable
Albillos A, Calleja JL. Randomised trial of fibrin glue versus polidocanol for bleeding peptic ulcer. *Lancet* 1997;**350**:1397–8	Not a RCT
Al-Fayez M. *Fibrin Glue vs. Suture Fixation of Limbal Conjunctival Autograft for Pterygium*. American Academy of Ophthalmology; 2008. URL: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/968/CN-00745968/frame.html (accessed 19 May 2015)	Abstract/full text unavailable
Alió JL, Mulet E, Sakla HF, Gobbi F. Efficacy of synthetic and biological bioadhesives in scleral tunnel phacoemulsification in eyes with high myopia. *J Cataract Refract Surg* 1998;**24**:983–8	Outcomes not of interest
Anghelacopoulos SE, Tagarakis GI, Pilpilidis I, Kartsounis C, Chryssafis G. Albumin-glutaraldehyde bioadhesive ('Bioglue') for prevention of postoperative complications after stapled hemorrhoidopexy: a randomized controlled trial. *Wien Klin Wochenschr* 2006;**118**:469–72	Did not meet population/ intervention criteria
Anon. *TISSEEL Fibrin Sealant*. 2013. URL: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/847/CN-00862847/frame.html (accessed July 2013)	Not a RCT
Arslani N, Patrlj L, Kopljar M, Rajkovic Z, Altarac S, Papes D, *et al.* Advantages of new materials in fascia transversalis reinforcement for inguinal hernia repair. *Hernia* 2010;**14**:617–21	Not a RCT
Ayala M. Results of pterygium surgery using a biologic adhesive. *Cornea* 2008;**27**:663–7	Not a RCT
Babicki A, Dobosz M. Second-look endoscopy with repeated injection of thrombin with adrenaline vs fibrin glue in bleeding peptic ulcer. *Br J Surg* 1988;**85**(Suppl. 2):113	Abstract/full text unavailable
Babicki A, Dobosz M, Marczewski R, Wajda Z. [Evaluation of using fibrin tissue adhesive (Beriplast) and preparations of thrombin and adrenalin in injection hemostasis methods for gastric and duodenal ulcer hemorrhage. Randomized, prospective clinical trial.] *Wiad Lek* 1997;**50**(Suppl. 1):383–7	Did not meet population/ intervention criteria
Bailey SH, Oni G, Guevara R, Wong C, Saint-Cyr M. Latissimus dorsi donor-site morbidity: the combination of quilting and fibrin sealant reduce length of drain placement and seroma rate. *Ann Plast Surg* 2012;**68**:555–8	Not a RCT
Ben-Rafael Z, Ashkenazi J, Shelef M, Farhi J, Voliovitch I, Feldberg D, *et al.* The use of fibrin sealant in in vitro fertilization and embryo transfer. *Int J Fertil Menopausal Stud* 1995;**40**:303–6	Did not meet population/ intervention criteria
Benyamini OG, Barkana Y, Hartstein M, Attas L, Avni I, Zadok D. Biological glue in pterygium surgery with a rotational flap or sliding flaps. *Cornea* 2008;**27**:911–15	Did not meet population/ intervention criteria
Beppu T, Iwatsuki M, Okabe H, Okabe K, Masuda T, Hayashi H, *et al.* A new approach to percutaneous transhepatic portal embolization using ethanolamine oleate iopamidol. *J Gastroenterol* 2010;**45**:211–17	Not a RCT
Berg P, Born P, Barina W, Simon W, Zellmer R, Paul F. [Fibrin glue versus Polidocanol by upper gastrointestinal bleeding.] *Gastroenterol* 1990;**28**:467	Abstract/full text unavailable

continued

TABLE 34 Excluded randomised controlled trials (*continued*)

Study excluded	Reason for exclusion
Berg PL, Barina W, Born P. Endoscopic injection of fibrin glue versus polidocanol in peptic ulcer hemorrhage: a pilot study. *Endoscopy* 1994;**26**:528–30	Did not meet population/ intervention criteria
Bernardo L, Bernardo WM, Shu EB, Roz LM, Almeida CC, Monaco BA, *et al.* Does the use of DuraSeal in head and spinal surgeries reduce the risk of cerebrospinal fluid leaks and complications when compared to conventional methods of dura mater closure? *Rev Assoc Med Bras* 2012;**58**:402–3	Review
Bernasek TL, Burris RB, Fujii H, Levering MF, Polikandriotis JA, Patterson JJ. Effect on blood loss and cost-effectiveness of pain cocktails, platelet-rich plasma, or fibrin sealant after total knee arthroplasty. *J Arthroplasty* 2012;**27**:1448–51	Not a RCT
Biedner B, Rosenthal G. Conjunctival closure in strabismus surgery: Vicryl versus fibrin glue. *Ophthalmic Surg Lasers* 1996;**27**:967	Not a RCT
Blinder D, Manor Y, Martinowitz U, Taicher S, Hashomer T. Dental extractions in patients maintained on continued oral anticoagulant: comparison of local hemostatic modalities. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999;**88**:137–40	Not a RCT
Bochicchio G, Singla N, Gupta NY, Porter R, Renkens KL, Pattyn P, *et al.* An international, multicenter, randomized, single-blind, controlled trial of a dry-powder, fibrin sealant for mild to moderate perioperative surgical bleeding. *J Am Coll Surg* 2014;**219**(Suppl. 1):e13–14	Abstract/full text unavailable
Boereboom C, Watson NFS, Liptrot SA, Lund JN, Tierney GM. A randomised trial of fibrin glue versus surgery for pilonidal disease: results and long term follow up. *Colorectal Dis* 2010;**12**:20	Abstract/full text unavailable
Buciarelli P, Ginelli G, Misani M, Moia M. Fibrin glue plus tranexamic acid mouthwashing in patients on oral anticoagulants undergoing dental extractions: a randomised study. *Thrombosis Haemostasis* 1997;(Suppl.):37	Abstract/full text unavailable
Calabrò B, Ponsetto M, Greco R, Peradotto F, Personnettaz E, Obialero M. [Treatment of leg ulcers with fibrin glue.] *Minerva Chir* 1995;**50**:569–74	Not a RCT
Caldas Neto S, Oliveira RL, Caldas N. Use of in fibrin glue in the prevention of postoperative bleeding and hematomas after septoplasty. *Revista Brasileira de Otorrinolaringologia* 2002;**68**:635–8	Did not meet population/ intervention criteria
Calvet X, Vergara M, Brullet E, Gisbert JP, Campo R. Addition of a second endoscopic treatment following epinephrine injection improves outcome in high-risk bleeding ulcers. *Gastroenterology* 2004;**126**:441–50	Review
Campanelli G, Champault G, Pascual MH, Hoeferlin A, Kingsnorth A, Rosenberg J, *et al.* Randomized, controlled, blinded trial of Tissucol/Tisseel for mesh fixation in patients undergoing Lichtenstein technique for primary inguinal hernia repair: rationale and study design of the TIMELI trial. *Hernia* 2008;**12**:159–65	Not a RCT
Canonico S. The use of human fibrin glue in the surgical operations. *Acta Bio-Medica* 2003;**74**(Suppl. 2):21–5	Not a RCT
Cardillo G, Lococo A, De Massimi AR, D'Agostino A, Carleo F, Larocca V, *et al.* Adverse effects of fibrin sealants in thoracic surgery. The safety of a new fibrin sealant: multicentre, controlled, prospective, parallel group randomised clinical trial. *Interact Cardiovasc Thorac Surg* 2011;**13**:S56	Did not meet population/ intervention criteria
Carter TI, Fong ZV, Hyslop T, Lavu H, Tan WP, Hardacre J, *et al.* A dual-institution randomized controlled trial of remnant closure after distal pancreatectomy: Does the addition of falciform patch and fibrin glue improve outcomes? *Gastroenterology* 2012;**142**(Suppl. 1):1042–3	Abstract/full text unavailable
Cedin AC, Atallah ÁN, Andriolo RB, Cruz OL, Pignatari SN. Surgery for congenital choanal atresia. *Cochrane Database Syst Rev* 2012;**2**:CD008993	Review
Cesana G, Olmi S, Croce E. Trans-abdominal pre-peritoneal laparoscopic inguinal hernia repair versus classical inguinotomic repair: a randomized study. *Surg Endosc* 2011;**25:**S7	Abstract/full text unavailable
Chan MS, Melissa CS, Teoh AY, Bun TA, Chan KW, Wing CK, *et al.* Randomized double-blinded prospective trial of fibrin sealant spray versus mechanical stapling in laparoscopic total extraperitoneal hernioplasty. *Ann Surg* 2014;**259**:432–7	Letter/commentary/erratum

TABLE 34 Excluded randomised controlled trials (*continued*)

Study excluded	Reason for exclusion
Chang YR, Jang JY, Kwon W, Kang MJ, Choi DW, Choi SH, *et al.* Interim analysis of prospective randomized controlled study comparing clinical early outcome including pancreatic fistula between external and internal pancreatic drainage in pancreaticoduodenectomy. *HPB* 2014;**16**:112	Abstract/full text unavailable
Charles JF, Barra JA, Leroy JP. [Mesenteric fold by biological glue. Experimental study and clinical application (author's translation).] *Ann Chir* 1976;**30**:651–5	Not a RCT
Chiu CC. Randomized clinical trial of techniques for closure of the pancreatic remnant following distal pancreatectomy (*Br J Surg* 2009;**96**:602–7). *Br J Surg* 2009;**96**:1222	Review
Chou D, Cheng J, Chesnut R, Choudhri H, Gopinath S, Scott Graham R, *et al.* A prospective, multi-center, randomized controlled study to compare a low swell formulation of a PEG hydrogel spinal sealant as an adjunct to sutured dural repair with common dural sealing methods. *Spine J* 2010;**10**(Suppl. 1):80	Did not meet population/ intervention criteria
Chu FCK, Yao P, Morris DL. A randomized controlled study of the efficacy of fibrin glue in reducing fluid collections following liver surgery. *ANZ J Surg* 2008;**78**:A71	Abstract/full text unavailable
Codispoti M, Mankad PS. Significant merits of a fibrin sealant in the presence of coagulopathy following paediatric cardiac surgery: randomised controlled trial. *Eur J Cardiothorac Surg* 2002;**22**:200–5	Did not meet population/ intervention criteria
Conboy P, Brown DH. Use of tissue sealant for day surgery parotidectomy. *J Otolaryngol Head Neck Surg* 2008;**37**:208–11	Not a RCT
Copuroğlu C, Ercan S, Ozcan M, Ciftdemir M, Turan FN, Yalniz E. Comparison of autogenous bone graft donor site haemostatic agents used in spinal surgery. *Acta Orthop Traumatol Turc* 2011;**45**:359–64	Did not meet population/ intervention criteria
Cormio L, Perrone A, Pentimone S, Selvaggio O, Lorusso F, Di Fino G, *et al.* Tachosil-sealed tubeless percutaneous nephrolithotomy in supine antero-lateral position: a prospective study. *Eur Urol Suppl* 2010;**9**:35	Abstract/full text unavailable
Corral M, Ferko N, Hollmann S, Jamous N, Batiller J, Shen JX, *et al.* Clinician reported ease of use for a novel fibrin sealant patch for hemostasis: results from three randomized controlled trials. *J Thromb Haemost* 2014;**12**:31–2	Abstract/full text unavailable
Cruz-Korchin N, Korchin L. The use of fibrin sealant (Tisseel) in abdominoplasty. *Plastic Reconstruct Surg* 2005;**116**(Suppl. 3):23–5	Abstract/full text unavailable
Czerny *et al.* 2004[137]	Did not meet population/ intervention criteria
D'Andrea AA, Costantino V, Sperti C, Pedrazzoli S. Human fibrin sealant in pancreatic surgery: it is useful in preventing fistulas? A prospective randomized study. *Ital J Gastroenterol* 1994;**26**:283–6	Did not meet population/ intervention criteria
De Boer MT, Porte RJ. Reply: Re: Fibrin sealant for prevention of resection surface-related complications after liver resection: a randomized controlled trial. *Ann Surg* 2015;**261**:e78	Letter/commentary/erratum
Di Saverio S, Masetti M, Zanello M, De Blasiis MG, Jovine E. Re: Fibrin sealant for prevention of resection surface-related complications after liver resection: a randomized controlled trial. *Ann Surg* 2015;**261**:e77–8	Letter/commentary/erratum
Dobrilla G, Rutgeerts P, Rauws EAJ, Wara P, Hoos A, Dobrilla G, *et al.* Fibrin sealant (Beriplast) vs polidocanol 1% in the endoscopic treatment of bleeding gastroduodenal ulcers: final results of a phase III clinical trial on adjuvant intraportal infusion with heparin and 5 fluorouracil (5 FU) in resectable colon cancer (EORTC GITCCG 1983 1987). European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. *Eur J Cancer* 1997;**33**:1209–15	Letter/commentary/erratum
Dovellini EV, Taddeucci E, Trapani M, Valenti R, Moschi G, Cerisano G, *et al.* Pocket haematoma prevention in patients who required implantation/replacement of a pacemaker or implantable cardiac defibrillator. The PHP Study. *Eur Heart J* 2011;**32**:305	Abstract/full text unavailable
Draus JM, Huss SA, Harty NJ, Cheadle WG, Larson GM. Enterocutaneous fistula: are treatments improving? *Surgery* 2006;**140**:570–6	Not a RCT

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TABLE 34 Excluded randomised controlled trials (*continued*)

Study excluded	Reason for exclusion
Ebbehoj J, Gavrilyuk BK, Menzul VA, Paklin EL, Rochev YuA. Controlled trial of Biocol versus Jelonet on donor sites. *Burns* 1996;**22**:557–9	Did not meet population/ intervention criteria
Eimiller A, Berg P, Born P, Barina W, Paul F, Homann J. [Fibrin glue as a sclerotherapeutic agent.] *Gastroenterol* 1988;**26**:458	Abstract/full text unavailable
El Nakeeb A. Influence of fibrin glue on seroma formation after modified radical mastectomy: a prospective randomized study. *Breast J* 2009;**15**:671–2	Letter/commentary/erratum
Eriksen JR. Pain and convalescence following laparoscopic ventral hernia repair. *Danish Med Bulletin* 2011;**58**:B4369	Pre-results for Eriksen *et al.*[183]
Everts PA, Devilee RJ, Brown Mahoney C, Eeftinck-Schattenkerk M, Box HA, Knape JT, *et al.* Platelet gel and fibrin sealant reduce allogeneic blood transfusions in total knee arthroplasty. *Acta Anaesthesiol Scand* 2006;**50**:593–9	Not a RCT
Foster K, Greenhalgh D, Gamelli RL, Mozingo D, Gibran N, Neumeister M, *et al.* Efficacy and safety of a fibrin sealant for adherence of autologous skin grafts to burn wounds: results of a phase 3 clinical study. *J Burn Care Res* 2008;**29**:293–303	Did not meet population/ intervention criteria
Fullarton G, Galloway D. Randomised trial of fibrin glue versus polidocanol for bleeding peptic ulcer. *Lancet* 1997;**350**:1397–8	Letter/commentary/erratum
Fuller CW, Gillespie MB, Nguyen SA, Jones T, Hornig JD. A double-blind, randomized, placebo-controlled clinical trial evaluating fibrin sealant in thyroidectomy closure. *Otolaryngol Head Neck Surg* 2014;**151**(Suppl. 1):P160–1	Abstract/full text unavailable
Garcia-Olmo D, Herreros M, Guadalajara H, DeLaQuintana P, Trebol J, Georgiev-Hristov T, *et al.* Expanded adipose derived autologous stem cells for the treatment of complex cryptoglandular fistulas. A phase III clinical trial (fatt1: Fistulaadvanced therapy trial 1) and longterm evaluation (LTE). *Dis Colon Rectum* 2011;**54**:e68–e9	Abstract/full text unavailable
Genyk Y, Kato T, Pomposelli JJ, Lophaven KW, Chapman WC. Tachosil versus surgicel original for the secondary treatment of local bleeding in adult patients undergoing hepatic resection. *HPB* 2014;**16**:27	Abstract/full text unavailable
Gibran N, Luterman A, Herndon D, Lozano D, Greenhalgh DG, Grubbs L, *et al.* Comparison of fibrin sealant and staples for attaching split-thickness autologous sheet grafts in patients with deep partial- or full-thickness burn wounds: a phase 1/2 clinical study. *J Burn Care Res* 2007;**28**:401–8	Did not meet population/ intervention criteria
Gilly FN, Sayag-Beaujard AC, Francois Y. Efficacy of fibrin glue (Tisseel) in axillary lymph node removal for breast cancer: prospective randomized trial. *Eur J Surg Oncol* 1996;**22**:397–8	Abstract/full text unavailable
Gioffrè Florio MA, Mezzasalma F, Manganaro T, Pakravanan H, Cogliandolo A. [The use of fibrin glue in the surgery of breast carcinoma.] *G Chir* 1993;**14**:239–41	Unobtainable
Giovannacci L, Eugster T, Stierli P, Hess P, Gürke L. Does fibrin glue reduce complications after femoral artery surgery? A randomised trial. *Eur J Vasc Endovasc Surg* 2002;**24**:196–201	Did not meet population/ intervention criteria
Gipponi M, Reboa G, Testa T, Giannini G, Strada P. Tension-free primary closure with autologous platelet gel versus Vivostat™ for the definitive treatment of chronic sacrococcygeal pilonidal disease. *In Vivo* 2010;**24**:583–9	Did not meet population/ intervention criteria
Giusti G, Maugeri O, Piccinelli A, Graziotti P. Is sealing of percutaneous tract with hemostatic sealant really necessary after tubeless procedure? *Eur Urol Suppl* 2009;**8**:263	Abstract/full text unavailable
Glickman M, Gheissari A, Money S, Martin J, Ballard JL. A polymeric sealant inhibits anastomotic suture hole bleeding more rapidly than gelfoam/thrombin: results of a randomized controlled trial. *Arch Surg* 2002;**137**:326–31	Did not meet population/ intervention criteria
González HD, Figueras Felip J. [Topical hemostatic devices in surgery: between science and marketing.] *Cir Esp* 2009;**85**(Suppl. 1):23–8	Review
Gopal SC, Gangopadhyay AN, Mohan TV, Upadhyaya VD, Pandey A, Upadhyaya A, *et al.* Use of fibrin glue in preventing urethrocutaneous fistula after hypospadias repair. *J Pediatr Surg* 2008;**43**:1869–72	Did not meet population/ intervention criteria

TABLE 34 Excluded randomised controlled trials (*continued*)

Study excluded	Reason for exclusion
Greenhalgh DG, Gamelli RL, Lee M, Delavari M, Lynch JB, Hansbrough JF, *et al.* Multicenter trial to evaluate the safety and potential efficacy of pooled human fibrin sealant for the treatment of burn wounds. *J Trauma* 1999;**46**:433–40	Did not meet population/ intervention criteria
Grimaud JC, Munoz-Bongrand N, Siproudhis L, Abramowitz L, Sénéjoux A, Vitton V, *et al.* Fibrin glue is effective healing perianal fistulas in patients with Crohn's disease. *Gastroenterology* 2010;**138**:2275–81	Did not meet population/ intervention criteria
Grimm C, Polterauer S, Helmy S, Cibula D, Zikan M, Reinthaller A, *et al.* A collagen-fibrin patch (Tachosil) for the prevention of symptomatic lymphoceles after pelvic lymphadenectomy in women with gynecologic malignancies: a randomized clinical trial. *BMC Cancer* 2014;**14**:1–7	Not a RCT
Grossman JA, Capraro PA, Atagi T. A prospective, randomized, double-blind trial of the use of fibrin sealant for face lifts. *Plast Reconstr Surg* 2002;**110**:1371–2	Letter/commentary/erratum
Grund KE, Salm R, Fischer H, Becker HD. Endoscopic therapy of heavy ulcerous bleeding: obvious advantages of fibrin glue against polidocanol in a controlled randomised study. *Endoskopie Heute* 1993;**6**:46	Abstract/full text unavailable
Gugenheim J, Bredt LC, Iannelli A. A randomized controlled trial comparing fibrin glue and PlasmaJet on the raw surface of the liver after hepatic resection. *Hepatogastroenterology* 2011;**58**:922–5	Did not meet population/ intervention criteria
Günay H. [Transplantation of allogeneic freeze-preserved bone spongiosa into periodontal bone defects: clinical results.] *Schweiz Monatsschr Zahnmed* 1988;**98**:611–18	Did not meet population/ intervention criteria
Gust R, Kleine P, Fabel H. [Fibrin glue and tetracycline pleurodesis in recurrent malignant pleural effusions. A randomized comparative study.] *Med Klin* 1990;**85**:18–23	Unobtainable
Hammond TM, Grahn MF, Lunniss PJ. Fibrin glue in the management of anal fistulae. *Colorectal Dis* 2004;**6**:308–19	Review
Hayes Inc. *IntéguSeal Microbial Sealant (Kimberly-Clark Worldwide Inc.) for Prevention of Surgical Site Infection (Structured Abstract)*. 2009. URL: www.hayesinc.com/hayes/crd/?crd=10164 (accessed 19 May 2015)	Abstract/full text unavailable
Hayes Inc. *Tisseel VH (Baxter Healthcare Corp.) for Cardiac Surgery (Structured Abstract)*. 2008. URL: www.hayesinc.com/hayes/crd/?crd=7985 (accessed 19 May 2015)	Abstract/full text unavailable
Hayes Inc. *Tisseel VH (Baxter Healthcare Corp.) for Noncardiac Surgeries with Problematic Hemostasis (Structured Abstract)*. 2008. URL: www.hayesinc.com/hayes/crd/?crd=7986 (accessed 19/05/15)	Abstract/full text unavailable
Heldwein W, Avenhaus W, Schönekäs H, Kaess H, Müller-Lissner S, Hasford B, *et al.* Injection of fibrin tissue adhesive versus laser photocoagulation in the treatment of high-risk bleeding peptic ulcers: a controlled randomized study. *Endoscopy* 1996;**28**:756–60	Did not meet population/ intervention criteria
Herreros MD, Garcia-Arranz M, Guadalajara H, De-La-Quintana P, Garcia-Olmo D, FATT Collaborative Group. Autologous expanded adipose-derived stem cells for the treatment of complex cryptoglandular perianal fistulas: a phase III randomized clinical trial (FATT 1: fistula Advanced Therapy Trial 1) and long-term evaluation. *Dis Colon Rectum* 2012;**55**:762–72	Did not meet population/ intervention criteria
Hickey NC. Randomized clinical trial of tranexamic acid-free fibrin sealant during vascular surgical procedures. *Br J Surg* 2010;**97**:1790	Letter/commentary/erratum
Hidalgo M, Castillo MJ, Eymar JL, Hidalgo A. Lichtenstein inguinal hernioplasty: sutures versus glue. *Hernia* 2005;**9**:242–4	Not a RCT
Hilten JA, Verra WC, Honohan A, Wildt-Eggen J, Nelissen R. The effectiveness of a single-donor allogeneic fibrin sealant on functional knee recovery: a multicenter randomized controlled trial. *Transfusion* 2014;**54**:201a	Abstract/full text unavailable
Holle J. Early postoperative efficacy of fibrin glue in face lifts: a prospective randomized trial. *Plast Reconstr Surg* 2005;**115**:917–18	Discussion paper

continued

TABLE 34 Excluded randomised controlled trials (*continued*)

Study excluded	Reason for exclusion
Huang QS, Hong GX, Wang FB, Kang H, Weng YX, Chen ZB. Dynamic changes in countertraction intensity of the peripheral nerve repaired with the adhesion of fibrin glue. *Chin J Clin Rehabil* 2005;**9**:192–4	Not a RCT
Imhof M, Ohmann C, Röher HD, Glutig H, DUESUC study group. Endoscopic versus operative treatment in high-risk ulcer bleeding patients – results of a randomised study. *Langenbecks Arch Surg* 2003;**387**:327–36	Did not meet population/ intervention criteria
Inghilleri G, Aloni A, Santoleri L, Mancini L, Fonti E, Rondinara G, *et al.* Home-made versus commercial fibrin glue in liver surgery. *Transfus Altern Transfus Med* 2005;**7**(Suppl. 1):103	Not a RCT
Jackson MR. Tissue sealants: current status, future potential. *Nat Med* 1996;**2**:637–8	Review
Jain AK, Sukhija J. *Comparison of Cut-and-Paste with Cut-and-Suture Technique of Pterygium Surgery*. Poster session presented at American Academy of Ophthalmology, 2006, Las Vegas, TX, USA	Abstract/full text unavailable
Jiang J, Yang Y, Zhang M, Fu X, Bao X, Yao K. Comparison of fibrin sealant and sutures for conjunctival autograft fixation in pterygium surgery: one-year follow-up. *Ophthalmologica* 2008;**222**:105–11	Not a RCT
Jones BM, Grover R. Early postoperative efficacy of fibrin glue in face lifts: a prospective randomized trial. *Plast Reconstr Surg* 2007;**119**:433–4	Discussion paper
Kamal HM, Goda HAEB. Epidural fibrin glue for treatment of post-dural puncture headache (PDPH): comparative study with epidural blood patch. *Eg J Anaesth* 2009;**25**:41–7	Did not meet population/ intervention criteria
Kanemaru S, Umeda H, Kitani Y, Nakamura T, Hirano S, Ito J. Regenerative treatment for tympanic membrane perforation. *Otol Neurotol* 2011;**32**:1218–23	Did not meet population/ intervention criteria
Kim A, Lopez MA, Rojas V, Broman AT, Chuck RS, Batlle JF. Comparison of preserved amniotic membrane and dehydrated amniotic membrane allografting using fibrin glue or sutures for attachment after excision of primary pterygium. *IOVS* 2007;**48**:5316	Abstract/full text unavailable
Kitajiri S, Tabuchi K, Hiraumi H, Kaetsu H. Relief of post-tonsillectomy pain by release of lidocaine from fibrin glue. *Laryngoscope* 2001;**111**:642–4	Did not meet population/ intervention criteria
Klecker C, Knoll S, Moller T. [Adrenalin versus adrenalin and Beriplast as primary therapy of acute bleeding in the upper gastrointestinal tract]. *Gastroenterol* 2004;**42**:1219	Did not meet population/ intervention criteria
Klinfelder JW, Lange DE. Application of hydroxyapatite combined with fibrin glue in periodontal surgery. *J Dent Res* 1989;**68**:643	Abstract/full text unavailable
Kokesch-Häuser S, Beer M, Staehler G. [Effect of intraoperative fibrin gluing on lymph flow and lymphocele formation after kidney transplantation.] *Urologe A* 1993;**32**:334–8	Did not meet population/ intervention criteria
Kraus TW, Mehrabi A, Schemmer P, Kashfi A, Berberat P, Büchler MW. Scientific evidence for application of topical hemostats, tissue glues, and sealants in hepatobiliary surgery. *J Am Coll Surg* 2005;**200**:418–27	Review
Kurian A, Reghunadhan I, Nair KG. Autologous blood versus fibrin glue for conjunctival autograft adherence in sutureless pterygium surgery: a randomised controlled trial. *Br J Ophthalmol* 2015;**99**:464–70	Did not meet population/ intervention criteria
Lantis JC 2nd, Marston WA, Farber A, Kirsner RS, Zhang Y, Lee TD, *et al.* The influence of patient and wound variables on healing of venous leg ulcers in a randomized controlled trial of growth-arrested allogeneic keratinocytes and fibroblasts. *J Vasc Surg* 2013;**58**:433–9	Outcomes not of interest
Larsen T, Devantier A, Iversen E, Fischer A, Hansen R, Dragsted J. [Treatment of testicular hydrocele with fibrin adhesive.] *Ugeskr Laeg* 1986;**148**:896–7	Not a RCT
Lee S, Kim HR, Cho S, Huh DM, Lee EB, Ryu KM, *et al.* Staple line coverage after bullectomy for primary spontaneous pneumothorax: a randomized trial. *Ann Thorac Surg* 2014;**98**:2005–11	Did not meet population/ intervention criteria
Lei QF, Cai W. Clinical observation on fibrin glue application during pterygium surgery. *Int Eye Sci* 2015;**15**:364–6	Not a RCT

TABLE 34 Excluded randomised controlled trials (*continued*)

Study excluded	Reason for exclusion
Lesur G. Upper gastrointestinal hemorrhages not related to portal hypertension. *Hepatogastro* 2002;**9**:445–54	Review
Levitsky S. Further information on the fibrin sealant conference. *Transfusion* 1996;**36**:845–6	Letter/commentary/erratum
Levy O, Martinowitz U, Oran A, Tauber H, Liberman N, Salai M, *et al.* The use of fibrin tissue adhesive reduces blood loss and blood transfusion after total knee arthroplasty: a prospective, randomized, multi-centre study. *J Bone Joint Surg Am* 2000;**82**(Suppl. 3):221–2	Abstract/full text unavailable
Lin HJ, Hsieh YH, Tseng GY, Perng CL, Chang FY, Lee SD. Endoscopic injection with fibrin sealant versus epinephrine for arrest of peptic ulcer bleeding: a randomized, comparative trial. *J Clin Gastroenterol* 2002;**35**:218–21	Did not meet population/ intervention criteria
Lindsey I, Smilgin-Humphreys MM, Cunningham C, Mortensen NJ, George BD. Randomised trial of fibrin glue vs. conventional treatment for anal fistula. *Colorectal Dis* 2001;**3**(Suppl. 1):Oral 78	Abstract/full text unavailable
Liptrot S, Leveson S, Lund J. A prospective randomized controlled trial of fibrin glue versus surgery in the treatment of pilonidal sinus. *Br J Surg* 2007;**94**:5	Abstract/full text unavailable
Liptrot S, Leveson S, Lund J. Fibrin glue may be better than surgery for pilonidal sinus: results of a prospective, randomized, controlled trial and 2-year follow up. *Dis Colon Rectum* 2008;**51**:P80	Abstract/full text unavailable
Liu H, Wei RH, Huang Y, Yang RB, Zhang C, Zhao SZ. Clinical observation on fibrin glue technique in pterygium surgery under surface anaesthesia. *Int Eye Sci* 2014;**14**:1527–8	Did not meet population/ intervention criteria
Liu H, Wei RH, Huang Y, Yang RB, Zhang C, Zhao SZ. Clinical observation on fibrin glue technique in pterygium surgery performed with limbal autograft transplantation. *Int Eye Sci* 2013;**13**:1498–9	Chinese
Liu W, Zhang YP, Xie MF, Liu Y. Application of fibrin glue with bandage contact lens in pterygium surgery. *Int Eye Sci* 2014;**14**:879–81	Chinese
Llewellyn-Bennett R, English R, Turner J, Tsim N, Rayter Z, Winters Z. A randomised controlled trial to evaluate the role of Tisseel, a fibrin sealant on seroma formation in Latissimus dorsi breast reconstruction. *Eur J Surg Oncol* 2011;**37**:S16	Abstract/full text unavailable
Lockhart K, Teo E, Teo S, Dhillon M, van Driel Mieke L. Mesh versus non-mesh for inguinal and femoral hernia repair. *Cochrane Database Syst Rev* 2015;**2**:CD011517	Protocol
Lowe J, Luber J, Levitsky S, Hantak E, Montgomery J, Schiestl N, *et al.* Evaluation of the topical hemostatic efficacy and safety of TISSEEL VH S/D fibrin sealant compared with currently licensed TISSEEL VH in patients undergoing cardiac surgery: a phase 3, randomized, double-blind clinical study. *J Cardiovasc Surg* 2007;**48**:323–31	Did not meet population/ intervention criteria
Luke *et al.* 1986[223]	Not a RCT
Maca TH, Mlekusch W, Ahmadi A, Al AM, Haumer M, Sabeti S, *et al.* Treatment of iatrogenic pseudoaneurysms with injection of thrombin and fibrin glue. *Ann Hematol* 2003;**82**:S59	Abstract/full text unavailable
Malhotra C, Jain AK, Sawhney A, Nawani N, Ram J. Outcomes of fibrin glue-assisted conjunctival versus conjunctivolimbal autograft in primary pterygia with a new technique of conjunctival resection and tenon extended removal. *Cornea* 2015;**34**:193–8	Did not meet population/ intervention criteria
Martinazzoli A, Cangemi V, Cammarata A, Ceccobelli M, Costanzo F, Corradi R, *et al.* [Use of fibrin glue in breast prosthesis implantation immediately after bilateral adenectomy.] *G Chir* 1995;**16**:457–8	Did not meet population/ intervention criteria
Martinowitz U, Levy O, Tauber H, Horoszowski H. Prospective randomized multicenter study on efficacy and safety of fibrin tissue adhesive in knee arthroplasty. *Thromb Haemost* 1997;**78**:661–6	Abstract/full text unavailable
Martinowitz U, Levy O, Oran A, Tauber H, Heroszowski H. Fibrin tissue adhesive reduces blood loss and blood transfusion requirements after total knee arthroplasty: a prospective, randomized, multicenter study. *Haemophilia* 1998;**4**:186	Abstract/full text unavailable

continued

TABLE 34 Excluded randomised controlled trials (*continued*)

Study excluded	Reason for exclusion
Mercuriali F, Inghilleri G, Aloni A, Santoleri L, Angeloro D, Capitani D, *et al.* Autologous fibrin glue (AFG) reduces blood loss in patients submitted to total hip replacement (THR). *Vox Sang* 2004;**87**(Suppl. 3):35	Abstract/full text unavailable
Milic DJ, Perisic ZD, Zivic SS, Stanojkovic ZA, Stojkovic AM, Karanovic ND, *et al.* Prevention of pocket related complications with fibrin sealant in patients undergoing pacemaker implantation who are receiving anticoagulant treatment. *Europace* 2005;**7**:374–9	Did not meet population/ intervention criteria
Milne AA. Clinical impact of fibrin sealants. *Vox Sang* 2004;**87**(Suppl. 2):29–30	Letter/commentary/erratum
Miyamoto H, Sakao Y, Sakuraba M, Oh S, Takahashi N, Miyasaka Y, *et al.* The effects of sheet-type absorbable topical collagen hemostat used to prevent pulmonary fistula after lung surgery. *Ann Thorac Cardiovasc Surg* 2010;**16**:16–20	Did not meet population/ intervention criteria
Mohindra S, Mohindra S, Gupta K. Endoscopic repair of CSF rhinorrhea: necessity of fibrin glue. *Neurol India* 2013;**61**:396–9	Did not meet population/ intervention criteria
Moon YM, Kang JK, Park IS, Chon CY, Chung JB, Han KH. Comparison of hemostatic effect of endoscopic injection with fibrin glue (FG) and hypertonic saline – epinephrine (HSE) for peptic ulcer bleeding: a prospective randomized trial. *Korean J Gastrointest Endosc* 1995;**15**:12–25	Did not meet population/ intervention criteria
Moralee SJ, Carney AS, Cash MP, Murray JA. The effect of fibrin sealant haemostasis on post-operative pain in tonsillectomy. *Clin Otolaryngol Allied Sci* 1994;**19**:526–8	Did not meet population/ intervention criteria
Mulet Homs ME, Alio YSJL, Gobby F. Efficacy of fibrinogen as bioadhesive in cataract surgery through scleral tunnel. *Arch Soc Esp Oftalmol* 1997;**72**:427–30	Outcomes not of interest
Murphy WG, Milne AA, Ruckley CV, Kubba AK, Palmer KR. Fibrin sealant: update on clinical studies. *Transfus Sci* 1996;**17**:341–2	Not a RCT
Muzi MG, Nigro C, Cadeddu F, Andreoli F, Farinon AM. Randomized clinical trial of Lichtenstein's operation versus mesh plug for inguinal hernia repair. *Br J Surg* 2007;**94**:647	Did not meet population/ intervention criteria
Naga MI, Goubran HA, Said M, Burnouf-Radosevich M, Burnouf T, Huart JJ. A comparison between endoscopic injection of bleeding esophageal varices using ethanolamine oleate and fibrin glue sealant in patients with bilharzial liver fibrosis. *Endoscopy* 1999;**31**:405	Letter/commentary/erratum
NCT0212065. *Effect of the Fibrin Monomer in the Integrity of the Graft during Tympanoplasty Compared with the Effect of the Hemostatic Sponge*. Clinicaltrials.gov, 2012. URL: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/034/CN-01001034/frame.html (accessed 19 May 2015)	Insufficient data
Negro P, Basile F, Brescia A, Buonanno GM, Campanelli G, Canonico S, *et al.* Open tension-free Lichtenstein repair of inguinal hernia: use of fibrin glue versus sutures for mesh fixation. *Hernia* 2011;**15**:7–14	Not a RCT
Nervi C, Gamelli RL, Greenhalgh DG, Luterman A, Hansbrough JF, Achauer BM, *et al.* A multicenter clinical trial to evaluate the topical hemostatic efficacy of fibrin sealant in burn patients. *J Burn Care Rehabil* 2001;**22**:99–103	Did not meet population/ intervention criteria
Niekisch R. [Application possibilities of fibrin glue in dentistry and maxillofacial surgery.] *Zahn Mund Kieferheilkd Zentralbl* 1980;**68**:555–61	Not a RCT
Novik B. Randomized trial of fixation vs nonfixation of mesh in total extraperitoneal inguinal hernioplasty. *Arch Surg* 2005;**140**:811–12	Letter/commentary/erratum
Novik B. Fibrin glue mesh fixation in hernia repair. *Ann Surg* 2007;**246**:906–8	Letter/commentary/erratum
Öllinger R, Mihaljevic AL, Schuhmacher C, Bektas H, Vondran F, Kleine M, *et al.* A multicentre, randomized clinical trial comparing the Veriset haemostatic patch with fibrin sealant for the management of bleeding during hepatic surgery. *HPB (Oxford)* 2013;**15**:548–58	Did not meet population/ intervention criteria
Osbun JW, Ellenbogen RG, Chesnut RM, Chin LS, Connolly PJ, Cosgrove GR, *et al.* A multicenter, single-blind, prospective randomized trial to evaluate the safety of a polyethylene glycol hydrogel (Duraseal Dural Sealant System) as a dural sealant in cranial surgery. *World Neurosurg* 2012;**78**:498–504	Did not meet population/ intervention criteria
Ota Y, Ikemiyagi Y, Takizawa K, Yamada C, Rikitake R, Suzuki M. Efficacy of covering mucosal defects with polyglycolic acid sheets after ear or nose surgery. *Laryngoscope* 2015;**125**:567–70	Not a RCT

TABLE 34 Excluded randomised controlled trials (*continued*)

Study excluded	Reason for exclusion
Oz MC, Rondinone JF, Shargill NS. FloSeal Matrix: new generation topical hemostatic sealant. *J Card Surg* 2003;**18**:486–93	Not a RCT
Pal Singh B, Dhakad U. Re: TachoSil Sealed tubeless percutaneous nephrolithotomy to reduce urine leakage and bleeding: outcome of a randomized controlled study: L. Cormio, A. Perrone, G. di Fino, N. Ruocco, M. de Siati, J. de la Rosette and G. Carrieri. *J Urol* 2012;**188**:145–50. *J Urol* 2013;**189**:777–8	Letter/commentary/erratum
Pan I, Dendukuri N, McGregor M. *Efficacy and Cost-Effectiveness of Collatamp-G for Infection Prophylaxis in Cardiac Surgery.* 2009. URL: www.mcgill.ca/files/tau/COLLATAMP_CARDIAC_ REPORT.pdf (accessed 19 May 2015)	Review
Park DH, Iwashita T, Samarasena JB, Nakai Y, Chang KJ, Chao HH. Prospective randomized comparative study using hemoclip, endoloop, and fibrin sealant for endoscopic closure of iatrogenic duodenal perforation in a porcine model: HELLP study. *Gastrointest Endosc* 2011;**73**(Suppl. 1):AB156	Did not meet population/ intervention criteria
Park DH, Han JH, Jang JY, Lee SY. Effect of fibrin glue on post-tonsillectomy pain. *Korean J Otorhinolaryngol-Head Neck Surg* 2009;**52**:591–3	Korean
Patel MR, Caruso PA, Yousuf N, Rachlin J. CT-guided percutaneous fibrin glue therapy of cerebrospinal fluid leaks in the spine after surgery. *Am J Roentgenol* 2000;**175**:443–6	Not a RCT
Pescatore P, Jornod P, Borovicka J, Pantoflickova D, Suter W, Meyenberger C, *et al.* Epinephrine versus epinephrine plus fibrin glue injection in peptic ulcer bleeding: a prospective randomized trial. *Gastrointest Endosc* 2002;**55**:348–53	Did not meet population/ intervention criteria
Petersen B, Barkun A, Carpenter S, Chotiprasidhi P, Chuttani R, Silverman W, *et al.* Tissue adhesives and fibrin glues. *Gastrointest Endosc* 2004;**60**:327–33	Review
Petrov DB, Manolov EP, Minchev TR, Alexov SB, Botev CN. Additional intraoperative aerostasis with a 100% autologous fibrin glue in thoracic surgery. *Eur Respir J* 2001;**18**(Suppl. 33):524	Outcomes not of interest
Petter Puchner AH, Khakpour Z, May C, Mika K, Glaser KS, Redl H. The impact of atraumatic fibrin sealant vs. staple mesh fixation in tapp hernia repair on chronic pain and quality of life – results of a randomized controlled study. *Surg Endosc* 2010;**24**(Suppl. 1):S618	Abstract/full text unavailable
Pichon R, Augustovski GM, Garcia MS, Glujovsky D, Alcaraz A, Lopez A, *et al. Biological Tissue Adhesive Versus Standard Suture in Conjuctival Autograft for the Surgical Treatment of Pterygium*. 2012. URL: www.iecs.org.ar/iecs-visor-publicacion.php?cod_publicacion=1324& amp;origen_%20publicacion=publicaciones (accessed 19 May 2015)	Abstract/full text unavailable
Pini Prato GP, Cortellini P, Agudio G, Clauser C. Human fibrin glue versus sutures in periodontal surgery. *J Periodontol* 1987;**58**:426–31	Not a RCT
Porte RJ, Verhoef C, De Wilt JHW, Rijken AM, Klaase JM, Ayez N, *et al.* Fibrocaps™, a novel fibrin sealant, for bleeding during hepatic resection: results of a phase 2, randomized, controlled study. *HPB* 2012;**14**:133	Abstract/full text unavailable
Pulikkotil SJ, Nath S. Fibrin sealant as an alternative for sutures in periodontal surgery. *J Coll Physicians Surg Pak* 2013;**23**:164–5	Outcomes not of interest
Pulikkotil SJ, Nath S. Effect on interleukin-1beta and interleukin-8 levels following use of fibrin sealant for periodontal surgery. *Aust Dent J* 2014;**59**:156–64	Not a RCT
Raborn GW, Hohn FI, Grace MG, Arora BK. Tisseel, a two component fibrin tissue sealant system: report of a trial involving anticoagulated dental patients. *J Can Dent Assoc* 1990;**56**:779–81	Review
Rauws EAJ, Rutgeerts P, Wara P, Hoos A, Solleder E, Halttunen J, *et al.* Fibrin sealant (Beriplast®) v.s. polidocanol 1% in the endoscopic treatment of bleeding gastroduodenal ulcers. *Endoscopy* 1996;**28**:S19	Abstract/full text unavailable
Rehder J, Bosnardo CA, Kraft MB, Frade MA, Guillaumon AT, Batista FR. A comparative study of cell therapy and fibrin glue applied to chronic venous ulcers. *Procedia Engineering* 2013;**59:**85–91	Outcomes not of interest

continued

TABLE 34 Excluded randomised controlled trials (*continued*)

Study excluded	Reason for exclusion
Richter G, Prassler R, Rutgeerts P, Rauws E, Warn P, Hoos A, *et al.* Fibrin glue versus Polidocanol 1% in ulcerous bleeding therapy – results of a multi-centre study. *Endoskopie Heute* 1997;**10**:93	Abstract/full text unavailable
Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. *Cochrane Database Syst Rev* 2015;**12**:CD010957	Protocol
Rodig J, Dinkelaker F, Rahmanzadeh R. Reduction of ossification after cement-free hip replacement using fibrin glue. *Hefte zur Unfallheilkunde* 1990;**212**:465–6	Abstract/full text unavailable
Rodin IuV. [Local hemostasis during the carotid endarterectomy under condition of antithrombocytic therapy.] *Klin Khir* 2007;**10**:32–4	Not a RCT
Rousou J, Levitsky S, Gonzalez-Lavin L, Cosgrove D, Magilligan D, Weldon C, *et al.* Randomized clinical trial of fibrin sealant in patients undergoing resternotomy or reoperation after cardiac operations. A multicenter study. *J Thorac Cardiovasc Surg* 1989;**97**:194–203	Cross-over
Rutgeerts P, Rauws E, Wara P, Swain P, Hoos A, Solleder E, *et al.* Randomised trial of single and repeated fibrin glue compared with injection of polidocanol in treatment of bleeding peptic ulcer. *Lancet* 1997;**350**:692–6	Did not meet population/ intervention criteria
Sakoda T, Shibano A, Saitoh Y, Dake Y, Sogo H, Fujimura S, *et al.* [An office technique for myringoplasty without the use of fibrin glue.] *Nippon Jibiinkoka Gakkai Kaiho* 2000;**103**:836–9	Did not meet population/ intervention criteria
Sánchez M, Anitua E, Orive G, Mujika I, Andia I. Platelet-rich therapies in the treatment of orthopaedic sport injuries. *Sports Med* 2009;**39**:345–54	Abstract/full text unavailable
Sandrock D, Steinröder M, Emrich D. [Fibrin agglutination of thyroid gland cysts after fine needle puncture.] *Dtsch Med Wochenschr* 1993;**118**:1–5	Did not meet population/ intervention criteria
Santini F, Luciani GB, Pessotto R, Petrilli G, Fabbri A, Mazzucco A. Current techniques to reduce blood loss after the Ross procedure. *J Heart Valve Dis* 1997;**6**:343–6	Not a RCT
Scheer M, Steveling H, Schweigert HG, Neugebauer J, Kubler AC, Zoller JE. Efficacy of fibrinogen and thrombin coated collagen sponge (TachoComb) in anticoagulated patients undergoing dental surgery. *Chirug Dtsch Zahnarztl Z* 2004;**59**:220–6	Abstract/full text unavailable
Segal N, Puterman M, Rotem E, Niv A, Kaplan D, Kraus M, *et al.* A prospective randomized double-blind trial of fibrin glue for reducing pain and bleeding after tonsillectomy. *Int J Pediatr Otorhinolaryngol* 2008;**72**:469–73	Did not meet population/ intervention criteria
Segura-Castillo JL, Aguirre-Camacho H, González-Ojeda A, Michel-Perez J. Reduction of bone resorption by the application of fibrin glue in the reconstruction of the alveolar cleft. *J Craniofac Surg* 2005;**16**:105–12	Did not meet population/ intervention criteria
Sener BC, Saysel MY. The comparison between alloplastic bone chips with and without fibrin glue used in maxillary sinus lifting operations. *J Craniomaxillofac Surg* 1998;**26**(Suppl. 1):3–21	Abstract/full text unavailable
Shah HN, Hegde S, Shah JN, Mohile PD, Yuvaraja TB, Bansal MB. A prospective, randomized trial evaluating the safety and efficacy of fibrin sealant in tubeless percutaneous nephrolithotomy. *J Urol* 2006;**176**:2488–92	Did not meet population/ intervention criteria
Shcherba SN, Polovinkin VV. [Use of Tachocomb for prevention of postoperative lymphatic leaks in the abdomen.] *Vopr Onkol* 2011;**57**:269–70	Unobtainable
Shen L, Luo H, Tan S. Effect of fibrin glue on patients after high frequency electrocoagulatomy for gastrointestinal protuberant lesions. *Med J Wuhan Uni* 2003;**24**:377	Chinese
Simons MP. Randomized clinical trial of fibrin sealant versus titanium tacks for mesh fixation in laparoscopic umbilical hernia repair. *Br J Surg* 2011;**98**:1537–45	Letter/commentary/erratum
Singer M, Cintron J, Nelson R, Orsay C, Bastawrous A, Pearl R, *et al.* Treatment of fistulas-in-ano with fibrin sealant in combination with intra-adhesive antibiotics and/or surgical closure of the internal fistula opening. *Dis Colon Rectum* 2005;**48**:799–808	Did not meet population/ intervention criteria
Singh PK, Singh S, Vyas C, Singh M. Conjunctival autografting without fibrin glue or sutures for pterygium surgery. *Cornea* 2013;**32**:104–7	Did not meet population/ intervention criteria

TABLE 34 Excluded randomised controlled trials (*continued*)

Study excluded	Reason for exclusion
Soumian S, Al-Ani S, Sterne G. Randomized clinical trial on the effect of fibrin sealant on latissimus dorsi donor-site seroma formation after breast reconstruction (*Br J Surg* 2012;**99**:1381–1388). *Br J Surg* 2013;**100**:1671	Letter/commentary/erratum
Spinzi G, Minoli G. Injection of fibrin tissue adhesive versus laser photocoagulation in the treatment of high-risk bleeding peptic ulcers: a controlled randomized study. *Gastrointest Endosc* 1997;**46**:198–9	Did not meet population/ intervention criteria
Stabilini C, Fornaro R, Lazzara F, Mandolfino F, Imperatore M, Gianetta E. Suturless-lightweight hernioplasty vs traditional Lichtenstein repair. One year results on chronic postoperative pain. *Eur Surg Res* 2010;**45**:197	Abstract/full text unavailable
Stephens J, Robless P, Jenkins M, Cheshire N. Re: Does fibrin glue reduce complications after femoral artery surgery? A randomised trial. *Eur J Vasc Endovasc Surg* 2003;**25**:596	Letter/commentary/erratum
Stevens MH, Stevens DC. Pain reduction by fibrin sealant in older children and adult tonsillectomy. *Laryngoscope* 2005;**115**:1093–6	Letter/commentary/erratum
Stiller-Timor L, Goldbart AD, Segal N, Amash A, Huleihel M, Leiberman A, *et al.* Circulating cytokines in patients undergoing tonsillectomy with fibrin glue. *Int J Pediatr Otorhinolaryngol* 2012;**76**:419–22	Did not meet population/ intervention criteria
Stoeckli SJ, Moe KS, Huber A, Schmid S. A prospective randomized double-blind trial of fibrin glue for pain and bleeding after tonsillectomy. *Laryngoscope* 1999;**109**:652–5	Did not meet population/ intervention criteria
Strohm WD, Römmele UE, Barton E, Paul-Martin C. [Injection therapy of bleeding peptic ulcer with fibrin or polidocanol.] *Dtsch Med Wochenschr* 1994;**119**:249–56	Did not meet population/ intervention criteria
Stutz H, Hempelmann HCG. The use of autologous fibrin glue to reduce perioperative blood loss in total knee arthroplasty – results of a controlled study. *Orthopadische Praxis* 2004;**40**:1–3	Not a RCT
Suc B, Msika S, Piccinini M, Fourtanier G, Hay JM, Flamant Y, *et al.* Octreotide in the prevention of intra-abdominal complications following elective pancreatic resection: a prospective, multicenter randomized controlled trial. *Arch Surg* 2004;**139**:288–94	Did not meet population/ intervention criteria
Szczesny T, Kubiszewska I, Rybak A, Michalkiewicz J, Szymankiewicz M, Kowalewski J. The role of Tachosil in lymphostasis after mediastinal lymphadenectomy in lung cancer patients. *J Thorac Oncol* 2011;**6**(Suppl. 2):876–7	Abstract/full text unavailable
Tabatabaei S, Talab SS, Kloc LS, Siddiqui MM, Akhavein A, Vazquez R, *et al.* Use of evicel fibrin sealant for improving hemostasis following transurethral prostate debulking surgery in patients with BPH. *J Endourol* 2014;**28**:A131	Abstract/full text unavailable
Takeuchi J, Suzuki H, Murata M, Kakei Y, Ri S, Umeda M. Clinical evaluation of application of polyglycolic acid sheet and fibrin glue spray for partial glossectomy. *J Oral Maxillofac Surg* 2013;**71**:e126–31	Not a RCT
Tamaki H, Fukushima H, Nakamura H, Kanemaru S, Fukuyama Y, Tamura Y. Control of postoperative pain with Beriplast P in tonsillectomy. *Practica Otologica* 1996;**89**:1027–30	Did not meet population/ intervention criteria
Taylor *et al.* 2003[199]	Not a RCT
Testini M, Lissidini G, Poli E, Gurrado A, Lardo D, Piccinni G. A single-surgeon randomized trial comparing sutures, N-butyl-2-cyanoacrylate and human fibrin glue for mesh fixation during primary inguinal hernia repair. *Can J Surg* 2010;**53**:155–60	Did not meet population/ intervention criteria
Tian BY, Zhang H. Limbal stem cell transplantation with fibrin sealant for the treatment of recurrent pterygium. *Int J Ophthalmol* 2011;**11**:1066–7	Chinese
Tocchhetti EV, Carter G, Goss A, Lloyd JV. Local management of haemostasis with fibrin adhesive in patients with coagulopathies undergoing surgery. *Vox Sang* 2000;**79**(Suppl. 1):220	Abstract/full text unavailable
Tofuku K, Koga H, Yanase M, Komiya S. The use of antibiotic-impregnated fibrin sealant for the prevention of surgical site infection associated with spinal instrumentation. *Eur Spine J* 2012;**21**:2027–33	Not a RCT

continued

TABLE 34 Excluded randomised controlled trials (*continued*)

Study excluded	Reason for exclusion
Topiwala P, Bansal RK. Comparative evaluation of cyanoacrylate and fibrin glue for muscle recession in strabismus surgery. *J Pediatr Ophthalmol Strabismus* 2014;**51**:349–54	Did not meet population/ intervention criteria
Troisi RI, Bektas H, Pratschke J, Topal B, Buchler M, Schuhmacher CP, *et al.* A prospective, multi-center, randomized, single-blind study to compare the Veriset™ hemostatic patch to fibrin sealant (Tachosil) in subjects undergoing hepatic surgery. *HPB* 2012;**14**:104–5	Abstract/full text unavailable
Trombelli L, Scabbia A, Wikesjö UM, Calura G. Fibrin glue application in conjunction with tetracycline root conditioning and coronally positioned flap procedure in the treatment of human gingival recession defects. *J Clin Periodontol* 1996;**23**:861–7	Outcomes not of interest
Trombelli L, Scabbia A, Calura G. Effect of topical application of a fibrin-fibronectin sealing system on healing response following periodontal surgical procedures. *Clin Drug Invest* 1997;**14**:268–75	Outcomes not of interest
Trombelli L, Scabbia A, Scapoli C, Calura G. Clinical effect of tetracycline demineralization and fibrin-fibronectin sealing system application on healing response following flap debridement surgery. *J Periodontol* 1996;**67**:688–93. [Erratum published in *J Periodontol* 1996;**67**:1368.]	Outcomes not of interest
Tsai CH, Hsu HC, Chen YJ, Lin MJ, Chen HT. Using the growth factors-enriched platelet glue in spinal fusion and its efficiency. *J Spinal Disord Tech* 2009;**22**:246–50	Not a RCT
Upadhyaya VD, Gopal SC, Gangopadhyaya AN, Gupta DK, Sharma S, Upadyaya A, *et al.* Role of fibrin glue as a sealant to esophageal anastomosis in cases of congenital esophageal atresia with tracheoesophageal fistula. *World J Surg* 2007;**31**:2412–15	Did not meet population/ intervention criteria
Uy HS, Reyes JMG, Flores JP, Limbonsiong R. Human plasma derived fibrin glue (Beriplast P) in conjunctival autografts for pterygia. *IOVS* 2002;**43**:129	Not a RCT
Vaiman *et al.* 2002[188]	Not a RCT
Vaiman M, Eviatar E, Shlamkovich N, Segal S. Effect of modern fibrin glue on bleeding after tonsillectomy and adenoidectomy. *Ann Otol Rhinol Laryngol* 2003;**112**:410–14	Did not meet population/ intervention criteria
Valentini MF, Lissidini G, Gurrado A, Poli E, Ruggiero L, Piccinni G, *et al.* Comparison among three different methods of mesh fixation in patients undergoing plug and mesh technique for primary inguinal hernia repair: a prospective randomised controlled study. *Eur Surg Res* 2010;**45**:198–9	Abstract/full text unavailable
Visna P, Pasa L, Cizmár I, Hart R, Hoch J. Treatment of deep cartilage defects of the knee using autologous chondrograft transplantation and by abrasive techniques – a randomized controlled study. *Acta Chir Belg* 2004;**104**:709–14	Did not meet population/ intervention criteria
Wagner W, Wiltfang J, Pistner H, Yildirim M, Ploder B, Chapman M, *et al.* Bone formation with a biphasic calcium phosphate combined with fibrin sealant in maxillary sinus floor elevation for delayed dental implant. *Clin Oral Implants Res* 2012;**23**:1112–17	Did not meet population/ intervention criteria
Ware P, Rutgeerts P, Rauws EAJ, Hoos A, Solleder E. Endoscopic injection therapy of bleeding gastro-duodenal ulcers: fibrin glue (beriplast) vs. polidocanol 1%. *Gut* 1996;**39**(Suppl. 1):A5	Abstract/full text unavailable
Winters ZE, Llewellyn-Bennett R, English R, Turner J, Rayter Z, Greenwood R. A randomised controlled trial to evaluate the role of Tisseel, a fibrin sealant on seroma formation in latissimus dorsi breast reconstruction. *Cancer Res* 2011;**71**(Suppl. 3):P2-16-07	Abstract/full text unavailable
Wong K, Goldstraw P. Effect of fibrin glue in the reduction of postthoracotomy alveolar air leak. *Ann Thorac Surg* 1997;**64**:979–81	Did not meet population/ intervention criteria
Wurtz A, Chambon JP, Sobecki L, Batrouni R, Huart JJ, Burnouf T. [Use of a biological glue in partial pulmonary excision surgery. Results of a controlled trial in 50 patients.] *Ann Chir* 1991;**45**:719–23	Did not meet population/ intervention criteria
Yasumizu Y, Miyajima A, Maeda T, Hasegawa M, Takeda T, Shinoda K, *et al.* What prevents lymphocele development after laparoscopic radical prostatectomy? *J Endourol* 2011;**25**:A227	Abstract/full text unavailable
Yeung SN, Lichtinger A, Kim P, Elbaz U, Ku JY, Amiran MD, *et al.* Superior versus inferior conjunctival autografts combined with fibrin glue in the management of primary pterygia. *Cornea* 2013;**32**:1582–6	Did not meet population/ intervention criteria

TABLE 34 Excluded randomised controlled trials (*continued*)

Study excluded	Reason for exclusion
Yoshimura M, Tsubota N, Matsuoka H, Sakamoto T. Efficacy of a pedicled pericardial fat pad fixed with fibrin glue on postoperative alveolar air leakage. *Surg Today* 2002;**32**:26–8	Did not meet population/ intervention criteria
Yuasa K, Shimizu T, Matsubara J, Toyoda T. [Sealing effect of fibrin adhesive by various method on protection of air leakage in lung surgery.] *Kyobu Geka* 1998;**51**:1001–5	Did not meet population/ intervention criteria
Zhang SP, Cao B, Xiu XG, Wu BB. Local application of fibrin glue carrying gatifloxacin. *J Clin Rehabil Tissue Engin Res* 2011;**15**:431–5	Abstract/full text unavailable
Zhou LB, Guo SY, Zhang W, Du KH, Gong DQ. The efficacy of fibrin glue in radical mastectomy. *Acta Medicinae Sinica* 2003;**16**:14–15	Unobtainable
Ziaee SA, Sarhangnejad R, Abolghasemi H, Eshghi P, Radfar MH, Ahanian A, *et al.* Autologous fibrin sealant in tubeless percutaneous nephrolithotomy; a prospective study. *Urol J* 2013;**10**:999–1003	Not a RCT
Zimmer T, Rucktäschel F, Stölzel U, Liehr RM, Schuppan D, Stallmach A, *et al.* Endoscopic sclerotherapy with fibrin glue as compared with polidocanol to prevent early esophageal variceal rebleeding. *J Hepatol* 1998;**28**:292–7	Did not meet population/ intervention criteria
Zimmer TJ, Faiss S, Liehr RM, Breitkreutz C, Klein M, Stolzel U, *et al.* [Fibrin glue versus endoscopic ligature to stop acute bleeding and in the prophylaxis of early relapse of oesophagus varices. Results of a German multi-centre study.] *Gastroenterol* 2005;**43**:828	Abstract/full text unavailable

Note
A total of 26 duplicate studies were not included in this table.

Other

Chiu PWY, Lau TS, Kwong KH, Suen DTK, Kwok PY. Impact of programmed second endoscopy with appropriate re-treatment on peptic ulcer re-bleeding: a systematic review. *Ann Coll Surg Hong Kong* 2003;**7**:106–15.

Appendix 4 Tables of recent and ongoing studies

TABLE 35 ClinicalTrials.gov trials

NCT Number	Title	Recruitment	Start date	URL
NCT01828892	Glue application in the treatment of low-output fistulas	Recruiting	March 2014	http://ClinicalTrials.gov/show/NCT01828892
NCT02094885	The Bioseal vascular study	Completed	February 2014	http://ClinicalTrials.gov/show/NCT02094885
NCT01613664	Efficiency of TISSEEL for sleeve gastrectomy complications	Recruiting	February 2014	http://ClinicalTrials.gov/show/NCT01613664
NCT02040428	The Fibrin pad CV phase III study	Recruiting	January 2014	http://ClinicalTrials.gov/show/NCT02040428
NCT02034799	Phase IV Bioseal study in brain tumour surgery	Completed	November 2013	http://ClinicalTrials.gov/show/NCT02034799
NCT01993888	The EVARREST fibrin sealant patch liver study	Completed	October 2013	http://ClinicalTrials.gov/show/NCT01993888
NCT02011698	Absorbable sutures, non absorbable sutures or biologic fibrin glue for protesic mesh fixing in Lichtenstein technique for primitive groin hernia repair: a randomised prospective multicentric trial	Recruiting	October 2013	http://ClinicalTrials.gov/show/NCT02011698
NCT01902459	EVARREST fibrin sealant patch post-market study	Recruiting	July 2013	http://ClinicalTrials.gov/show/NCT01902459
NCT02153593	Postoperative bleeding prevention in massive bone tumour resection: a multicentric, randomised, parallel, controlled trial	Recruiting	March 2013	http://ClinicalTrials.gov/show/NCT02153593
NCT02150720	Prevention of postoperative bleeding in subcapital femoral fractures: a multicenter, randomised, controlled, parallel clinical trial	Recruiting	February 2013	http://ClinicalTrials.gov/show/NCT02150720
NCT01641718	Use of human fibrin glue versus staples for mesh fixation in laparoscopic transabdominal preperitoneal hernioplasty	Active, not recruiting	January 2013	http://ClinicalTrials.gov/show/NCT01641718

Note
All URLs accessed on 19 May 2015.

TABLE 36 Clinicaltrialsregister.eu trials

EudraCT number	Title	Recruitment	Start date	URL
2014–003954–15	A single blinded, randomised, controlled study to evaluate the safety and effectiveness of EVICEL® fibrin sealant (Human) compared to a hydrogel sealant as an adjunct to sutured dural repair	Ongoing	May 2015	www.clinicaltrialsregister.eu/ctr-search/trial/2014-003954-15/GB/
2013–004353–24	Wound management in post-bariatric surgery investigation for the reduction of the mean drainage volume in patients after abdominoplasty/lower body lift using Artiss fibrin sealant in comparison to the standard procedure	Ongoing	May 2014	www.clinicaltrialsregister.eu/ctr-search/trial/2013-004353-24/DE/
2013–002579–16	PHASE III clinical trial, single-centre, randomised, double blind in two groups parallel to compare the efficacy and safety of rich plasma growth factors (PRGF) in front of fibrin glue (Tissucol®) for sealing anal and criptoglandular fistula after 48 weeks	Ongoing	December 2014	www.clinicaltrialsregister.eu/ctr-search/trial/2013-002579-16/ES/
2013–002535–24	A phase iii randomised, controlled, superiority study evaluating EVARREST™ fibrin sealant patch versus standard of care treatment in controlling parenchymal bleeding during hepatic surgery	Ongoing	September 2013	www.clinicaltrialsregister.eu/ctr-search/trial/2013-002535-24/GB/

Note
All URLs accessed on 19 May 2015.

Appendix 5 Quality assessment

TABLE 37 Quality of RCTs

Study (author, year)	Random sequence generation	Allocation concealment	Blinding		Incomplete outcome data	Selective reporting	'Other bias'	Overall bias
			Patient	Outcome assessor				
Aguilera *et al.*, 2013[143]	✓	✓	✗	✗	?	?	?	?
Altinli *et al.*, 2007[206]	✗	✗	?	?	?	?	?	✗
Altomare *et al.*, 2011[217]	✓	✓	?	?	?	?	?	?
Anegg *et al.*, 2007[125]	?	?	?	?	?	?	?	?
Antuña *et al.*, 2013[155]	✓	?	?	?	?	?	?	?
Bahar *et al.*, 2006[159]	✗	?	?	?	?	?	?	?
Bahar *et al.*, 2007[169]	✗	?	?	?	?	?	?	✗
Bajardi *et al.*, 2009[194]	?	✓	?	?	?	?	?	?
Bektas *et al.*, 2014[65]	✓	✓	?	?	✓	?	?	✓
Belboul *et al.*, 2004[133]	✓	✓	?	✓	?	?	?	✓
Belcher *et al.*, 2010[131]	✓	?	✓	✗	?	?	?	?
Benevento *et al.*, 2014[109]	✓	?	✓	✓	?	?	?	?
Bercial *et al.*, 2012[213]	?	?	?	?	?	?	?	?
Berger *et al.*, 2001[107]	✓	?	✗	✗	?	?	?	?
Bochicchio *et al.*, 2015[239]	?	?	✓	✗	?	?	?	?
de Boer *et al.*, 2012[66]	✓	✓	✓	✓	✓	?	?	✓
Boldo, 2008[173]	✓	?	✓	✓	?	?	?	?
Bracale *et al.*, 2014[174]	✓	✓	✓	✓	?	?	?	✓
Bulbuller *et al.*, 2013[92]	?	?	?	?	?	?	?	?
Cambal *et al.*, 2012[175]	?	?	?	?	?	?	?	?
Campanelli *et al.*, 2012[176]	✓	✓	✓	✓	✗	?	?	✓
Canonico *et al.*, 1999[177]	?	?	?	?	?	?	?	?
Carlson *et al.*, 2008[94]	?	?	?	?	?	?	?	?
Carter *et al.*, 2003[229]	?	?	?	?	?	?	?	?

Study (author, year)	Random sequence generation	Allocation concealment	Blinding		Incomplete outcome data	Selective reporting	'Other bias'	Overall bias
			Patient	Outcome assessor				
Carter *et al.*, 2013[81]	✓	✓	?	?	?	?	?	?
Chalmers *et al.*, 2010[198]	✓	?	?	?	?	?	?	?
Chan *et al.*, 2014[178]	✓	✓	✓	✓	?	?	?	✓
Chapman *et al.*, 2000[67]	✓	✓	?	✓	?	?	?	✓
Choufani *et al.*, 2015[151]	✗	✗	✓	✗	?	?	?	✗
Cipolla *et al.*, 2010[110]	?	?	?	?	?	?	?	?
Cormio *et al.*, 2012[222]	✓	✓	?	?	?	?	?	?
Czerny *et al.*, 2000[205]	?	?	?	?	?	?	?	?
Czerny *et al.*, 2004[137]	✓	✓	?	?	?	?	?	?
Damiano *et al.*, 2014[184]	?	?	?	?	?	?	?	?
Danielsen *et al.*, 2008[209]	✓	✓	?	?	?	?	?	?
Danielsen *et al.*, 2010[79]	✓	✓	?	✓	?	?	?	✓
Diamond *et al.*, 2011[232]	?	?	?	✓	?	?	?	?
Dimo *et al.*, 1989[80]	?	✓	?	?	?	?	?	?
Dinsmore *et al.*, 2000[97]	?	?	?	?	?	?	?	?
Drake and Wong, 2003[207]	✓	?	?	?	?	?	?	?
Droghetti *et al.*, 2008[124]	?	?	?	?	?	?	?	?
Ellis and Clark, 2006[216]	?	x	?	?	?	?	?	?
Erba *et al.*, 2010[210]	✓	?	?	?	?	?	?	?
Eriksen *et al.*, 2013[183]	✓	✓	✓	✓	?	?	?	✓
Fabian *et al.*, 2003[128]	✓	✓	?	?	?	?	?	?
Falez *et al.*, 2013[154]	?	?	✓	✗	?	?	?	?
Fékété *et al.*, 1992[91]	✓	?	?	?	?	?	?	?
Fernandez Fernandez *et al.*, 1996[63]	?	?	?	?	?	?	?	?
Figueras *et al.*, 2007[71]	?	✗	?	?	?	?	?	?

continued

TABLE 37 Quality of RCTs (*continued*)

Study (author, year)	Random sequence generation	Allocation concealment	Blinding		Incomplete outcome data	Selective reporting	'Other bias'	Overall bias
			Patient	Outcome assessor				
Filosso *et al.*, 2013[136]	?	?	?	?	?	?	?	?
Fischer *et al.*, 2011[72]	✓	✓	✗	✗	✓	?	?	?
Fischer *et al.*, 2013[241]	✓	✓	✗	✗	?	?	?	?
Frilling *et al.*, 2005[73]	?	✓	✗	✗	?	?	?	?
Fu *et al.*, 2009[78]	✓	?	?	?	?	?	?	?
Furrer *et al.*, 1993[116]	?	?	?	?	?	?	?	?
Gilly *et al.*, 1994[115]	✓	?	✗	✗	?	?	?	?
Gilly *et al.*, 1998[108]	?	✓	✗	✗	?	?	?	?
Gonfiotti *et al.*, 2011[130]	?	?	✗	✗	?	?	?	?
Hall *et al.*, 2009[160]	?	✓	?	?	?	?	?	?
Hammond *et al.*, 2011[219]	?	✓	?	?	?	?	?	?
Hanks *et al.*, 2003[238]	✓	?	?	?	?	?	?	?
Healy *et al.*, 2013[211]	✓	✓	✓	✗	?	?	?	✓
Hester *et al.*, 2013[231]	?	?	✓	✗	?	?	?	?
Heyse *et al.*, 2014[142]	✓	✓	?	?	?	?	?	?
Huang and Qian, 2014[93]	✓	?	?	?	?	?	?	?
Huang *et al.*, 2015[64]	?	?	?	?	?	?	?	?
Hutter *et al.*, 2014[237]	✓	✓	✓	✓	?	?	?	✓
Hwang and Chen, 1996[61]	?	?	✗	✗	?	?	?	?
Jackson *et al.*, 1999[193]	✓	✓	✗	✗	?	?	?	?
Jain *et al.*, 2004[99]	✓	✓	✓	✗	?	?	?	?
Johnson *et al.*, 2005[100]	?	?	?	?	?	?	?	?
Joseph *et al.*, 2004[200]	?	✓	✗	✗	?	?	?	?
Kakaei *et al.*, 2013[74]	✓	✓	?	✓	?	?	?	✓

Study (author, year)	Random sequence generation	Allocation concealment	Blinding		Incomplete outcome data	Selective reporting	'Other bias'	Overall bias
			Patient	Outcome assessor				
Karalezli *et al.*, 2008[161]	?	?	✓	?	?	?	?	?
Kjaergard and Trumbull, 1998[138]	?	?	?	?	?	?	?	?
Kjaergard and Trumbull, 2000[139]	✗	✗	✗	✗	?	?	?	✗
Kluba *et al.*, 2012[145]	✓	?	?	?	?	?	?	?
Ko *et al.*, 2009[102]	✓	✓	?	✓	?	?	?	?
Kohno *et al.*, 1992[75]	?	✓	?	?	?	?	?	?
Koranyi *et al.*, 2005[162]	✓	✓	?	?	?	?	?	?
Kucukerdonmez *et al.*, 2010[157]	✓	✓	✓	?	?	?	?	✓
Lang *et al.*, 2004[134]	?	?	✗	✗	?	?	?	?
Lassen *et al.*, 2006[141]	✓	?	?	?	?	?	?	?
Lau, 2005[172]	?	✓	?	?	?	?	?	?
Lee *et al.*, 2009[227]	?	?	✗	✓	?	?	?	?
Levy *et al.*, 1999[14]	✓	✓	?	?	?	?	?	?
Lillemoe *et al.*, 2004[83]	✓	?	?	?	?	?	?	?
Lindsey *et al.*, 2002[218]	✓	✓	✗	✗	?	?	?	?
Lionetti *et al.*, 2012[179]	?	?	?	?	?	?	?	?
Liu and Lui, 1993[69]	?	?	?	?	?	?	?	?
Llewellyn-Bennett *et al.*, 2012[101]	✓	✓	✓	✓	?	?	?	✓
Lopez *et al.*, 2013[129]	✓	?	✗	✗	?	?	?	?
Lovisetto *et al.*, 2007[180]	✓	?	✓	✓	?	?	?	?
Luke *et al.*, 1986[223]	?	?	?	?	?	?	?	?
Mabrouk *et al.*, 2013[214]	?	?	?	?	?	?	?	?
Maggiore *et al.*, 2011[233]	✓	✓	x	✓	?	?	?	?
Maharaj *et al.*, 2006[230]	?	✓	✓	✓	?	?	?	?
Maisano *et al.*, 2009[140]	✓	✓	✗	✗	?	?	?	?

continued

TABLE 37 Quality of RCTs (*continued*)

Study (author, year)	Random sequence generation	Allocation concealment	Blinding		Incomplete outcome data	Selective reporting	'Other bias'	Overall bias
			Patient	Outcome assessor				
Malik and Kumar, 2010[171]	?	?	?	?	?	?	?	?
Marchac and Greensmith, 2005[226]	✗	✗	✗	✗	?	?	?	✗
Marta *et al.*, 2010[135]	✓	✓	✗	✗	?	?	?	?
Martin and Au, 2013[86]	✗	✓	✗	✗	?	?	?	✗
Mawatari *et al.*, 2006[152]	✓	✓	?	?	?	?	?	?
McConnell *et al.*, 2011[156]	?	✓	✓	✗	?	?	?	?
McConnell *et al.*, 2012[146]	?	✓	✗	✓	?	?	?	?
Mellin and Kondler, 1989[170]	?	?	?	?	?	?	?	?
Milne *et al.*, 1995[201]	✓	✓	✗	✗	?	?	?	?
Milne *et al.*, 1996[203]	✓	✓	✗	✗	?	?	?	?
Miri Bonjar *et al.*, 2012[103]	?	?	?	?	?	?	?	?
Moench *et al.*, 2010[250]	✓	✓	✓	?	?	?	?	✓
Molloy *et al.*, 2007[147]	✓	✓	✓	✓	?	?	?	✓
Di Monta *et al.*, 2012[117]	?	?	✗	✓	?	?	?	?
Montorsi *et al.*, 2012[84]	✗	?	✗	✗	?	?	?	✗
Moore *et al.*, 1997[106]	✓	?	✓	✗	?	?	?	?
Moore *et al.*, 2001[111]	?	?	?	?	?	?	?	?
Mortenson *et al.*, 2008[120]	✓	✓	?	?	?	?	?	?
Moser *et al.*, 2008[126]	?	✓	✗	✓	?	?	?	?
Mouritzen *et al.*, 1993[132]	?	?	?	?	?	?	?	?
Musella *et al.*, 2014[88]	✓	?	?	?	?	?	?	?
Mustonen *et al.*, 2004[104]	?	?	?	?	?	?	?	?
Nakamura *et al.*, 2005[236]	?	?	?	?	?	?	?	?
Nativ *et al.*, 2012[59]	?	✓	?	?	?	?	?	?

Study (author, year)	Random sequence generation	Allocation concealment	Blinding		Incomplete outcome data	Selective reporting	'Other bias'	Overall bias
			Patient	Outcome assessor				
Neuss *et al.*, 2009[118]	✓	?	✓	?	?	?	?	?
Nielsen *et al.*, 1985[123]	?	?	?	?	?	?	?	?
Noun *et al.*, 1996[70]	?	?	?	?	?	?	?	?
Oliver *et al.*, 2001[228]	✓	✓	?	✓	?	?	?	✓
Oliver *et al.*, 2002[215]	✓	✓	?	?	?	?	?	?
Oliver *et al.*, 2012[87]	✓	✓	?	?	?	?	?	?
Olmi *et al.*, 2007[259]	?	?	✓	✓	?	?	?	?
Pilone *et al.*, 2012[89]	✓	✓	?	?	?	?	?	?
Prado *et al.*, 2006[187]	✓	?	?	✓	?	?	?	?
Pryor *et al.*, 2008[186]	?	✓	?	?	?	?	?	?
Randelli *et al.*, 2014[149]	✓	✓	?	?	?	?	?	?
Ratnalingam *et al.*, 2010[165]	✓	✓	?	?	?	?	?	?
Rena *et al.*, 2009[127]	?	✓	?	?	?	?	?	?
Rubin *et al.*, 2011[166]	?	?	?	?	?	?	?	?
Sabatini *et al.*, 2012[148]	?	?	?	?	?	?	?	?
Safan *et al.*, 2009[235]	?	?	?	?	?	?	?	?
Saha *et al.*, 2011[204]	?	?	✓	?	?	?	?	?
Saha *et al.*, 2012[197]	?	?	✓	?	?	?	?	?
Sati *et al.*, 2014[163]	✓	?	✓	?	?	?	?	?
Schenk *et al.*, 2002[196]	?	✓	?	?	?	?	?	?
Schenk *et al.*, 2003[195]	✓	✓	?	?	?	?	?	?
Scholz *et al.*, 2002[121]	✓	?	?	?	?	?	?	?
Schultz and Christiansen, 1985[224]	?	?	?	?	?	?	?	?
Schwartz *et al.*, 2004[77]	✓	✓	?	✓	?	?	?	✓
Segura-Castillo *et al.*, 2005[105]	?	?	?	?	?	?	?	?

continued

TABLE 37 Quality of RCTs (*continued*)

Study (author, year)	Random sequence generation	Allocation concealment	Blinding		Incomplete outcome data	Selective reporting	'Other bias'	Overall bias
			Patient	Outcome assessor				
Sharma *et al.*, 2003[164]	✓	?	?	?	?	?	?	?
Shiono *et al.*, 1998[261]	✓	?	?	?	?	?	?	?
Siemer *et al.*, 2007[221]	✓	✓	✗	✗	?	?	?	?
Siim *et al.*, 1994[114]	?	?	?	?	✗	?	?	?
Silecchia *et al.*, 2008[62]	✓	✓	✗	✗	?	?	?	?
Simonato *et al.*, 2009[119]	?	?	?	?	?	?	?	?
Sintler *et al.*, 2005[202]	✓	✓	?	?	?	?	?	?
Skovgaard *et al.*, 2013[150]	✓	✓	?	✓	?	?	?	✓
Sözen *et al.*, 2011[212]	?	?	?	?	?	?	?	?
Srinivasan *et al.*, 2009[167]	?	✗	?	✓	?	?	?	?
Sroka *et al.*, 2015[90]	✓	✓	✓	?	?	?	?	✓
Suc *et al.*, 2003[85]	✓	✓	✓	✓	?	?	?	✓
Suzuki *et al.*, 1995[82]	?	✓	?	?	✗	?	?	?
Swan *et al.*, 2011[113]	✓	✓	✓	✓	?	?	?	✓
Tachibana *et al.*, 2003[122]	?	?	?	✓	?	?	?	?
Takeuchi *et al.*, 2005[234]	✗	?	?	?	?	?	?	?
Tavilla *et al.*, 2015[60]	?	?	?	?	?	?	?	?
Taylor *et al.*, 2003[199]	?	✓	✓	?	?	?	?	?
Tolver *et al.*, 2013[181]	✓	✓	✓	✓	?	?	?	✓
Udén *et al.*, 1993[98]	?	?	?	?	?	?	?	?
Uetsuji *et al.*, 1994[68]	?	?	?	?	✗	?	?	?
Ulusoy *et al.*, 2003[96]	?	?	?	?	?	?	?	?

Study (author, year)	Random sequence generation	Allocation concealment	Blinding		Incomplete outcome data	Selective reporting	'Other bias'	Overall bias
			Patient	Outcome assessor				
Uwiera *et al.*, 2005[225]	✓	✓	✓	✓	?	?	?	✓
Uy *et al.*, 2005[168]	✗	✓	?	?	?	?	?	?
Vaiman *et al.*, 2002[188]	?	?	?	?	?	?	?	?
Vaiman *et al.*, 2005[189]	✓	✓	?	?	?	?	?	?
Vaiman *et al.*, 2005[191]	?	✓	?	?	?	?	?	?
Vaiman *et al.*, 2006[192]	✓	✓	?	?	?	?	?	?
van der Hagen *et al.*, 2011[220]	✓	✓	?	?	?	?	?	?
Vanscheidt *et al.*, 2007[208]	?	?	✗	✗	?	?	?	?
Vaxman *et al.*, 1995[251]	?	?	?	?	?	?	?	?
Verhoef *et al.* 2015[240]	?	?	?	?	?	?	?	?
Wang *et al.*, 2001[144]	?	?	?	?	?	?	?	?
Wang *et al.*, 2003[153]	✓	✓	?	?	?	?	?	?
Wong *et al.*, 2011[182]	✓	✓	?	?	?	?	?	?
Yu *et al.*, 2014[190]	✓	✓	?	?	?	?	?	?
Yüksel *et al.*, 2010[158]	✗	✗	?	?	?	?	?	✗
Zhibo and Miaobo, 2009[95]	?	?	?	?	?	?	?	?

✓, low risk of bias; ?, unclear risk of bias; ✗, high risk of bias.
Owing to the nature of the intervention, surgeons could not be blinded to the intervention as they had to apply the fibrin sealant.

TABLE 38 Quality of observational studies

Study (author, year)	Were the adverse events assessed independently?	Are the measurement instruments described?	Is the timing and duration of follow-up reported?	Was a standard or validated measurement instrument used?	Were the measurements objective?	Was the adverse effect(s) attributed to the intervention?	Was the process blinded to the assigned treatment?	Are the terms used to identify adverse events clearly explained?	Are all adverse events from the population reported?
Cagatay *et al.*, 2014[242]	✓	✗	✗	✗	✗	✓	✗	✓	✓
Jiang *et al.*, 2008[243]	✗	✓	✓	✓	?	✗	?	✓	✓
Choi *et al.*, 2010[244]	✗	✗	✗	✗	✗	✓	✗	✓	✓
Efthimiou *et al.*, 2010[245]	✗	✓	✗	?	?	✓	?	✓	✓
Ibele *et al.*, 2014[246]	✗	✓	✓	✓	?	✓	✗	✓	✓
Nanashima *et al.*, 2012[247]	✗	✗	✗	✗	✗	✓	✗	✓	✓
Marchac and Sándor, 1994[248]	✗	✓	✗	✗	✗	✓	✗	✓	✓
Sakic *et al.*, 2013[249]	✓	✓	✓	✓	✓	✓	✗	✓	✓

✓, yes; ?, unclear; ✗, no.

Appendix 6 Funnel plots for meta-analyses

Primary outcomes

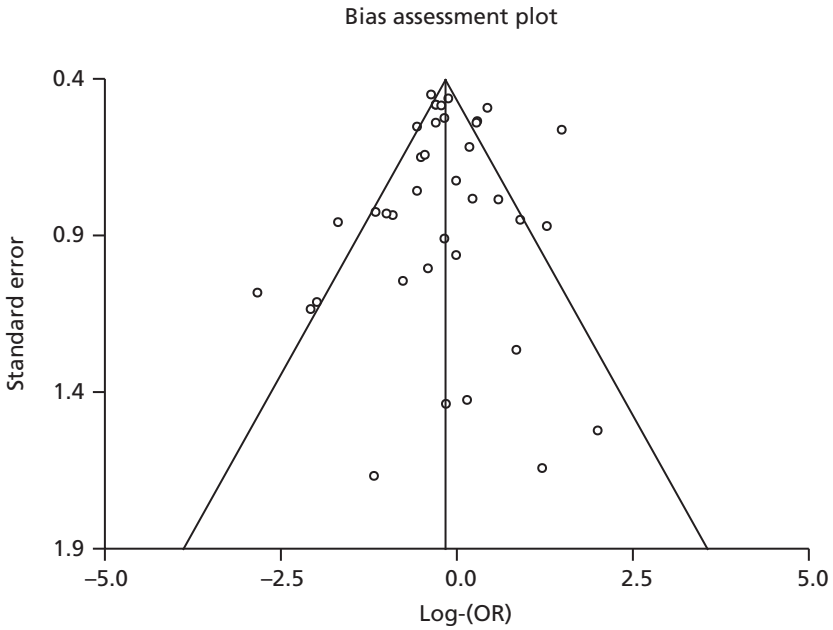

FIGURE 42 Funnel plot for the seroma. Egger bias = –0.47 (95% CI –1.50 to 0.56; $p = 0.36$).

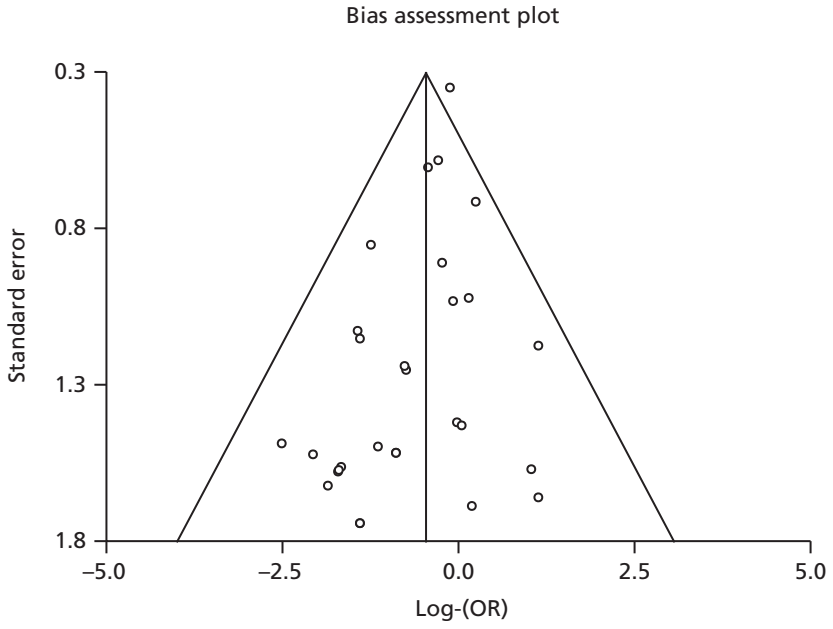

FIGURE 43 Funnel plot for haematoma. Egger bias = –0.63 (95% CI –1.20 to –0.06; $p = 0.03$).

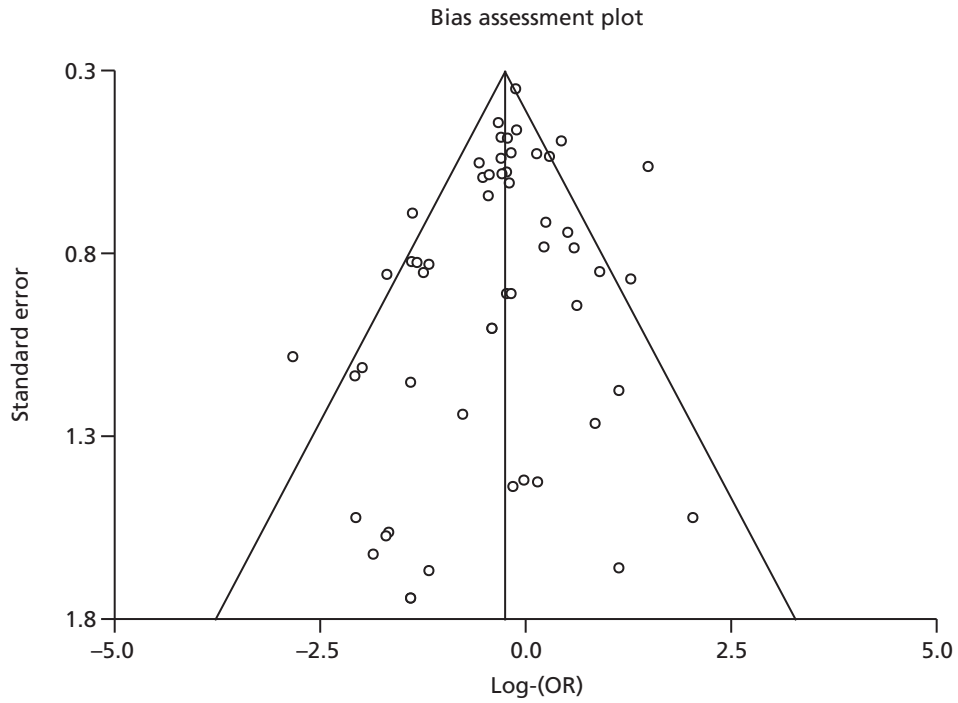

FIGURE 44 Funnel plot for combined seroma and haematoma. Egger bias = –0.67 (95% CI –1.38 to 0.03; $p = 0.06$).

Secondary outcomes

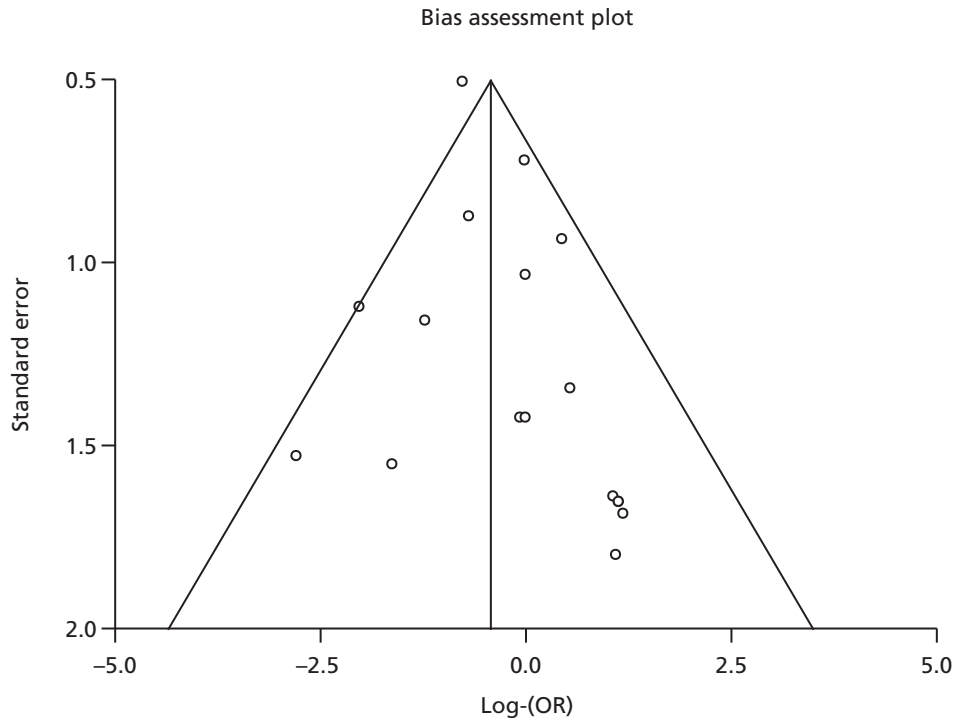

FIGURE 45 Funnel plot for haemorrhage (bleeding). Egger bias = 0.65 (95% CI –0.53 to 1.82; $p = 0.26$).

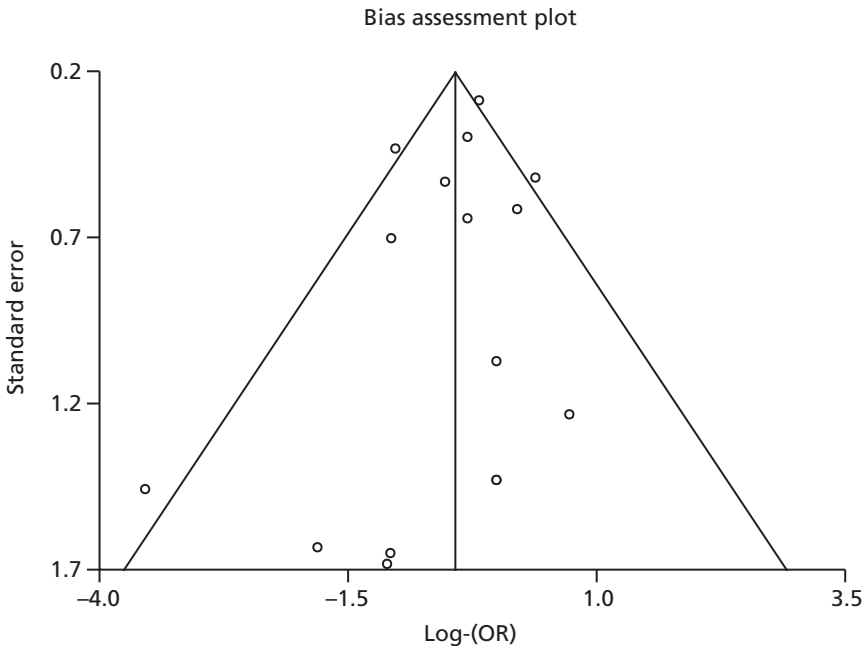

FIGURE 46 Funnel plot for reoperation. Egger bias = –0.47 (95% CI –1.47 to 0.53; $p = 0.33$).

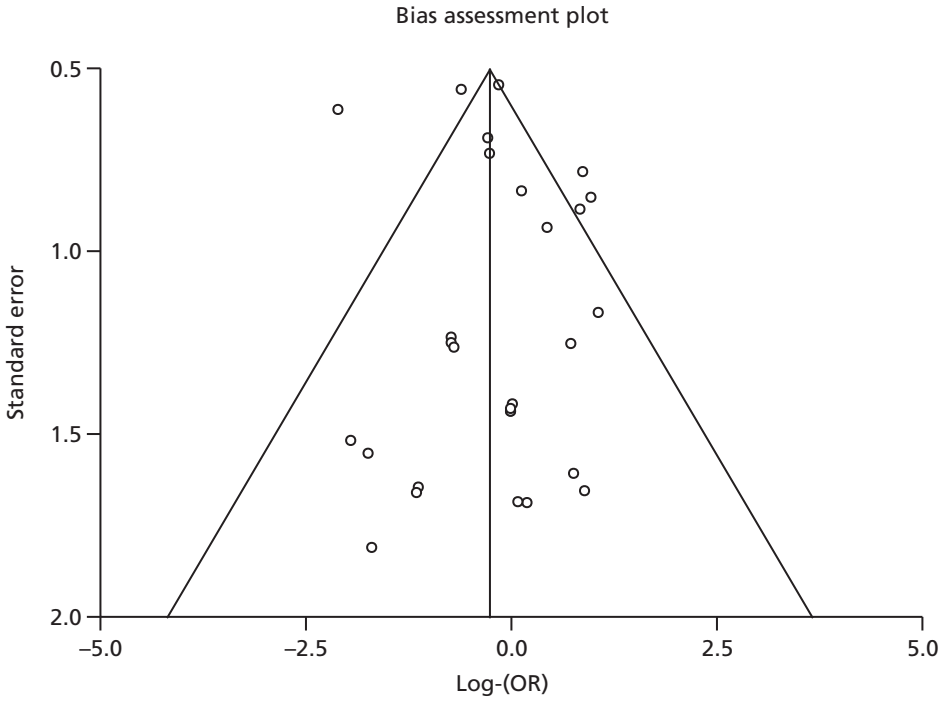

FIGURE 47 Funnel plot for infections. Egger bias = 0.22 (95% CI –0.74 to 1.18; $p = 0.64$).

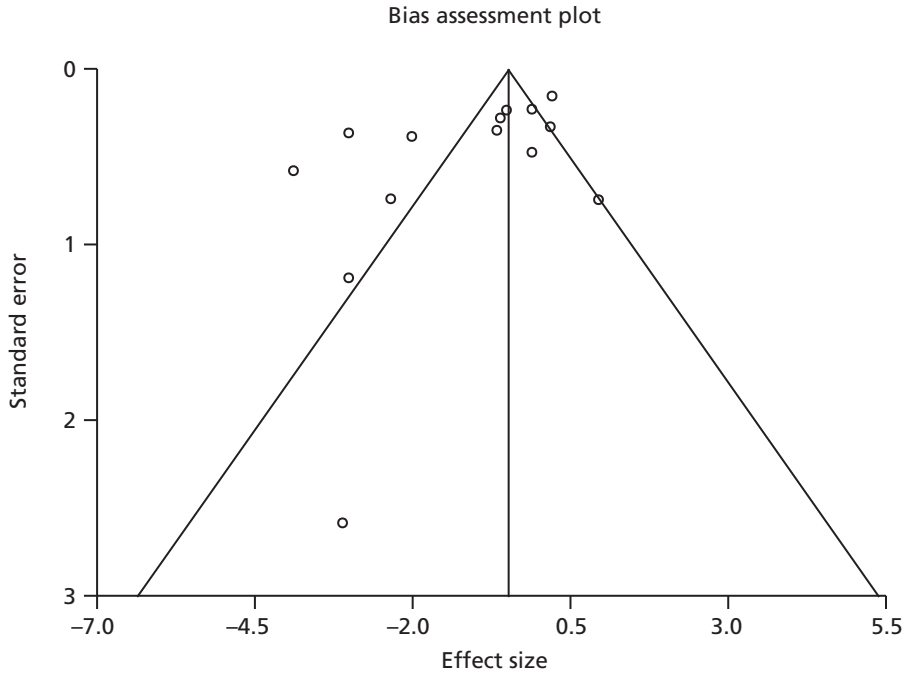

FIGURE 48 Funnel plot for duration of drainage in breast surgery. Egger bias = –3.40 (95% CI –6.75 to –0.05; $p = 0.05$).

No funnel plot for the duration of operation and length of hospital stay meta-analysis is reported as there was an insufficient number of studies (< 10).

Appendix 7 Tables of excluded observational studies

TABLE 39 Excluded observational studies

Study excluded	Reason for exclusion
Abdeen K, Kato Y, Kiya N, Yoshida K, Kanno T. Neuroendoscopy in microvascular decompression for trigeminal neuralgia and hemifacial spasm: technical note. *Neurol Res* 2000;**22**:522–6	No comparison group
Abdulla A, Neff M. Laparoscopic repair of perforated duodenal ulcer in child's class C cirrhotic patient. *Surg Endosc* 2011;**25**:S364	No comparison group
Abe T, Goda M, Kamida T, Fujiki M, Kobayashi H, Nakano T, *et al.* Overlapping free bone graft with galea-pericranium in reconstruction of the anterior skull base to prevent CSF leak and sequestrum formation. *Acta Neurochir* 2007;**149**:771–5	Not a comparative observational study
Abel ME, Chiu YS, Russell TR, Volpe PA. Autologous fibrin glue in the treatment of rectovaginal and complex fistulas. *Dis Colon Rectum* 1993;**36**:447–9	No comparison group
Abu Hilal M, Hallam MJ, Zeidan BA, Pearce NW. Management of a ruptured pseudoaneurysm of common hepatic artery following pancreaticoduodenectomy. *Sci World J* 2007;**7**:1658–62	No comparison group
Abuzayed B, Kafadar AM, Oğuzoğlu SA, Canbaz B, Kaynar MY. Duraplasty using autologous fascia lata reinforced by on-site pedicled muscle flap: technical note. *J Craniofac Surg* 2009;**20**:435–8	No comparison group
Achauer BM, Miller SR, Lee TE. The hemostatic effect of fibrin glue on graft donor sites. *J Burn Care Rehabil* 1994;**15**:24–8	RCT
Acholonu E, Eckstein J, Patel S, Abu-Jaish W, Szomstein S. Indications, complications and long term outcomes of remnant gastrectomy for gastrogastric fistula after divided Roux-en-Y gastric bypass for morbid obesity. *Surg Endosc* 2010;**24**(Suppl. 1):300	No comparison group
Acholonu E, Eckstein J, Patel S, Szomstein S, Rosenthal RJ. Indications, complications and long term outcomes of remnant gastrectomy for gastro-gastric fistula after divided Roux-en-Y gastric bypass for morbid obesity. *Obes Surg* 2010;**20**:1005	Duplicate
Adamian LV, Mynbaev OA, Dzhakhan I. [The use of fibrin glue in obstetrics and gynecology.] *Akush Ginekol* 1991;**11**:3–4	Not a comparative observational study
Agarwal A, Kumar DA, Jacob S, Baid C, Agarwal A, Srinivasan S. Fibrin glue-assisted sutureless posterior chamber intraocular lens implantation in eyes with deficient posterior capsules. *J Cataract Refract Surg* 2008;**34**:1433–8	Not a comparative observational study
Aghamir SM, Khazaeli MH, Meisami A. Use of Surgicel for sealing nephrostomy tract after totally tubeless percutaneous nephrolithotomy. *J Endourol* 2006;**20**:293–5	RCT
Agha-Mir-Salim P, Beck R, Bloching M, Berghaus A. [Endoscopic treatment of iatrogenic esophageal perforation.] *Laryngorhinootologie* 2000;**79**:39–42	No comparison group
Agresta F. Re: Spray application of fibrin glue as risk factor for subcutaneous emphysema in laparoscopic transabdominal inguinal hernia repair. *Surg Laparosc Endosc Percutan Tech* 2007;**17**:222	Letter/commentary/reply
Agresta F, Baldazzi GA, Ciardo LF, Trentin G, Giuseppe S, Ferrante F, *et al.* Lightweight partially absorbable monofilament mesh (polypropylene/poliglecaprone 25) for TAPP inguinal hernia repair: Initial experience. *Surg Laparosc Endosc Percutan Tech* 2007;**17**:91–4	No comparison group
Agresta F, Bedin N. Transabdominal laparoscopic inguinal hernia repair: is there a place for biological mesh? *Hernia* 2008;**12**:609–12	No comparison group
Aguilar PH, De Oliveira EP. The use of fibrin glue to stop venous bleeding in the epidural space, vertebral venous plexus, and anterior cavernous sinus: Technical note – commentary. *Neurosurgery* 2007;**61**(Suppl.):E51	Letter/commentary/reply

continued

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Aguilera *et al.* 2013[143]	RCT
Agus GB, Bono AV, Mira E, Olivero S, Peilowich A, Homdrum E, *et al.* Hemostatic efficacy and safety of TachoComb in surgery. Ready to use and rapid hemostatic agent. *Int Surg* 1996;**81**:316–19	No comparison group
Aida H, Kagaya S. [Successful repair of left ventricular free wall rupture with repeated mydriasis and loss of light reflex.] *Kyobu Geka* 2011;**64**:1168–71	No comparison group
Aigner C, Wolner E, Mohl W. Management of central coronary sinus ruptures using the pericardial patch repair technique. *Ann Thorac Surg* 2006;**81**:1275–8	No comparison group
Aitola P, Hiltunen KM, Matikainen M. Fibrin glue in perianal fistulas – a pilot study. *Ann Chir Gynaecol* 1999;**88**:136–8	No comparison group
Ak G, Alpkılıç Başkırt E, Kürklü E, Koray M, Tanyeri H, Zülfikar B. The evaluation of fibrin sealants and tissue adhesives in oral surgery among patients with bleeding disorders. *Turk J Haematol* 2012;**29**:40–7	RCT
Akaogi E, Mitsui K, Sohara Y, Endo S, Ishikawa S, Hori M. Treatment of postoperative chylothorax with intrapleural fibrin glue. *Ann Thorac Surg* 1989;**48**:116–18	No comparison group
Akhras J, Tobi M, Zagnoon A. Endoscopic fibrin sealant injection with application of hemostatic clips: a novel method of closing a refractory gastrocutaneous fistula. *Dig Dis Sci* 2005;**50**:1872–4	No comparison group
Al Harakeh AB. Complications of laparoscopic Roux-en-Y gastric bypass. *Surg Clin North Am* 2011;**91**:1225–37	Not fibrin sealant
Alashwal AH, Yaakub A, Noor RAM, Tajudin LSA. Fibrin glue for sealing early bleb leak: a case report. *Int J Ophthalmol* 2009;**9**:831–2	No comparison group
Albala DM, Wood C, Fischer C, Hart J, Batiller J, Shen J. A randomized trial of aprotinin free fibrin sealant versus absorbable hemostat. *J Endourol* 2011;**25**:A95	RCT
Albéniz Arbizu E, López San Román A, Garcia González M, Foruny Olcina JR, Garcia-Hoz Rosales F, Bárcena Marugán R, *et al.* Fibrin-glue sealed liver biopsy in patients with a liver transplantation or in liver transplantation waiting list: preliminary results. *Transplant Proc* 2003;**35**:1911–12	No comparison group
Albera R, Canale A, Lacilla M, Cavalot AL, Ferrero V. Delayed vertigo after stapes surgery. *Laryngoscope* 2004;**114**:860–2	No comparison group
Albert JG. Closure of an ischemic duodenal fistula with an over-the-scope clip. *Video J Encyclopedia GI Endosc* 2013;**1**:219–20	No comparison group
Ali A, Zayed H, Kizilates K, El Sakka K, Brown J, Halawa M, *et al.* The feasibility and safety of drainless carotid endarterectomy. *Interact Cardiovasc Thorac Surg* 2009;**8**:S72	No comparison group
Ali SN, Gill P, Oikonomou D, Sterne GD. The combination of fibrin glue and quilting reduces drainage in the extended latissimus dorsi flap donor site. *Plast Reconstr Surg* 2010;**125**:1615–19	RCT
Alibai EA, Rahmanian AK, Razmkon A, Nabavizadeh SA. Tension pneumocephalus following pterional craniotomy for treatment of intracavernous internal carotid artery aneurysm. *Emerg Radiol* 2008;**15**:441–4	No comparison group
Alio JL, Mulet E, Sakla HF, Gobbi F. Efficacy of synthetic and biological bioadhesives in scleral tunnel phacoemulsification in eyes with high myopia. *J Cataract Refract Surg* 1998;**24**:983–8	RCT
Alio JL, Rodriguez AE, Martinez LM, Rio AL. Autologous fibrin membrane combined with solid platelet-rich plasma in the management of perforated corneal ulcers: a pilot study. *JAMA Ophthalmol* 2013;**131**:745–51	No comparison group
Alizadeh Ghavidel A, Mirmesdagh Y, Samiei N, Gholampour Dehaki M. Haemostatic role of TachoSil surgical patch in cardiac surgery. *J Cardiovasc Thorac Res* 2014;**6**:91–5	No adverse effects related to fibrin reported
Al-khudari S, Vitale L, Ghanem T, McLean S. Recurrent high output chyle fistula post neck dissection resolution with conservative management. *Laryngoscope* 2010;**120**(Suppl. 4):141	No comparison group

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Allende CA, Allende BT, Allende BL, Bitar I, Gonzalez G. Intercondylar distal humerus fractures – surgical treatment and results. *Chir Main* 2004;**23**:85–95	No adverse effects related to fibrin reported
Alleyne Jr CH, Pearce JE. Nonsuture dural repair using polyglycolic acid mesh and fibrin glue: clinical application to spinal surgery – commentary. *Surg Neurol* 2006;**65**:142–3	Letter/commentary/reply
Almer ZE, Miller NR. Delayed third cranial nerve palsy after aneurysm wrapping. *J Neuroophthalmol* 2008;**28**:359	Letter/commentary/reply
Al-Mutairi M, AlEnezi F, Al-Einati T. Left main coronary artery ostial stenosis with biologic glue post-Bentall procedure. *Kuwait Med J* 2008;**40**:321–3	No comparison group
Al-Qahtani K. Initial experience with hemostatic fibrin glue as adjuvant during drainless parotidectomy. *Saudi Dent J* 2011;**23**:67–71	No comparison group
Altomare *et al.* 2011[217]	RCT
Alvarez JA, Bermejo F, Algaba A, Hernandez MP, Grau M. Surgical repair and biological therapy for fecal incontinence in Crohn's disease involving both sphincter defects and complex fistulas. *J Crohns Colitis* 2011;**5**:598–607	No comparison group
Rubio Alvarez J, Sierra Quiroga J, Martinez de Alegria A, Delgado Dominguez C. Pulmonary embolism due to biological glue after repair of type A aortic dissection. *Interact Cardiovasc Thorac Surg* 2011;**12**:650–1	No comparison group
Al-Yamany M, Del Maestro RF. Prevention of subdural fluid collections following transcortical intraventricular and/or paraventricular procedures by using fibrin adhesive. *J Neurosurg* 2000;**92**:406–12	Included children
Amano J, Suzuki A. Surgical treatment of cardiac involvement in Takayasu arteritis. *Heart Vessels* 1992;**7**(Suppl. 7):168–78	No comparison group
Ambriz-Gonzalez G, Velazquez-Ramirez GA, Garcia-Gonzalez JL, De Leon-Gomez JMG, Mucino-Hernandez MI, Gonzalez-Ojeda A, *et al.* Use of fibrin sealant in hypospadias surgical repair reduces the frequency of postoperative complications. *Urol Int* 2007;**78**:37–41	Included children
Ambruoso G, Aimè G, Borsa R, Cordara G, Governa G, Polledro P, *et al.* [Urethro-vesical anastomosis after radical prostatectomy and bladder replacement with the Camey II approach.] *Minerva Urol Nefrol* 1994;**46**:159–61	No comparison group
Anagiotos A, Feyka M, Gostian AO, Lichtenstein T, Henning TD, Guntinas-Lichius O, *et al.* Endoscopic laser-assisted diverticulotomy without versus with wound closure in the treatment of Zenker's diverticulum. *Eur Arch Otorhinolaryngol* 2014;**271**:765–70	No comparison group
Anderson NJ, Hardten DR. Fibrin glue for the prevention of epithelial ingrowth after laser in situ keratomileusis. *J Cataract Refract Surg* 2003;**29**:1425–9	No comparison group
Andree C, Munder BIJ, Behrendt P, Hellmann S, Audretsch W, Voigt M, *et al.* Improved safety of autologous breast reconstruction surgery by stabilisation of microsurgical vessel anastomoses using fibrin sealant in 349 free DIEP or fascia-muscle-sparing (fms)-TRAM flaps: a two-centre study. *Breast* 2008;**17**:492–8	No comparison group
Andress HJ, Mewes A, Lange V. Endoscopic hemostasis of a bleeding diverticulum of the sigma with fibrin sealant. *Endoscopy* 1993;**25**:193	Letter/commentary/reply
Andrychowski J, Czernicki Z, Taraszewska A, Frontczak-Baniewicz M, Przytula E, Zebala M. Granulomatous inflammation of dura mater – a rare side effect after application of hemostatic and insulation materials in case of two-stage operation of huge meningioma. *Folia Neuropathol* 2012;**50**:417–24	No comparison group
Angioli R, Plotti F, Ricciardi R, Terranova C, Zullo MA, Damiani P, *et al.* The use of novel hemostatic sealant (Tisseel) in laparoscopic myomectomy: a case-control study. *Surg Endosc* 2012;**26**:2046–53	RCT
Anonymous. [Additional aerostasis with a 100% autologous fibrin glue in lung surgery – a prospective randomised trial.] *Khirurgiia* 2009;**1**:10–18	RCT
Anonymous. Additional aerostasis with a 100% autologous fibrin glue in lung surgery – a prospective randomised trial. *Khirurgiia* 2009;**1**:10–18	No comparison group

continued

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Anwar HM, El-Danasoury A, Hashem AN. The use of fibrin glue to seal Descemet membrane microperforations occurring during deep anterior lamellar keratoplasty. *Cornea* 2012;**31**:1193–6	No comparison group
Apestegui C, Breitenstein S, Dutkowski P, Clavien PA. Control of severe portal bleeding by carrier-bound fibrin sealant. *Surg Today* 2009;**39**:363–5	No comparison group
Arbes H, Bosch P, Lintner F, Salzer M. First clinical experience with heterologous cancellous bone grafting combined with the fibrin adhesive system (F.A.S.). *Arch Orthop Trauma Surg* 1981;**98**:183–8	No comparison group
Argiriou M, Patris V, Lama N, Argiriou O, Charitos C. Off pump repair of left ventricular rupture following mitral valve replacement: the crucial assistance of the intraaortic balloon pump. *Int J Surg Case Rep* 2013;**4**:5–6	No comparison group
Arlt F, Trantakis C, Krupp W, Renner C, Winkler D, Strauss G, *et al.* Cerebrospinal fluid leak after microsurgical surgery in vestibular schwannomas via retrosigmoidal craniotomy. *Neurol Res* 2011;**33**:947–52	No comparison group
Arndt S, Maier W, Aschendorff A, Klenzner T, Schipper J. [Ethisorb/Ethisorb durapatch for the transnasal duraplasty procedure?] *Laryngorhinootologie* 2006;**85**:260–4	No comparison group
Asato R, Honda K, Tsuji J, Kanda T, Ushiro K, Wtanabe Y. A new method of covering mucosal defect after oral cancerresection – a combination of polyglycolic acid (PGA) sheet and sprayed fibrin glue. *Oral Oncol* 2011;**47**:S150–1	Not fibrin sealant
Asensio Samper JM, Fabregat Cid G, Valia-Vera JC, De Andres JA. [Epidural fibrin glue injection as a conservative treatment for persistent cerebrospinal fluid leakage after spinal catheterization.] *Rev Esp Anestesiol Reanim* 2011;**58**:391–3	Letter/commentary/reply
Asrani SG, Wilensky JT. Management of bleb leaks after glaucoma filtering surgery. Use of autologous fibrin tissue glue as an alternative. *Ophthalmology* 1996;**103**:294–8	No comparison group
Assalia A. A novel method for the management of gastric fistula complicating laparoscopic sleeve gastrectomy: biological glue application in a combined percutaneous and endoscopic approach. *Obes Surg* 2014;**24**:1145	No comparison group
Atallah J, Gage E, Koning J, Duggan J, Ramsey-Williams V, Scott S, *et al.* Treatment of post-dural puncture headache using epidural injection of fibrin sealant as an alternative to autologous epidural blood patch (case report). *Scand J Pain* 2014;**5**:170–2	No comparison group
Athanasiadis S, Kuhlgatz C, Girona I. [Experiences with fibrin adhesives in surgery of the rectum and colon.] *Zentralbl Chir* 1984;**109**:1107–11	No comparison group
Athanassiadi K, Kalavrouziotis G, Bellenis I. Bronchopleural fistula after pneumonectomy: a major challenge. *Acta Chir Hung* 1999;**38**:5–7	Not fibrin sealant
Aurangzeb A, Ahmed E, Khan SA, Ali A, Ihsan A, Mehmood S. Outcome of transcranial repair of traumatic CSF rhinorrhea. *J Ayub Med Coll Abbottabad* 2012;**24**:47–9	No comparison group
Avalos-Gonzalez J, Portilla-deBuen E, Leal-Cortes CA, Orozco-Mosqueda A, Estrada-Aguilar MC, Velazquez-Ramirez GA, *et al.* Reduction of the closure time of postoperative enterocutaneous fistulas with fibrin sealant. *World J Gastroenterol* 2010;**16**:2793–800	No adverse effects related to fibrin reported
Avanoglu A, Celik A, Ulman I, Ozcan C, Kavakli K, Nişli G, *et al.* Safer circumcision in patients with haemophilia: the use of fibrin glue for local haemostasis. *BJU Int* 1999;**83**:91–4	Included children
Avisar R, Vaiman M, Sarfaty S, Shlamkovich N, Segal S, Eviatar E, *et al.* Using fibrin glue in endonasal surgery (multiple letters). *Isr Med Assoc J* 2005;**7**:823–4	Letter/commentary/reply
Aydin A, Ozden BC, Mersa B. Complications of microsurgical reconstruction of obstetrical brachial plexus palsy. *Plast Reconstr Surg* 2005;**115**:353–4	Letter/commentary/reply
Aydin K, Cokluk C, Kocabicak E, Celik B, Taslak Sengul A. Cervical screw extrusion into the trachea leading to perforation: a case report. *Chirurgia* 2012;**25**:355–7	Not fibrin sealant
Ayloo S, Bueno R. Band erosion: laparoscopic removal of lap-band. *Surg Endosc* 2009;**23**:657–8	No comparison group

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Bacciu A, Falcioni M, Pasanisi E, Di Lella F, Lauda L, Flanagan S, *et al.* Intracranial facial nerve grafting after removal of vestibular schwannoma. *Am J Otolaryngol* 2009;**30**:83–8	No comparison group
Bachet J, Gigou F, Laurian C, Bical O, Goudot B, Guilmet D. Four-year clinical experience with the gelatin-resorcine-formol biological glue in acute aortic dissection. *J Thorac Cardiovasc Surg* 1982;**83**:212–17	Not fibrin sealant
Bachleda P, Utikal P, Kalinova L, Herman J. TachoSil® in the treatment of postoperative groin lymphatic fistula. *Ann Acad Med Singap* 2012;**41**:534–5	Letter/commentary/reply
Bagot d'Arc M, Daculsi G, Emam N. Biphasic ceramics and fibrin sealant for bone reconstruction in ear surgery. *Ann Otol Rhinol Laryngol* 2004;**113**:711–20	No comparison group
Bahar *et al.* 2006[159]	RCT
Bahar *et al.* 2007[169]	RCT
Bailey SH, Oni G, Guevara R, Wong C, Saint-Cyr M. Latissimus dorsi donor-site morbidity: the combination of quilting and fibrin sealant reduce length of drain placement and seroma rate. *Ann Plast Surg* 2012;**68**:555–8	No adverse effects related to fibrin reported
Baiocchi G, Portolani N, Gheza F, Giulini SM. Collagen-based biological glue after Appleby operation for advanced gastric cancer. *World J Gastroenterol* 2011;**17**:4044–7	No comparison group
Bajardi *et al.* 2009[194]	RCT
Bakeer M, Abd El-Gawad T, El-Metwaly Ali R, El-Morsi A, El-Badrawy M, El-Sharawy S. Low cost biological lung volume reduction therapy for advanced emphysema. *Eur Respir J* 2014;**44**(Suppl. 58):P3705	Abstract
Balint B, Gazivoda D, Todorovic-Balint M, Lazic Z, Pavlovic M, Kanjuh V. 'Triple-way' approach for the treatment of dry socket: surgery and drugs plus fibrin sealant – as a biomatrix for 'ultra-concentrated' platelets. *Transfus Apher Sci* 2014;**51**:221–2	Letter/commentary/reply
Bänninger H, Hardegger T, Tobler A, Barth A, Schüpbach P, Reinhart W, *et al.* Fibrin glue in surgery: frequent development of inhibitors of bovine thrombin and human factor V. *Br J Haematol* 1993;**85**:528–32	No comparison group
Barbagli G, De Stefani S, Sighinolfi MC, Annino F, Micali S, Bianchi G. Bulbar urethroplasty with dorsal onlay buccal mucosal graft and fibrin glue. *Eur Urol* 2006;**50**:467–74	No comparison group
Barbosa MD, Gregh SL, Passanezi E. Fibrin adhesive derived from snake venom in periodontal surgery. *J Periodontol* 2007;**78**:2026–31	No adverse effects related to fibrin reported
Bardaxoglou E, Campion JP, Landen S, Manganas D, Siriser F, Chareton B, *et al.* Oesophageal perforation: primary suture repair reinforced with absorbable mesh and fibrin glue. *Br J Surg* 1994;**81**:399	No comparison group
Barthelemy C, Fayard MO, Etaix JP, Audigier JC, Fraisse H. [Esophagobronchial fistula following sclerosis of esophageal varices. Treatment by injection of biological glue.] *Gastroenterol Clin Biol* 1984;**8**:772–3	Unobtainable
Basmak H, Erdogan H, Sahin A, Gürsoy H. Scleral dellen after fibrin glue use in strabismus surgery. *J Pediatr Ophthalmol Strabismus* 2010;**47**:e1–3	No comparison group
Basmak H, Gursoy H, Cakmak Aİ, Niyaz L, Yildirim N, Sahin A. Tissue adhesives as an alternative for conjunctival closure in strabismus surgeries. *Strabismus* 2011;**19**:59–62	Included children
Basso N. Staple-line leaks management after laparoscopic sleeve gastrectomy. *Obes Surg* 2009;**19**:1050	Not fibrin sealant
Batman C, Ozdamar Y, Aslan O, Sonmez K, Mutevelli S, Zilelioglu G. Tissue glue in sutureless vitreoretinal surgery for the treatment of wound leakage. *Ophthalmic Surg Lasers Imaging* 2008;**39**:100–6	No comparison group
Batman C, Ozdamar Y, Mutevelli S, Sonmez K, Zilelioglu G, Karakaya J. A comparative study of tissue glue and vicryl suture for conjunctival and scleral closure in conventional 20-gauge vitrectomy. *Eye* 2009;**23**:1382–7	Not a comparative observational study

continued

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Baumann P, Schumacher H, Husing J, Luntz S, Knaebel HP. A randomized, controlled, prospective trial to evaluate the haemostatic effect of Lyostypt versus Surgicel in arterial bypass anastomosis: 'COBBANA' trial. 2009;**10**:91	RCT
Baumann WR, Ulmer JL, Ambrose PG, Garvey MJ, Jones DT. Closure of a bronchopleural fistula using decalcified human spongiosa and a fibrin sealant. *Ann Thorac Surg* 1997;**64**:230–3	No comparison group
Bazan A, Samper A, Lasso JM. The use of fibrin glue in vaginal reconstruction with a pudendal thigh flap. *Ann Plast Surg* 1999;**43**:576	Letter/commentary/reply
Beer GM, Goldscheider E, Weber A, Lehmann K. Prevention of acute hematoma after face-lifts. *Aesthetic Plast Surg* 2010;**34**:502–7	Not a valid comparison
Beese RC, Tomlinson MA, Buckenham TM. Endoluminal embolization of bilateral atherosclerotic common iliac aneurysms with fibrin tissue glue (Beriplast). *Cardiovasc Intervent Radiol* 2000;**23**:239–41	No comparison group
Beierlein W, Scheule AM, Antoniadis G, Braun C, Schosser R. An immediate, allergic skin reaction to aprotinin after reexposure to fibrin sealant. *Transfusion* 2000;**40**:302–5	No comparison group
Beitzke M, Leber KA, Deutschmann H, Gattringer T, Poltrum B, Fazekas F. Cerebrovascular complications and granuloma formation after wrapping or coating of intracranial aneurysms with cotton gauze and human fibrin adhesives: results from a single-center patient series over a 5-year period. *J Neurosurg* 2013;**119**:1009–14	Not a valid comparison
Bekkers JA, Raap GB, Takkenberg JJ, Bogers AJ. Acute type A aortic dissection: long-term results and reoperations. *Eur J Cardiothorac Surg* 2013;**43**:389–96	Not a valid comparison
Bektas H, Nadalin S, Schmidt J, Szabo I, Ploder B, Sharkhawy M. Hemostatic efficacy of latest generation fibrin sealant after hepatic resection; a randomized controlled clinical study. *HPB* 2013;**15**:6–7	RCT
Bektas *et al.* 2014[65]	RCT
Belboul *et al.* 2004[133]	RCT
Belcher *et al.* 2010[136]	RCT
Bellini LP, Brum GS. Cataract incision closure using fibrin adhesive. *J Cataract Refract Surg* 2008;**34**:343–4	Letter/commentary/reply
Benevento *et al.* 2014[109]	No comparison group
Benfatto G, Benfatto SM, Strazzanti A, Giovinetto RM, Jiryis A, Salina GM, *et al.* [Fibrin sealant in tension free hernioplasty: our experience.] *G Chir* 2006;**27**:392–4	No adverse effects related to fibrin reported
Benizri EI, Rahili A, Avallone S, Balestro JC, Caï J, Benchimol D. Open inguinal hernia repair by plug and patch: the value of fibrin sealant fixation. *Hernia* 2006;**10**:389–94	No adverse effects related to fibrin reported
Benkó I, Molnár TF, Horváth OP. A case of fibrin sealant application for closing benign trachea-esophageal fistula (TEF). *Acta Chir Hung* 1997;**36**:25–6	No comparison group
Bense L. Intrabronchial selective coagulative treatment of hemoptysis. Report of three cases. *Chest* 1990;**97**:990–6	RCT
Benyamini OG, Barkana Y, Hartstein M, Attas L, Avni I, Zadok D. Biological glue in pterygium surgery with a rotational flap or sliding flaps. *Cornea* 2008;**27**:911–15	No comparison group
Beppu T, Iwatsuki M, Okabe H, Okabe K, Masuda T, Hayashi H, *et al.* A new approach to percutaneous transhepatic portal embolization using ethanolamine oleate iopamidol. *J Gastroenterol* 2010;**45**:211–17	Not a valid comparison
Bercial *et al.* 2012[213]	RCT
Berg PL, Barina W, Born P. Endoscopic injection of fibrin glue versus polidocanol in peptic ulcer hemorrhage: a pilot study. *Endoscopy* 1994;**26**:528–30	RCT
Berger *et al.* 2001[107]	RCT

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Bergeron E, Roux A, Demers J, Vanier LE, Moore L. A 40-year-old woman with cauda equina syndrome caused by rectothecal fistula arising from an anterior sacral meningocele. *Neurosurgery* 2010;**67**:E1464–7	No comparison group
Berkoff DJ, Kanaan M, Kamath G. Fibrin glue as a non-invasive outpatient treatment for post-arthroscopic knee seromas. *Knee Surg Sports Traumatol Arthrosc* 2013;**21**:1922–4	No comparison group
Bernal JM, Naranjo S, Trugeda M, Sarralde A, Diago C, Revuelta JM. [Cardiac surgery in Jehovah's Witnesses. Experience in Santander, Spain.] *Rev Esp Cardiol* 2006;**59**:507–9	No comparison group
Bernard RW, Greenwald JA, Beran SJ, Morello DC. Enhancing upper lid aesthetics with the lateral subcutaneous brow lift. *Aesthet Surg J* 2006;**26**:19–23	No comparison group
Bernardo L, Bernardo WM, Shu EB, Roz LM, Almeida CC, Monaco BA, *et al.* Does the use of DuraSeal in head and spinal surgeries reduce the risk of cerebrospinal fluid leaks and complications when compared to conventional methods of dura mater closure? *Rev Assoc Med Bras* 2012;**58**:402–3	Not fibrin sealant
Bernasek TL, Burris RB, Fujii H, Levering MF, Polikandriotis JA, Patterson JJ. Effect on blood loss and cost-effectiveness of pain cocktails, platelet-rich plasma, or fibrin sealant after total knee arthroplasty. *J Arthroplasty* 2012;**27**:1448–51	No adverse effects related to fibrin reported
Berney CR. The Endoloop technique for the primary closure of direct inguinal hernia defect during the endoscopic totally extraperitoneal approach. *Hernia* 2012;**16**:301–5	No comparison group
Berney CR, Yeo AE. Mesh fixation with fibrin sealant during endoscopic totally extraperitoneal inguinal hernia approach: a review of 640 repairs. *Hernia* 2013;**17**:709–17	No comparison group
Berruyer M, Amiral J, Ffrench P, Belleville J, Bastien O, Clerc J, *et al.* Immunization by bovine thrombin used with fibrin glue during cardiovascular operations. Development of thrombin and factor V inhibitors. *J Thorac Cardiovasc Surg* 1993;**105**:892–7	No comparison group
Berzofsky CE, Holiday RA, Pitman MJ. Variability of postoperative esophagrams after endoscopic cricopharyngeal myotomy: technique dependence. *Ann Otol Rhinol Laryngol* 2012;**121**:145–50	Not fibrin sealant
Bhavana K, Kumar R, Keshri A, Aggarwal S. Minimally invasive technique for repairing CSF leaks due to defects of posterior table of frontal sinus. *J Neurol Surg B Skull Base* 2014;**75**:183–6	No comparison group
Binenbaum SJ, Dressner RM, Borao FJ. Laparoscopic repair of a free perforation of a marginal ulcer after Roux-en-Y gastric bypass: a safe alternative to open exploration. *JSLS* 2007;**11**:383–8	No comparison group
Birmingham B. TEE diagnosis of mechanical AVR dysfunction associated with biological glue. *Anesth Analg* 2001;**93**:1627–8	Letter/commentary/reply
Birth M, Figueras J, Bernardini S, Troen T, Gunther K, Mirza D, *et al.* Collagen fleece-bound fibrin sealant is not associated with an increased risk of thromboembolic events or major bleeding after its use for haemostasis in surgery: a prospective multicentre surveillance study. *Patient Saf Surg* 2009;**3**:13	No comparison group
Bischoff G, Muehling B, Orend K, Bischoff M, Sunder-Plassmann L. A new treatment concept for bronchial stump insufficiency. *Thorac Cardiovasc Surg* 2010;**58**:169–74	Not a valid comparison
Bittner R, Gmähle E, Gmähle B, Schwarz J, Aasvang E, Kehlet H. Lightweight mesh and noninvasive fixation: an effective concept for prevention of chronic pain with laparoscopic hernia repair (TAPP). *Surg Endosc* 2010;**24**:2958–64	No adverse effects related to fibrin reported
Bittner R, Leibl BJ, Kraft B, Schwarz J. One-year results of a prospective, randomised clinical trial comparing four meshes in laparoscopic inguinal hernia repair (TAPP). *Hernia* 2011;**15**:503–10	RCT
Black P. Cerebrospinal fluid leaks following spinal or posterior fossa surgery: use of fat grafts for prevention and repair. *Neurosurg Focus* 2000;**9**:e4	No comparison group
Black P. Cerebrospinal fluid leaks following spinal surgery: use of fat grafts for prevention and repair. Technical note. *J Neurosurg* 2002;**96**(Suppl. 2):250–2	No comparison group

continued

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Blinder D, Manor Y, Martinowitz U, Taicher S, Hashomer T. Dental extractions in patients maintained on continued oral anticoagulant: comparison of local hemostatic modalities. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999;**88**:137–40	No adverse effects related to fibrin reported
Blumenkranz MS, Ohana E, Shaikh S, Chang S, Coll G, Morse LS, *et al.* Adjuvant methods in macular hole surgery: intraoperative plasma-thrombin mixture and postoperative fluid-gas exchange. *Ophthalmic Surg Lasers* 2001;**32**:198–207	No comparison group
Blute ML. Fibrin sealant for retrograde ureteroscopic closure of urine leak after partial nephrectomy. French DB, Marcovich R, Department of Urology, University of Texas Health Science Center, San Antonio, TX. *Urol Oncol Seminars Orig Invest* 2006;**24**:554–5	No comparison group
Boadas A, Fernandez-Palazzi F, De Bosch NB, Cedeno M, Ruiz-Saez A. Elective surgery in patients with congenital coagulopathies and inhibitors: experience of the National Haemophilia Centre of Venezuela. *Haemophilia* 2011;**17**:422–7	No comparison group
Boaventura PN, Sobreira ML, Yoshida WB, Rollo HA. Treatment of postoperative inguinal lymphocele with fibrin glue injection: case report. *J Vasc Brasileiro* 2007;**6**:190–2	No comparison group
Bochicchio G, Singla N, Gupta NY, Porter R, Renkens KL, Pattyn P, *et al.* An international, multicenter, randomized, single-blind, controlled trial of a dry-powder, fibrin sealant for mild to moderate perioperative surgical bleeding. *J Am Coll Surg* 2014;**219**(Suppl. 1):e13–14	RCT
Bochicchio *et al.* 2015[239]	RCT
Bock HC, Cohnen J, Keric N, Kantelhardt SR, Giese A. Occlusion of surgical opening of the ventricular system with fibrinogen-coated collagen fleece: a case collection study. *Acta Neurochir* 2011;**153**:533–9	RCT
Bodner L, Weinstein JM, Baumgarten AK. Efficacy of fibrin sealant in patients on various levels of oral anticoagulant undergoing oral surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998;**86**:421–4	No comparison group
Boenisch M, Nolst Trenité GJ. [Fibrin glue for operative correction of septal deviations.] *HNO* 2004;**52**:963–7	No comparison group
Boldo 2008[173]	RCT
Boldo E, Armelles A, Perez de Lucia G, Martin F, Aracil JP, Miralles JM, *et al.* Pain after laparascopic bilateral hernioplasty : Early results of a prospective randomized double-blind study comparing fibrin versus staples. *Surg Endosc* 2008;**22**:1206–9. [Erratum appears in *Surg Endosc* 2008;**22**:1210]	Duplicate
Boonstra EA, Molenaar IQ, Porte RJ, de Boer MT. Topical haemostatic agents in liver surgery: do we need them? *HPB* 2009;**11**:306–10	Not a comparative observational study
Borgeskov S, Balslev E. [Use of fibrin adhesive (Tisseel) in pacemaker pockets. An experimental study.] *Ugeskr Laeg* 1987;**149**:1059–61	Not a comparative observational study
Born P, Ott R, Rösch T. Endoscopic hemostasis using fibrin sealant for postsphincterotomy bleeding: report of two cases. *Gastrointest Endosc* 2000;**51**:731–3	No comparison group
Borowiec AM, McCall M, Lees GM. The trans-sphincteric posterior sagittal repair of recto-urinary and recto-vaginal fistulae using Surgisis™ mesh and fibrin sealant. *Tech Coloproctol* 2014;**18**:201–3	No comparison group
Botti G, Pascali M, Botti C, Bodog F, Gentile P, Cervelli V. Comparison of commercial fibrin sealants in facelift surgery: a prospective study. *Clin Cosmet Investig Dermatol* 2013;**6**:273–80	Letter/commentary/reply
Bou Monsef J, Buckup J, Waldstein W, Cornell C, Boettner F. Fibrin sealants or cell saver eliminate the need for autologous blood donation in anemic patients undergoing primary total knee arthroplasty. *Arch Orthop Trauma Surg* 2014;**134**:53–8	No adverse effects related to fibrin reported
Bouchot O, Bouchot-Hermouet FB, Karam G, Glemain P, Pannier M, Auvigne J. [Prevention of complications in inguinal lymphadenectomy.] *J Urol* 1990;**96**:279–83	No comparison group
Boulos PR, Harissi-Dagher M, Kavalec C, Hardy I, Codere F. Intralesional injection of Tisseel fibrin glue for resection of lymphangiomas and other thin-walled orbital cysts. *Ophthal Plast Reconstr Surg* 2005;**21**:171–6	No comparison group

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Bouwmeester SJ, Beckers JM, Kuijer R, van der Linden AJ, Bulstra SK. Long-term results of rib perichondrial grafts for repair of cartilage defects in the human knee. *Int Orthop* 1997;**21**:313–17	No comparison group
Boylu U, Basatac C, Tahra A, Onol FF, Gumus E. Laparoscopic ureterolithotomy with fibrin sealant in the treatment of large impacted proximal ureteral stone. *J Endourol* 2013;**27**:A432–3	No comparison group
Bozorg Grayeli A, Mosnier I, Julien N, El Garem H, Bouccara D, Sterkers O. Long-term functional outcome in facial nerve graft by fibrin glue in the temporal bone and cerebellopontine angle. *Eur Arch Otorhinolaryngol* 2005;**262**:404–7	No comparison group
Bracale *et al.* 2014[174]	RCT
Bradford TJ, Wolf JS. Percutaneous injection of fibrin glue for persistent nephrocutaneous fistula after partial nephrectomy. *Urology* 2005;**65**:799	No comparison group
Bradley JP, Gabbay JS, Taub PJ, Heller JB, O'Hara CM, Benhaim P, *et al.* Monobloc advancement by distraction osteogenesis decreases morbidity and relapse. *Plast Reconstr Surg* 2006;**118**:1585–97	Not fibrin sealant
Brady AP, Malone DE, Deignan RW, O'Donovan N, McGrath FP. Fibrin sealant in interventional radiology: a preliminary evaluation. *Radiology* 1995;**196**:573–8	Not a comparative observational study
Brady AP, Malone DE, Tam P, McGrath FP. Closure of a duodenal fistula with fibrin sealant. *J Vasc Interv Radiol* 1993;**4**:525–7	No comparison group
Braga Ade F, Rousselet MS, Zambelli H, Sbragia L, Barini R. [Anesthesia for intrauterine myelomeningocele correction: case report.] *Rev Bras Anestesiol* 2005;**55**:329–35	No comparison group
Brandão RA, Costa BS, Dellaretti MA, de Carvalho GT, Faria MP, de Sousa AA. Efficacy and safety of a porcine collagen sponge for cranial neurosurgery: a prospective case-control study. *World Neurosurg* 2013;**79**:544–50	Not fibrin sealant
Breda A, Stepanian SV, Lam JS, Liao JC, Gill IS, Colombo JR, *et al.* Use of haemostatic agents and glues during laparoscopic partial nephrectomy: a multi-institutional survey from the United States and Europe of 1347 cases. *Eur Urol* 2007;**52**:798–803	Not a comparative observational study
Brega Massone PP, Magnani B, Conti B, Lequaglie C, Cataldo I. Cauterization versus fibrin glue for aerostasis in precision resections for secondary lung tumors. *Ann Surg Oncol* 2003;**10**:441–6	No adverse effects related to fibrin reported
Breugem SJM, Rijcken THP, Albers GHR. Recurrent hemarthrosis after total knee arthroplasty caused by pseudoaneurysm. *Curr Orthop Pract* 2011;**22**:382–4	No comparison group
Briceño J, Naranjo A, Ciria R, Díaz-Nieto R, Sánchez-Hidalgo JM, Luque A, *et al.* A prospective study of the efficacy of clinical application of a new carrier-bound fibrin sealant after liver resection. *Arch Surg* 2010;**145**:482–8	No adverse effects related to fibrin reported
Briones-Estebanez JL, Zaragoza-Garcia JM, Martinez-Parreno C, Al-Raies Bolanos B, Plaza-Martinez A, Blanes-Mompo JI, *et al.* The treatment of iatrogenic pseudoaneurysms: a comparison of the ultrasound compression technique with the ultrasound-guided injection of human thrombin. *Angiologia* 2006;**58**:445–50	Not surgery
Brolin RE, Lin JM. Treatment of gastric leaks after Roux-en-Y gastric bypass: a paradigm shift. *Surg Obes Relat Dis* 2013;**9**:229–33	Not surgery
Brountzos EN, Malagari K, Papathanasiou MA, Gougoulakis A, Kelekis DA. Internal iliac artery aneurysm embolization with fibrin sealant: a simple and effective solution. *Cardiovasc Intervent Radiol* 2003;**26**:76–80	No comparison group
Brown JA, Hubosky SG, Gomella LG, Strup SE. Hand assisted laparoscopic partial nephrectomy for peripheral and central lesions: a review of 30 consecutive cases. *J Urol* 2004;**171**:1443–6	No comparison group
Brown NE, Grundfast KM, Jabre A, Megerian CA, O'Malley BW, Rosenberg SI. Diagnosis and management of spontaneous cerebrospinal fluid-middle ear effusion and otorrhea. *Laryngoscope* 2004;**114**:800–5	Not a valid comparison
Bruck HG. Fibrin tissue adhesion and its use in rhytidectomy: a pilot study. *Aesthetic Plast Surg* 1982;**6**:197–202	No comparison group

continued

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Brückner M, Grimm H, Nam VC, Soehendra N. Endoscopic treatment of a pancreatic abscess originating from biliary pancreatitis. *Surg Endosc* 1990;**4**:227–9	No comparison group
Bruner JP, Richards WO, Tulipan NB, Arney TL. Endoscopic coverage of fetal myelomeningocele in utero. *Am J Obstet Gynecol* 1999;**180**:153–8	No comparison group
Bruns J, Klima H. [Osteochondritis dissecans of the knee joint. Results of follow-up.] *Z Orthop Ihre Grenzgeb* 1993;**131**:413–19	Included children
Buchanan GN, Bartram CI, Phillips RK, Gould SW, Halligan S, Rockall TA, *et al.* Efficacy of fibrin sealant in the management of complex anal fistula: a prospective trial. *Dis Colon Rectum* 2003;**46**:1167–74	No comparison group
Buckley RC, Breazeale EE, Edmond JA, Brzezienski MA. A simple preparation of autologous fibrin glue for skin-graft fixation. *Plast Reconstr Surg* 1999;**103**:202–6	No comparison group
Buda A, Fruscio R, Pirovano C, Signorelli M, Betti M, Milani R. The use of TachoSil for the prevention of postoperative complications after groin dissection in cases of gynecologic malignancy. *Int J Gynaecol Obstet* 2012;**117**:217–19	No adverse effects related to fibrin reported
Buda A, Pirovano C, Fruscio R, Betti M, Cuzzocrea M, Dell'Orto F, *et al.* Tachosil patch for the prevention of postoperative complications after inguinofemoral lymphadenectomy in gynecological malignancy: a single institution case-control study. *Ital J Gynaecol Obstet* 2011;**23**:133–8	No adverse effects related to fibrin reported
Buda A, Pirovano C, Giuliani D, Signorelli M, Lissoni AA, Chiappa V, *et al.* Tachosil patch plus surgical clips for prevention of postoperative complications after inguinofemoral lymphadenectomy for vulvar cancer: a single institution experience. *Int J Gynecol Cancer* 2011;**21**(Suppl. 3):S894	No adverse effects related to fibrin reported
Bulajic P, Savic N, Djordjevic Z, Kecmanovic D, Bulajic M, Milicevic M, *et al.* Role of autologous fibrin tissue adhesive in abdominal surgery. *Acta Chir Iugosl* 1999;**46**:43–5	Not a comparative observational study
Bulbuller *et al.* 2013[92]	RCT
Bullocks JM, Echo A, Guerra G, Stal S, Yuksel E. A novel autologous scaffold for diced-cartilage grafts in dorsal augmentation rhinoplasty. *Aesthetic Plast Surg* 2011;**35**:569–79	No comparison group
Burnouf T, Chen TM, Tsai JC. A novel technique combining single-donor platelet gel and fibrin glue with skin graft to heal recalcitrant lower extremity ulcers. *Vox Sanguinis* 2010;**99**:264	No comparison group
Busuttil RW. A comparison of antifibrinolytic agents used in hemostatic fibrin sealants. *J Am Coll Surg* 2003;**197**:1021–8	Not a comparative observational study
Butler CE. Treatment of refractory donor-site seromas with percutaneous instillation of fibrin sealant. *Plast Reconstr Surg* 2006;**117**:976–85	No comparison group
Bylund JR, Clark CJ, Crispen PL, Lagrange CA, Strup SE. Hand-assisted laparoscopic partial nephrectomy without formal collecting system closure: perioperative outcomes in 104 consecutive patients. *J Endourol* 2011;**25**:1853–7	No comparison group
Byrne DJ, Hardy J, Wood RA, McIntosh R, Hopwood D, Cuschieri A. Adverse influence of fibrin sealant on the healing of high-risk sutured colonic anastomoses. *J R Coll Surg Edinb* 1992;**37**:394–8	Not fibrin sealant
Byun CS, Hwang JJ, Choi JH. Single-incision vats bullectomy with suture-lift method in primary spontaneous pneumothorax. *Innovations* 2013;**8**:145–6	No comparison group
Caccavale A, Romanazzi F, Imparato M, Negri A, Porta A, Ferentini F. Ropivacaine for topical anesthesia in pterygium surgery with fibrin glue for conjunctival autograft. *Cornea* 2010;**29**:375–6	No comparison group
Cachaldora-del Rio JA, Hernandez-Lahoz Ortiz I, Sanchez-Abuin J, Rielo-Arias FJ, Gallegos-Vidal M, Fernandez-Fernandez JC, *et al.* Treatment of iatrogenic arterial pseudoaneurysms with human thrombin injections. *Angiologia* 2002;**54**:390–6	No comparison group
Caers J, Reekmans A, Jochmans K, Naegels S, Mana F, Urbain D, *et al.* Factor V inhibitor after injection of human thrombin (tissucol) into a bleeding peptic ulcer. *Endoscopy* 2003;**35**:542–4	No comparison group
Calabrò B, Ponsetto M, Greco R, Peradotto F, Personnettaz E, Obialero M. [Treatment of leg ulcers with fibrin glue.] *Minerva Chir* 1995;**50**:569–74	Not surgery

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Calado E, Ayres-de-Campos D. Premature rupture of membranes at 20 weeks: report of a successful outcome after transcervical application of fibrin glue. *Fetal Diagn Ther* 2007;**22**:14–17	No comparison group
Caldas Neto S, Oliveira RL, Caldas N. Use of in fibrin glue in the prevention of postoperative bleeding and hematomas after septoplasty. *Rev Bras Otorrinolaringol* 2002;**68**:635–8	RCT
Callari C, Perretta S, Diana M, Dagostino J, Dallemagne B, Marescaux J. Multimedia manuscript. Thoracoscopic management of chylothorax after esophagectomy. *Surg Endosc* 2012;**26**:1160	Not fibrin sealant
Cambal *et al.* 2012[175]	RCT
Campanelli G, Champault G, Pascual MH, Hoeferlin A, Kingsnorth A, Rosenberg J, *et al.* Randomized, controlled, blinded trial of Tissucol/Tisseel for mesh fixation in patients undergoing Lichtenstein technique for primary inguinal hernia repair: rationale and study design of the TIMELI trial. *Hernia* 2008;**12**:159–65	RCT
Campanelli *et al.* 2012[176]	RCT
Campanelli G, Sfeclan C, Cavalli M, Biondi A. Reducing postoperative pain: the use of Tisseel for mesh fixation in inguinal hernia repair. *Surg Technol Int* 2012;**22**:134–9	RCT
Campbell ML, Abboud EC, Dolberg ME, Sanchez JE, Marcet JE, Rasheid SH. Treatment of refractory perianal fistulas with ligation of the intersphincteric fistula tract: preliminary results. *Am Surg* 2013;**79**:723–7	No comparison group
Campos F, Fujio S, Sugata S, Tokimura H, Hanaya R, Bohara M, *et al.* Effect of thrombin concentration on the adhesion strength and clinical application of fibrin glue-soaked sponge. *Neurol Med Chir (Tokyo)* 2013;**53**:17–20	No comparison group
Campos JM, Pereira EF, Evangelista LF, Siqueira L, Neto MG, Dib V, *et al.* Gastrobronchial fistula after sleeve gastrectomy and gastric bypass: endoscopic management and prevention. *Obes Surg* 2011;**21**:1520–9	No comparison group
Campos JM, Siqueira LT, Meira MR, Ferraz AA, Ferraz EM, Guimaraes MJ. Gastrobronchial fistula as a rare complication of gastroplasty for obesity: a report of two cases. *J Bras Pneumol* 2007;**33**:475–9	No comparison group
Canby-Hagino ED, Morey AF, Jatoi I, Perahia B, Bishoff JT. Fibrin sealant treatment of splenic injury during open and laparoscopic left radical nephrectomy. *J Urol* 2000;**164**:2004–5	No comparison group
Canonico S, Benevento R, Della Corte A, Fattopace A, Canonico R. Sutureless tension-free hernia repair with human fibrin glue (Tissucol) in soccer players with chronic inguinal pain: initial experience. *Int J Sports Med* 2007;**28**:873–6	No comparison group
Canonico S, Benevento R, Perna G, Guerniero R, Sciaudone G, Pellino G, *et al.* Sutureless fixation with fibrin glue of lightweight mesh in open inguinal hernia repair: effect on postoperative pain: a double-blind, randomized trial versus standard heavyweight mesh. *Surgery* 2013;**153**:126–30	RCT
Canonico S, Pacifico F, Santoriello A. The prophylaxis of haemocoagulative complications after prosthetic surgery of inguinal hernias. *Chirurgia* 1995;**8**:88–92	No adverse effects related to fibrin reported
Canonico S, Santoriello A, Campitiello F, Fattopace A, Corte AD, Sordelli I, *et al.* Mesh fixation with human fibrin glue (Tissucol) in open tension-free inguinal hernia repair: a preliminary report. *Hernia* 2005;**9**:330–3	No comparison group
Canonico *et al.* 1999[177]	RCT
Canziani M, Agrusti S, Bertocchi V, Cavalli M, Campanelli G, Cavaliere D, *et al.* The tailored surgery in incisional hernia repair. *Eur Surg Res* 2010;**45**(3–4):168	Abstract
Canziani M, Frattini F, Cavalli M, Agrusti S, Somalvico F, Campanelli G. Sutureless mesh fibrin glue incisional hernia repair. *Hernia* 2009;**13**:625–9	No comparison group
Cappabianca P. The awake endoscope-guided sealant technique with fibrin glue in the treatment of postoperative cerebrospinal fluid leak after extended transsphenoidal surgery: technical note. *World Neurosurg* 2014;**82**:e479–85	No comparison group

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TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Cappabianca P, Cavallo LM, Valente V, Romano I, D'Enza AI, Esposito F, *et al.* Sellar repair with fibrin sealant and collagen fleece after endoscopic endonasal transsphenoidal surgery. *Surg Neurol* 2004;**62**:227–33	Fibrin was used in both groups
Cappabianca P, Esposito F, Cavallo LM, Messina A, Solari D, di Somma LG, *et al.* Use of equine collagen foil as dura mater substitute in endoscopic endonasal transsphenoidal surgery. *Surg Neurol* 2006;**65**:144–8	No comparison group
Capussotti L, Ferrero A, Viganò L, Sgotto E, Muratore A, Polastri R. Bile leakage and liver resection: where is the risk? *Arch Surg* 2006;**141**:690–4	Included children
Carbon RT, Baar S, Waldschmidt J, Huemmer HP, Simon SI. Innovative minimally invasive pediatric surgery is of therapeutic value for splenic injury. *J Pediatr Surg* 2002;**37**:1146–50	Included children
Cardillo G, Carbone L, Carleo F, Batzella S, Jacono RD, Lucantoni G, *et al.* Tracheal lacerations after endotracheal intubation: a proposed morphological classification to guide non-surgical treatment. *Eur J Cardiothorac Surg* 2010;**37**:581–7	No comparison group
Cardillo *et al.* 2012[41]	RCT
Cardillo G, Galetta D, van Schil P, Zuin A, Filosso P, Cerfolio RJ, *et al.* Completion pneumonectomy: a multicentre international study on 165 patients. *Eur J Cardiothorac Surg* 2012;**42**:405–9	RCT
Carey JN, Sheckter CC, Watt AJ, Lee GK. Intra-abdominal pedicled rectus abdominis muscle flap for treatment of high-output enterocutaneous fistulae: case reports and review of literature. *J Plast Reconstr Aesthet Surg* 2013;**66**:1145–8	No comparison group
Carini M, Serni S, Lapini A, Selli C, Menchi I. Endoscopic treatment of refluxing ureteric stump following nephrectomy with Tissucol and teflon injection. *Eur Urol* 1989;**16**:312–14	No comparison group
Carlson *et al.* 2008[94]	RCT
Carter *et al.* 2003[229]	RCT
Carter G, Goss AN, Lloyd J, Tocchetti R. Local haemostasis with autologous fibrin glue following surgical enucleation of a large cystic lesion in a therapeutically anticoagulated patient. *Br J Oral Maxillofac Surg* 2003;**41**:275–6	No comparison group
Carter *et al.* 2013[81]	No comparison group
Caruso A, Manta R, Melotti G, Conigliaro R. Endoscopic treatment of a large post-surgical fistula using combined fibrin glue spray and vicryl mesh. *Dig Liver Dis* 2012;**44**:85–6	No comparison group
Casarotto A, Militello V, Piatto G, Gruppo M, Militello C. Hernioplasty in elderly high-risk adults: efficacy of fibrin glue. *J Am Geriatr Soc* 2012;**60**:1193–4	Letter/commentary/reply
Casas VE, Kheirkhah A, Blanco G, Tseng SC. Surgical approach for scleral ischemia and melt. *Cornea* 2008;**27**:196–201	Not a valid comparison
Casella G, Soricelli E, Rizzello M, Trentino P, Fiocca F, Fantini A, *et al.* Nonsurgical treatment of staple line leaks after laparoscopic sleeve gastrectomy. *Obes Surg* 2009;**19**:821–6	Duplicate
Cavallini M, Tallerini A, Stipa F. [Occlusion of the duct with a fibrin glue and preservation of the pylorus after resection of the duodenum and head of the pancreas for periampullary carcinoma.] *Minerva Chir* 1991;**46**:733–9	No comparison group
Cavallo LM, Messina A, Esposito F, de Divitiis O, Dal Fabbro M, de Divitiis E, *et al.* Skull base reconstruction in the extended endoscopic transsphenoidal approach for suprasellar lesions. *J Neurosurg* 2007;**107**:713–20	No comparison group
Cavallo LM, Solari D, Somma T, Di Somma A, Chiaramonte C, Cappabianca P. Use of equine pericardium sheet (LYOMESH) as dura mater substitute in endoscopic endonasal transsphenoidal surgery. *Transl Med USA* 2013;**7**:23–8	No comparison group
Cavallo LM, Solari D, Somma T, Savic D, Cappabianca P. The awake endoscope-guided sealant technique with fibrin glue in the treatment of postoperative cerebrospinal fluid leak after extended transsphenoidal surgery: technical note. *World Neurosurg* 2014;**82**:e479–85	No comparison group

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Ceccarelli G, Casciola L, Pisanelli MC, Bartoli A, Di Zitti L, Spaziani A, *et al.* Comparing fibrin sealant with staples for mesh fixation in laparoscopic transabdominal hernia repair: a case control-study. *Surg Endosc* 2008;**22**:668–73	No adverse effects related to fibrin reported
Cecchi M, Sepich CA, Pagni G, Ippolito C, Minervini R, Fiorentini L. Painless treatment of hydrocele: EMLA cream anaesthesia and fibrin adhesive sclerotherapy. *Int Urol Nephrol* 1997;**29**:457–9	No comparison group
Cederholm-Williams SA. Benefits of adjuvant fibrin glue in skin grafting. *Med J Aust* 1994;**161**:575	Letter/commentary/reply
Cederholm-Williams SA, Dean MG, Nicholls MD. Benefits of adjuvant fibrin glue in skin grafting. *Med J Aust* 1994;**161**:575	Duplicate
Cedin AC, Fujita R, Cruz OL. Endoscopic transeptal surgery for choanal atresia with a stentless folded-over-flap technique. *Otolaryngol Head Neck Surg* 2006;**135**:693–8	No comparison group
Celia A, Zeccolini G, Guazzoni G, Pansadoro V, Disanto V, Porpiglia F, *et al.* Laparoscopic nephron sparing surgery: a multi-institutional European survey of 592 cases. *Arch Ital Urol Androl* 2008;**80**:85–91	No comparison group
Celiento M, Scioti G, Pratali S, Bortolotti U. Repair of coronary artery perforation following angioplasty using TachoSil patches. *Interact Cardiovasc Thorac Surg* 2010;**10**:328–30	No comparison group
Cellier C, Landi B, Faye A, Wind P, Frileux P, Cugnenc PH, *et al.* Upper gastrointestinal tract fistulae: endoscopic obliteration with fibrin sealant. *Gastrointest Endosc* 1996;**44**:731–3	No comparison group
Cellini C, Manta R, Caruso A, Mirante VG, Bertani H, Manno M, *et al.* Endoscopic treatment of post-surgical gastrointestinal fistulas: experience of a tertiary referral centre. *Dig Liver Dis* 2014;**46**:S139	Not a valid comparison
Cennamo V, Fuccio L, Giampalma E, Terzi E, Eusebi LH, Mosconi C, *et al.* Choledochoscope-assisted percutaneous fibrin glue sealing of bile leak complicating transarterial chemoembolization of hepatocellular carcinoma after liver transplantation. *Endoscopy* 2011;**43**(Suppl. 2):E238–9	No comparison group
Cerfolio RJ, Allen MS, Deschamps C, Trastek VF, Pairolero PC. Postoperative chylothorax. *J Thorac Cardiovasc Surg* 1996;**112**:1361–5	No comparison group
Cernea CR, Hojaij FC, De Carlucci D Jr, Tavares MR, Araujo-Filho VJ, Silva-Filho GB, *et al.* Abdominal compression: a new intraoperative manoeuver to detect chyle fistulas during left neck dissections that include level IV. *Head Neck* 2012;**34**:1570–3	No comparison group
Cerný M, Havlícek K, Sákra L, Flasar J. [Massive hemothorax following canylation of the subcalvian vein – a case review.] *Rozhl Chir* 2008;**87**:376–9	No comparison group
Cerwenka H, Bacher H, Werkgartner G, El-Shabrawi A, Mischinger HJ. Massive liver haemorrhage and rupture caused by HELLP-syndrome treated by collagen fleeces coated with fibrin glue. *Eur J Surg* 1998;**164**:709–11	No comparison group
Cesana G, Olmi S, Croce E. Trans-abdominal pre-peritoneal laparoscopic inguinal hernia repair versus classical inguinotomic repair: a randomized study. *Surg Endosc* 2011;**25**:S7	RCT
Cestaro G, De Rosa M, Gentile M. Treatment of fistula in ano with fibrin glue: preliminary results from a prospective study. *Minerva Chir* 2014;**69**:225–8	RCT
Cha HG, Kang SG, Shin HS, Kang MS, Nam SM. Does fibrin sealant reduce seroma after immediate breast reconstruction utilizing a latissimus dorsi myocutaneous flap? *Arch Plast Surg* 2012;**39**:504–8	No adverse effects related to fibrin reported
Cha HS, Kim A, Nowzari H, Chang HS, Ahn KM. Simultaneous sinus lift and implant installation: prospective study of consecutive two hundred seventeen sinus lift and four hundred sixty-two implants. *Clin Implant Dent Relat Res* 2014;**16**:337–47	Not fibrin sealant
Chabok SY, Safaie M, Ashraf A, Emamhadi M, Behzadnia H, Alijani B, *et al.* Effect of fat graft on dural tear repair in lumbar spine laminectomy surgery. *Neurosurg Q* 2014;**24**:1–4	Not a valid comparison
Chalmers *et al.* 2010[198]	RCT

continued

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Chan K, Dickinson J. Surgical results following full-thickness skin grafting with tisseel in the periocular region-cosmetic outcomes and incidence of complications. *Clin Experiment Ophthalmol* 2013;**41**:88	No comparison group
Chan *et al.* 2014[178]	RCT
Chapman WC, Clavien P, Fung JJ, Block JE. Managing hepatic bleeding with autologous plasma/collagen-based fibrin sealant. *Arch Surg* 2001;**136**:967	Letter/commentary/reply
Chapman *et al.* 2000[67]	RCT
Chartrand C, Dumont L, Stanley P. Value of fibrin sealant in heart transplantation. *Transplant Proc* 1989;**21**:3347–8	Not in humans
Chawla B, Tandon R. Sutureless amniotic membrane fixation with fibrin glue in symptomatic bullous keratopathy with poor visual potential. *Eur J Ophthalmol* 2008;**18**:998–1001	No comparison group
Chen ML, Tomaszewski JJ, Matoka DJ, Ost MC. Management of urine leak after laparoscopic cyst decortication with retrograde endoscopic fibrin glue application and ureteral stent placement. *J Endourol* 2011;**25**:71–4	No comparison group
Chen RJ, Fang JF, Lin BC, Hsu YB, Kao JL, Kao YC, *et al.* Selective application of laparoscopy and fibrin glue in the failure of nonoperative management of blunt hepatic trauma. *J Trauma* 1998;**44**:691–5	No comparison group
Chen TM, Tsai JC, Burnouf T. A novel technique combining platelet gel, skin graft, and fibrin glue for healing recalcitrant lower extremity ulcers. *Dermatol Surg* 2010;**36**:453–60	No comparison group
Chen WL, Huang ZQ, Chai Q, Zhang DM, Wang YY, Wang HJ, *et al.* Percutaneous sclerotherapy of massive macrocystic lymphatic malformations of the face and neck using fibrin glue with OK-432 and bleomycin. *Int J Oral Maxillofac Surg* 2011;**40**:572–6	Included children
Chen WL, Huang ZQ, Li JS, Chai Q, Zhang DM. Percutaneous sclerotherapy of juvenile nasopharyngeal angiofibroma using fibrin glue combined with OK-432 and bleomycin. *Int J Pediatr Otorhinolaryngol* 2010;**74**:422–5	No comparison group
Chen WL, Huang ZQ, Zhang DM, Chai Q. Percutaneous sclerotherapy of massive venous malformations of the face and neck using fibrin glue combined with OK-432 and pingyangmycin. *Head Neck* 2010;**32**:467–72	No comparison group
Chen WL, Zhang LP, Huang ZQ, Zhou B. Percutaneous sclerotherapy of sialoceles after parotidectomy with fibrin glue, OK-432, and bleomycin. *Br J Oral Maxillofac Surg* 2013;**51**:786–8	No comparison group
Cheng HT, Hsu YC, Wu CI. Quilting sutures, fibrin tissue adhesive or both in reducing the incidence of seroma in the latissimus dorsi flap donor site? An evidence-based analysis. *J Plast Reconstr Aesthet Surg* 2014;**67**:881–2	Letter/commentary/reply
Chernousov AF, Khororykh TV, Urzhumtseva GA, Urakova IaCh. [Endoscopic hemostasis of erosive-ulcerous gastroduodenal bleeding with fibrin glue at critically ill patients.] *Khirurgiia* 2006;**8**:17–20	No comparison group
Chi JH, Sughrue M, Kunwar S, Lawton MT. The 'yo-yo' technique to prevent cerebrospinal fluid rhinorrhea after anterior clinoidectomy for proximal internal carotid artery aneurysms. *Neurosurgery* 2006;**59**:ONS–101	No comparison group
Chin Ai, Ragavendra N, Hilborne L, Gritsch HA. Fibrin sealant sclerotherapy for treatment of lymphoceles following renal transplantation. *J Urol* 2003;**170**:380–3	No comparison group
Chin CJ, Kus L, Rotenberg BW. Use of duraseal in repair of cerebrospinal fluid leaks. *J Otolaryngol Head Neck Surg* 2010;**39**:594–9	Letter/commentary/reply
Chirletti P, Caronna R, Fanello G, Schiratti M, Stagnitti F, Peparini N, *et al.* Pancreaticojejunostomy with application of fibrinogen/thrombin-coated collagen patch (TachoSil) in Roux-en-Y reconstruction after pancreaticoduodenectomy. *J Gastrointest Surg* 2009;**13**:1396–8	Letter/commentary/reply
Chisholm RA, Jones SN, Lees WR. Fibrin sealant as a plug for the post liver biopsy needle track. *Clin Radiol* 1989;**40**:627–8	No comparison group

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Cho JM, Ahn JY, Chang JH, Kim SH. Prevention of cerebrospinal fluid rhinorrhea after transsphenoidal surgery by collagen fleece coated with fibrin sealant without autologous tissue graft or postoperative lumbar drainage. *Neurosurgery* 2011;**68**(Suppl.):130–6	No comparison group
Cho S, Huh DM, Kim BH, Lee S, Kwon OC, Ahn WS, *et al.* Staple line covering procedure after thoracoscopic bullectomy for the management of primary spontaneous pneumothorax. *Thorac Cardiovasc Surg* 2008;**56**:217–20	No comparison group
Cho S, Ryu KM, Jheon S, Sung SW, Kim BH, Huh DM. Additional mechanical pleurodesis after thoracoscopic wedge resection and covering procedure for primary spontaneous pneumothorax. *Surg Endosc* 2009;**23**:986–90	Not a valid comparison
Choi *et al.* 2010[244]	No comparison group
Chou D, Cheng J, Chesnut R, Choudhri H, Gopinath S, Scott Graham R, *et al.* A prospective, multi-center, randomized controlled study to compare a low swell formulation of a PEG hydrogel spinal sealant as an adjunct to sutured dural repair with common dural sealing methods. *Spine J* 2010;**10**:80S	RCT
Chou D, Wang VY, Khan AS. Primary dural repair during minimally invasive microdiscectomy using standard operating room instruments. *Neurosurgery* 2009;**64**(Suppl. 2):356–8	No comparison group
Choudhari NS, Neog A, Sharma A, Iyer GK, Srinivasan B. Our experience of fibrin sealant-assisted implantation of Ahmed glaucoma valve. *Indian J Ophthalmol* 2013;**61**:23–7	No comparison group
Choufani *et al.* 2015[151]	RCT
Chouillard EK, Fingerhut AL. Sutureless repair of bronchial tears using fibrin sealant-reinforced Vicryl bridge. *ANZ J Surg* 2006;**76**:419	Letter/commentary/reply
Christenson JT, Kalangos A. Autologous fibrin glue reinforced by platelets in surgery of ascending aorta. *Thorac Cardiovasc Surg* 2004;**52**:225–9	RCT
Christine B, Carson CC. The use of adjunct hemostatic agents during peyronie's plaque incision and grafting: Less frequent complications secondary to hematoma formation at the site of the graft may be possible. *J Sex Med* 2012;**9**:28	Not a valid comparison
Chryssagis K, Klugl S, Liangos A, Gutleben KJ, Brachmann J, Diegeler A. Surgical feasibility of the injection of fibrin sealant in cardiac fat pads to reduce the incidence of postoperative atrial fibrillation after coronary artery bypass grafting or valve surgery a pilot study. *Innovations* 2008;**3**:151–4	No comparison group
Chu W, Chien GW, Finley DS. Novel ureteroscopic technique for treatment of prolonged caliceal leak after partial nephrectomy. *J Endourol* 2015;**29**:397–400	No comparison group
Chung HW, Mehta JS. Fibrin glue for Gundersen flap surgery. *Clin Ophthalmol* 2013;**7**:479–84	No comparison group
Chung SG, Lee SY, Kim W. Treatment of lateral epicondylitis using allogeneic adipose-derived mesenchymal stem cells. *PMR* 2014;**6**(Suppl. 1):177	RCT
Chung W, Ko D, Sun C, Raval MJ, Brown CJ, Phang PT. Outcomes of anal fistula surgery in patients with inflammatory bowel disease. *Am J Surg* 2010;**199**:609–13	No adverse effects related to fibrin reported
Ciavarella N, Schiavoni M, Valenzano E, Mangini F, Inchingolo F. Use of recombinant factor VIIa (NovoSeven) in the treatment of two patients with type III von Willebrand's disease and an inhibitor against von Willebrand factor. *Haemostasis* 1996;**26**(Suppl. 1):150–4	No comparison group
Cintron JR, Park JJ, Orsay CP, Pearl RK, Nelson RL, Abcarian H. Repair of fistulas-in-ano using autologous fibrin tissue adhesive. *Dis Colon Rectum* 1999;**42**:607–13	No comparison group
Cipolla *et al.* 2010[110]	RCT
Citardi MJ, Cox AJ 3rd, Bucholz RD. Acellular dermal allograft for sellar reconstruction after transsphenoidal hypophysectomy. *Am J Rhinol* 2000;**14**:69–73	No comparison group
Ciurtin DH, Maghiar AM, Sfirlea M, Sookha PR, Suta A, Purza A, *et al.* Intraoperative complications in laparoscopic cholecystectomy. *Surg Endosc* 2011;**25**:S119	No comparison group

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TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Clajus C, Stockhammer F, Rohde V. The intra- and postoperative management of accidental durotomy in lumbar spine surgery: results of a German survey. *Acta Neurochir* 2015;**157**:525–30	Not a comparative observational study
Cleaveland P, Tang V, Pollard A, Adeyoju A. Management of a patient with a chronic nephrocutaneous fistula after partial nephrectomy using a novel technique. *Int J Urol* 2015;**22**:232–3	No comparison group
Cocero N, Pucci F, Messina M, Pollio B, Mozzati M, Bergamasco L. Autologous plasma rich in growth factors in the prevention of severe bleeding after teeth extractions in patients with bleeding disorders: a controlled comparison with fibrin glue. *Blood Transfus* 2015;**13**:287–94	RCT
Codispoti M, Mankad PS. Significant merits of a fibrin sealant in the presence of coagulopathy following paediatric cardiac surgery: randomised controlled trial. *Eur J Cardiothorac Surg* 2002;**22**:200–5	RCT
Coenen VA, Gilsbach JM. Effect of arachnoid plasty using fibrin glue membrane after clipping of ruptured aneurysm on the occurrence of complications and outcome in the elderly patients: commentary. *Acta Neurochir* 2006;**148**:631	Letter/commentary/reply
Cohen I, Heim M, Martinowitz U, Chechick A. Orthopaedic outcome of total knee replacement in haemophilia A. *Haemophilia* 2000;**6**:104–9	No comparison group
Cohen J, Jayram G, Mullins JK, Ball MW, Allaf ME. Do fibrin sealants impact negative outcomes after robot-assisted partial nephrectomy? *J Endourol* 2013;**27**:1236–9	No adverse effects related to fibrin reported
Cohen-Gadol AA, Bellew MP, Akard W, Payner TD. The application of n-butyl 2-cyanoacrylate to repair CSF fistulas for 221 patients who underwent transsphenoidal surgery. *Minim Invasive Neurosurg* 2010;**53**:207–9	Not fibrin sealant
Cohen-Gadol AA, Mokri B, Piepgras DG, Meyer FB, Atkinson JL. Surgical anatomy of dural defects in spontaneous spinal cerebrospinal fluid leaks. *Neurosurgery* 2006;**58**(Suppl. 4):ON238–45	Not fibrin sealant
Colm SJ. The use of a fibrin sealant to control intraoperative bleeding during a Le Fort I osteotomy: report of a case. *J Oral Maxillofac Surg* 1996;**54**:1014–16	No comparison group
Conboy P, Brown DH. Use of tissue sealant for day surgery parotidectomy. *J Otolaryngol Head Neck Surg* 2008;**37**:208–11	No comparison group
Conde SM, Aguilar LT, Moreno AB, Macias MS, Garcia DM, Borrero IS, *et al.* A new technique for laparoscopic ventral hernia repair: double crown with one /third of tackers and fibrin glue. *Surg Endosc* 2011;**25**:S6	No comparison group
Copuroğlu C, Ercan S, Ozcan M, Ciftdemir M, Turan FN, Yalniz E. Comparison of autogenous bone graft donor site haemostatic agents used in spinal surgery. *Acta Orthop Traumatol Turc* 2011;**45**:359–64	RCT
Coral-Ghanem R, Oliveira RF, Furlanetto E, Ghanem MA, Ghanem VC. [Conjunctival autologous transplantation using fibrin glue in primary pterygium.] *Arq Bras Oftalmol* 2010;**73**:350–3	No adverse effects related to fibrin reported
Cormio L, Perrone A, Pentimone S, Selvaggio O, Lorusso F, Di Fino G, *et al.* Tachosil-sealed tubeless percutaneous nephrolithotomy in supine antero-lateral position: a prospective study. *Eur Urol Suppl* 2010;**9**:35	RCT
Correa ME, Annicchino-Bizzacchi JM, Jorge J, Paes de Almeida O, Ozelo MC, Aranha FJ, *et al.* Clinical impact of oral health indexes in dental extraction of hemophilic patients. *J Oral Maxillofac Surg* 2006;**64**:785–8	No comparison group
Cothren CC, McIntyre RC, Johnson S, Stiegmann GV. Management of low-output pancreatic fistulas with fibrin glue. *Am J Surg* 2004;**188**:89–91	No comparison group
Crawford RW, Giangrande P, Murray D. Fibrin sealant reduces blood loss in total hip arthroplasty. *Hip Int* 1999;**9**:127–32	No adverse effects related to fibrin reported
Crul BJ, Gerritse BM, van Dongen RT, Schoonderwaldt HC. Epidural fibrin glue injection stops persistent postdural puncture headache. *Anesthesiology* 1999;**91**:576–7	No comparison group
Curcio G, Badas R, Miraglia R, Barresi L, Tarantino I, Traina M. Duodenal stump fistula following Roux-en-Y gastrectomy, treated with single-balloon enteroscopy using the tulip bundle technique and fibrin glue injection. *Endoscopy* 2012;**44**(Suppl 2 UCTN):E364–5	No comparison group

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Czepko R, Kwinta B. [The use of TachoComb for the rhinorrhea repair in pituitary transsphenoidal surgery.] *Polim Med* 2006;**36**:3–9	No adverse effects related to fibrin reported
Czerny *et al.* 2000[205]	RCT
Dadeya S, Ms K. Strabismus surgery: fibrin glue versus vicryl for conjunctival closure. *Acta Ophthalmol Scand* 2001;**79**:515–17	Included children
Dagnini G, Caldironi MW, Marin G, Patella M. Fibrin sponge plugging of hemorrhage from laparoscopic biopsy. *Gastrointest Endosc* 1985;**31**:35–6	Technical note
Dal Pizzol MM, Roggia MF, Kwitko S, Marinho DR, Rymer S. [Use of fibrin glue in ocular surgery.] *Arq Bras Oftalmol* 2009;**72**:308–12	No comparison group
Damiano *et al.* 2014[184]	RCT
D'Andrea AA, Costantino V, Sperti C, Pedrazzoli S. Human fibrin sealant in pancreatic surgery: it is useful in preventing fistulas? A prospective randomized study. *Ital J Gastroenterol* 1994;**26**:283–6	RCT
Daneshrad P, Chin GY, Rice DH. Fibrin glue prevents complications of septal surgery: findings in a series of 100 patients. *Ear Nose Throat J* 2003;**82**:196–7	No comparison group
D'Arcy FT, Jaffry SQ. A review of 100 consecutive Sutureless child and adult circumcisions. *Ir J Med Sci* 2011;**180**:51–3	No comparison group
Darnis E, Mutungwa I, Guillaume M, Pagneux JM. Conization with fibrin sealant: retrospective study of 150 cases. *Ref Gynecol Obstet* 2002;**9**:60–5	No comparison group
Datta D, Vlavianos P, Alisa A, Westaby D. Use of fibrin glue (beriplast) in the management of bleeding gastric varices. *Endoscopy* 2003;**35**:675–8	No comparison group
Dattola A, Alberti A, Parisi A, Maccarone P, Dattola P, Celi S, *et al.* [Minimally invasive percutaneous ultrasonography-guided treatment of postoperative splenic abscess. Personal experience with 5 clinical cases.] *Chir Ital* 1999;**51**:451–7	Not a valid comparison
Davis BR, Sándor GK. Use of fibrin glue in maxillofacial surgery. *J Otolaryngol* 1998;**27**:107–12	No comparison group
de Boer MT, Boonstra EA, Lisman T, Porte RJ. Role of fibrin sealants in liver surgery. *Dig Surg* 2012;**29**:54–61	Not a comparative observational study
de Boer *et al.* 2012[66]	Not a comparative observational study
de Boer MT, Porte RJ. Reply to letter: 'Fibrin sealants do not prevent resection surface-related complications after liver resection'. *Ann Surg* 2015;**261**:e82–3	Not a comparative observational study
de Boer MT, Porte RJ. Reply: Re: Fibrin sealant for prevention of resection surface-related complications after liver resection: A randomized controlled trial. *Ann Surg* 2015;**261**:e78	RCT
de Boer MT, Porte RJ. Reply: Fibrin sealant for prevention of resection surface-related complications after liver resection in living liver donors. *Ann Surg* 2015;**261**:e82–3	Letter/commentary/reply
de Gracia J, de la Rosa D, Catalán E, Alvarez A, Bravo C, Morell F. Use of endoscopic fibrinogen-thrombin in the treatment of severe hemoptysis. *Respir Med* 2003;**97**:790–5	No comparison group
de Hingh IH, Nienhuijs SW, Overdevest EP, Scheele K, Everts PA. Mesh fixation with autologous platelet-rich fibrin sealant in inguinal hernia repair. *Eur Surg Res* 2009;**43**:306–9	No comparison group
de la Garza JL, Rumsey E. Fibrin glue and hemostasis in liver trauma: a case report. *J Trauma* 1990;**30**:512–13	No comparison group
de Oca J, Del Rio C, Millan M, Fraccalvieri D, Kreisler E, Golda T, *et al.* Long-term results of fibrin glue for treatment of transsphincteric perianal fistula: a prospective cohort study. *Colorectal Dis* 2011;**13**:37	No comparison group
de Oca J, Millán M, Jiménez A, Golda T, Biondo S. Long-term results of surgery plus fibrin sealant for anal fistula. *Colorectal Dis* 2012;**14**:e12–15	No comparison group

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TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
De Stefano A, Bettarini F, Di Mare G, Neri A. [Enteric anastomosis and Tachosil®.] *Minerva Chir* 2011;**66**:183–8	No adverse effects related to fibrin reported
de Vries J, Menovsky T, Grotenhuis JA, van Overbeeke JJ. Protective coating of cranial nerves with fibrin glue (Tissucol) during cranial base surgery: technical note. *Neurosurgery* 1998;**43**:1242–6	No comparison group
de Wit D, Athanasiadis I, Sharma A, Moore J. Sutureless and glue-free conjunctival autograft in pterygium surgery: a case series. *Eye* 2010;**24**:1474–7	No comparison group
Defrere J, Franckart A. Teflon/polyurethane arthroplasty of the knee: the first 2 years preliminary clinical experience in a new concept of artificial resurfacing of full thickness cartilage lesions of the knee. *Acta Chir Belg* 1992;**92**:217–27	No comparison group
Delanois RE, Mont MA. Does tranexamic acid reduce blood loss in total knee arthroplasty? Commentary on an article by X. Aguilera, MD, *et al.*: 'Efficacy and safety of fibrin glue and tranexamic acid to prevent postoperative blood loss in total knee arthroplasty. A randomized controlled clinical trial'. *J Bone Joint Surg Am* 2013;**95**:e179	RCT
Della Corte A, Baldascino F, La Marca F, Scardone M, Nappi G, Cefarelli M, *et al.* Hemostatic modifications of the Bentall procedure: imbricated proximal suture and fibrin sealant reduce postoperative morbidity and mortality rates. *Tex Heart Inst J* 2012;**39**:206–10	No comparison group
Dello Russo N. Questions concerning the safety of the tissue adhesive (Tissucol). *J Periodontol* 1986;**57**:652	Letter/commentary/reply
Depondt J, Koka VN, Nasser T, Portier F, Guedon C, Barry B, *et al.* Use of fibrin glue in parotidectomy closure. *Laryngoscope* 1996;**106**:784–7	Included children
Descottes B, Bagot d'Arc M. Fibrin sealant in inguinal hernioplasty: an observational multicentre study in 1,201 patients. *Hernia* 2009;**13**:505–10	No comparison group
Deutsch M, Meinhart J, Zilla P, Howanietz N, Gorlitzer M, Froeschl A, *et al.* Long-term experience in autologous in vitro endothelialization of infrainguinal ePTFE grafts. *J Vasc Surg* 2009;**49**:352–62	Not a valid comparison
Di Carlo I, Pulvirenti E, Toro A, Ardiri A, Bertino G. Localized fluid collection after carrier-bound fibrin sealant application on liver: complication or proof of efficacy? A long-term clinical observational study. *Hepatogastroenterology* 2011;**58**:937–42	No comparison group
DiMonta *et al.* 2012[117]	RCT
Di Saverio S, Masetti M, Zanello M, De Blasiis MG, Jovine E. Re: Fibrin sealant for prevention of resection surface-related complications after liver resection: a randomized controlled trial. *Ann Surg* 2015;**261**:e77–8	RCT
Diamond *et al.* 2011[232]	RCT
Dick B, Kohnen T, Hessemer V. Fibrin glue in temporal clear corneal tunnel incision. *Eur J Implant Refract Surg* 1995;**7**:224–8	No comparison group
Dimaio CJ, Dorfman MP, Gardner GJ, Nash GM, Schattner MA, Markowitz AJ, *et al.* The use of covered esophageal self-expanding metal Stents (CSEMS) for the management of post-operative colo-rectal anastomotic leaks. *Gastrointest Endosc* 2012;**75**(Suppl. 1):AB425–6	No comparison group
Dimitrakakis G, Podila SR, O'Keefe PA, Kulatilake NE. Biological glue: a word of careful assessment! *Interact Cardiovasc Thorac Surg* 2011;**13**:244–5	Letter/commentary/reply
Dimitrakakis G, von Oppell UO. The use of biological glues in cardiothoracic surgery. *Interact Cardiovasc Thorac Surg* 2011;**13**:118	Letter/commentary/reply
Dimo *et al.* 1989[80]	RCT
Diner EK, Patel SV, Kwart AM. Does fibrin sealant decrease immediate urinary leakage following radical retropubic prostatectomy? *J Urol* 2005;**173**:1147–9	RCT
Dinsmore *et al.* 2000[97]	RCT
Docimo G, Limongelli P, Conzo G, Gili S, Bosco A, Rizzuto A, *et al.* Axillary lymphadenectomy for breast cancer in elderly patients and fibrin glue. *BMC Surg* 2013;**13**(Suppl. 2):8	No adverse effects related to fibrin reported

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Dolay K, Aras B, Tuğcu V, Ozbay B, Aygün E, Taşçi AI. Combined treatment of iatrogenic rectourethral fistula with endoscopic fibrin glue application and clipping. *J Endourol* 2007;**21**:433–6	No comparison group
Dong N, Li C, Chen WS, Qin WJ, Xue YH, Wu HP. Fibrin glue-assisted for the treatment of corneal perforations using glycerin-cryopreserved corneal tissue. *Int J Ophthalmol* 2014;**7**:62–5	No comparison group
Donnez J, Nisolle M. Laparoscopic management of large ovarian endometrial cyst: use of fibrin sealant. *J Gynecol Surg* 1991;**7**:163–6	No adverse effects related to fibrin reported
Dovellini EV, Taddeucci E, Trapani M, Valenti R, Cerisano G, Moschi G, *et al.* Pocket haematoma prevention in patients who required implantation/replacement of a pacemaker or implantable cardiac defibrillator. The PHP study. *G Ital Cardiol* 2011;**12**(Suppl. 1):140S	RCT
Dovellini EV, Taddeucci E, Trapani M, Valenti R, Moschi G, Cerisano G, *et al.* Pocket haematoma prevention in patients who required implantation/replacement of a pacemaker or implantable cardiac defibrillator. The PHP Study. *Eur Heart J* 2011;**32**:305	Duplicate
Doyama H, Tominaga K, Yoshida N, Takemura K, Yamada S. Endoscopic tissue shielding with polyglycolic acid sheets, fibrin glue and clips to prevent delayed perforation after duodenal endoscopic resection. *Dig Endosc* 2014;**26**(Suppl. 2):41–5	No comparison group
Draus JM, Huss SA, Harty NJ, Cheadle WG, Larson GM. Enterocutaneous fistula: are treatments improving? *Surgery* 2006;**140**:570–6	No adverse effects related to fibrin reported
Droghetti *et al.* 2008[124]	RCT
Drumheller GW. Fibrin glue. *Ear Nose Throat J* 2003;**82**:483	Letter/commentary/reply
Du J, Qiu B, Tao J, Ou S, Wang Y. Sellar reconstruction using biomaterials after transsphenoidal surgery in 449 cases of pituitary adenomas. *Neurosurg Q* 2014;**24**:22–6	No comparison group
Du X, Guo W, Liu XP, Jia X, Zhang MH, Yin T, *et al.* [Treatment of type II endoleak after abdominal aortic aneurysm endovascular repair.] *Zhonghua Yi Xue Za Zhi* 2011;**91**:2955–8	No comparison group
Duchesne B, Tahi H, Galand A. Use of human fibrin glue and amniotic membrane transplant in corneal perforation. *Cornea* 2001;**20**:230–2	No comparison group
Dumonceau JM, Cremer M, Lalmand B, Devière J. Esophageal fistula sealing: choice of stent, practical management, and cost. *Gastrointest Endosc* 1999;**49**:70–8	No comparison group
Ebner FM, Paul A, Peters J, Hartmann M. Venous air embolism and intracardiac thrombus after pressurized fibrin glue during liver surgery. *Br J Anaesth* 2011;**106**:180–2	No comparison group
Edelman DS. Fibrin glue fixation of bioactive extracellular matrix mesh compared with soft prolene mesh for laparoscopic hernia repair. *Surg Laparosc Endosc Percutan Tech* 2008;**18**:569–72	No comparison group
Edelman DS. Robotic, laparoscopic inguinal hernia repair. *Surg Endosc* 2015;**29**:S467	No comparison group
Edelman DS, Selesnick H. 'Sports' hernia: treatment with biologic mesh (Surgisis): a preliminary study. *Surg Endosc* 2006;**20**:971–3	No comparison group
Eden CG, Sultana SR, Murray KH, Carruthers RK. Extraperitoneal laparoscopic dismembered fibrin-glued pyeloplasty: medium-term results. *Br J Urol* 1997;**80**:382–9	No comparison group
Eder F, Meyer F, Nestler G, Halloul Z, Lippert H. Sealing of the hepatic resection area using fibrin glue reduces significant amount of postoperative drain fluid. *World J Gastroenterol* 2005;**11**:5984–7	No adverse effects related to fibrin reported
Ederle A, Scattolini C, Vantgini I, Bulighin G, Scuro LA. Human fibrin sealant in upper G.I. tract bleeding. *Endoscopy* 1989;**21**:112	Letter/commentary/reply
Eichler C, Dahdouh F, Sauerwald A, Warm M. Seroma suppression using TissuGlu® in a high-risk patient post-mastectomy: a case report. *J Med Case Rep* 2013;**7**:138	No comparison group
Eide E, Jurgeit H. [Use of fibrin glue in pronounced Dupuytren contracture.] *Handchir Mikrochir Plast Chir* 1985;**17**:145–6	No comparison group

continued

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
El Feghaly M, Chahine E, Abi Ghanem M, Abou Zahr O, Alayli M, Abu Khalil B. Acute limb ischaemia due to embolisation of biological glue 45 days after surgery. *Eur J Vasc Endovasc Surg* 2011;**41**:518–20	No comparison group
El Nakeeb A. Influence of fibrin glue on seroma formation after modified radical mastectomy: a prospective randomized study. *Breast J* 2009;**15**:671–2	RCT
El-Banhawy OA, Halaka AN, El-Hafiz Shehab El-Dien A, Ayad H. Subcranial transnasal repair of cerebrospinal fluid rhinorrhea with free autologous grafts by the combined overlay and underlay techniques. *Minim Invasive Neurosurg* 2004;**47**:197–202	Included children
Elderkin SJ, Epstein RJ, Seldomridge DL. Successful treatment of recurrent epithelial ingrowth associated with interface fluid syndrome, flap necrosis, and epithelial defects following LASIK. *J Refract Surg* 2011;**27**:70–3	No comparison group
Eleftheriadis E, Kotzampassi K. Therapeutic fistuloscopy: an alternative approach in the management of postoperative fistulas. *Dig Surg* 2002;**19**:230–5	Not a valid comparison
Eleftheriadis E, Tzartinoglou E, Kotzampassi K, Aletras H. Early endoscopic fibrin sealing of high-output postoperative enterocutaneous fistulas. *Acta Chir Scand* 1990;**156**:625–8	No comparison group
El-Gazzaz G, Hull T, Mignanelli E, Hammel J, Gurland B, Zutshi M. Analysis of function and predictors of failure in women undergoing repair of Crohn's related rectovaginal fistula. *J Gastrointest Surg* 2010;**14**:824–9	Not a valid comparison
Ellis DA, Pelausa EO. Fibrin glue in facial plastic and reconstructive surgery. *J Otolaryngol* 1988;**17**:74–7	Not a comparative observational study
Ellis DA, Shaikh A. The ideal tissue adhesive in facial plastic and reconstructive surgery. *J Otolaryngol* 1990;**19**:68–72	No adverse effects related to fibrin reported
Ellis DA, Pelausa EO. Fibrin glue in facial plastic and reconstructive surgery. *J Otolaryngol* 1988;**17**:74–7	Duplicate
Ellis DA, Shaikh A. The ideal tissue adhesive in facial plastic and reconstructive surgery. *J Otolaryngol* 1990;**19**:68–72	Duplicate
Eloy JA, Choudhry OJ, Friedel ME, Kuperan AB, Liu JK. Endoscopic nasoseptal flap repair of skull base defects: is addition of a dural sealant necessary? *Otolaryngol Head Neck Surg* 2012;**147**:161–6	Not fibrin sealant
Eltorai IM, Montroy RE, Kaplan SL, Ho WH. Pneumocephalus secondary to cerebrospinal fluid leak associated with a lumbar pressure ulcer in a man with paraplegia. *J Spinal Cord Med* 2003;**26**:262–9	No comparison group
Emmert MY, Salzberg SP, Theusinger OM, Felix C, Plass A, Hoerstrup SP, *et al.* How good patient blood management leads to excellent outcomes in Jehovah's witness patients undergoing cardiac surgery. *Interact Cardiovasc Thorac Surg* 2011;**12**:183–8	No comparison group
Engler S, Dorlars D, Riemann JF. [Endoscopic fibrin gluing of a pancreatic duct fistula following acute pancreatitis.] *Dtsch Med Wochenschr* 1996;**121**:1396–400	No comparison group
Enoki C, Higashi S, Oohata M, Tanaka T. [A case of acute erythroblastic anemia due to infection with human parvovirus B19 after coronary artery bypass grafting.] *Kyobu Geka* 2002;**55**:116–19	No comparison group
Epstein NE. Wound-peritoneal shunts: part of the complex management of anterior dural lacerations in patients with ossification of the posterior longitudinal ligament. *Surg Neurol* 2009;**72**:630–4	No comparison group
Epstein NE. Tisseel utilized as hemostatic in spine surgery impacts time to drain removal and length of stay. *Surg Neurol Int* 2014;**5**(Suppl. 7):354–61	Not a relevant comparison
Epstein NE. Hemostasis and other benefits of fibrin sealants/glues in spine surgery beyond cerebrospinal fluid leak repairs. *Surg Neurol Int* 2014;**5**(Suppl. 7):304–14	Not a comparative observational study
Erba *et al.* 2010[210]	RCT
Erbagci I, Bekir N. Sutureless closure of the conjunctiva with a commercial fibrin sealant in extraocular muscle surgery for strabismus. *Strabismus* 2007;**15**:89–94	No comparison group

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Erdogan A, Gurses G, Keskin H, Demircan A. The sealing effect of a fibrin tissue patch on the esophageal perforation area in primary repair. *World J Surg* 2007;**31**:2199–203	Emergency surgery
Erdogru T, Sanli A, Celik O, Baykara M. Laparoscopic transvesical repair of recurrent vesicovaginal fistula using with fleece-bound sealing system. *Arch Gynecol Obstet* 2008;**277**:461–4	No comparison group
Eriksen JR. Pain and convalescence following laparoscopic ventral hernia repair. *Dan Med Bull* 2011;**58**:B4369	Not a relevant comparison
Eriksen *et al.* 2013[183]	Not a comparative observational study
Esposito F, Cappabianca P, Fusco M, Cavallo LM, Bani GG, Biroli F, *et al.* Collagen-only biomatrix as a novel dural substitute. Examination of the efficacy, safety and outcome: clinical experience on a series of 208 patients. *Clin Neurol Neurosurg* 2008;**110**:343–51	No comparison group
Esposito F, Grimod G, Cavallo LM, Lanterna L, Biroli F, Cappabianca P. Collagen-only biomatrix as dural substitute: what happened after a 5-year observational follow-up study. *Clin Neurol Neurosurg* 2013;**115**:1735–7	No comparison group
Esquenazi S, Rand W, Velazquez G, Grunstein L. Novel therapeutic approach in the management of band keratopathy using amniotic membrane transplantation with fibrin glue. *Ophthalmic Surg Lasers Imaging* 2008;**39**:418–21	No comparison group
Esteban F, Delgado-Rodríguez M, Mochón A, Solano J, Soldado L, Solanellas J. [Study of in-patient hospital stay following total laryngectomy: multivariable retrospective analysis of a 442 total laryngectomies.] *Acta Otorrinolaringol Esp* 2006;**57**:176–82	Not a relevant comparison
Etienney I, Rabahi N, Cuenod CA, Hoffmann P, Charachon A, Bauer P. Fibrin glue sealing in the treatment of a recto-urethral fistula in Crohn's disease: a case report. *Gastroenterol Clin Biol* 2009;**33**:1094–7	No comparison group
Evans LA, Ferguson KH, Foley JP, Rozanski TA, Morey AF. Fibrin sealant for the management of genitourinary injuries, fistulas and surgical complications. *J Urol* 2003;**169**:1360–2	No comparison group
Evaristo-Méndez G, Sánchez-Hernández AT, Melo-Velázquez A, Ventura-Sauceda FA, Sepúlveda-Castro RR. [Sigmoido-buttock fistula by diverticulitis: report of a rare complication.] *Cir Cir* 2013;**81**:158–62	No comparison group
Everts PA, Devilee RJ, Brown Mahoney C, Eeftinck-Schattenkerk M, Box HA, Knape JT, *et al.* Platelet gel and fibrin sealant reduce allogeneic blood transfusions in total knee arthroplasty. *Acta Anaesthesiol Scand* 2006;**50**:593–9	Not a relevant comparison
Fabian *et al.* 2003[128]	RCT
Falavarjani KG, Modarres M, Foroutan A, Bakhtiari P. Fibrin glue-assisted sutureless scleral fixation. *J Cataract Refract Surg* 2009;**35**:795	Letter/commentary/reply
Falez *et al.* 2013[154]	RCT
Falsaperla M, Autorino R, Puglisi M, Damiano R, Salerno GL, Motta M, *et al.* Haemostatic agents during laparoscopic nephron-sparing surgery: what about TachoSil? *BJU Int* 2009;**104**:270–1	Letter/commentary/reply
Falworth MS, Butler PM, Powell BW. The use of fibrin glue to prevent seroma formation following sentinel node biopsy. *Plast Reconstr Surg* 1999;**104**:2331–2	Letter/commentary/reply
Fanari M, Serra S, Corona A, De Lisa A. [Use of TachoSil in laparoscopic enucleoresection of renal masses smaller than 4 cm: our preliminary experience of 41 cases.] *Urologia* 2012;**79**(Suppl. 19):131–3	No comparison group
Farhat F, Durand M, Delahaye F, Jegaden O. Prosthetic valve sewing-ring sealing with antibiotic and fibrin glue in infective endocarditis. A prospective clinical study. *Interact Cardiovasc Thorac Surg* 2007;**6**:16–20	No comparison group
Farr IJ, Cole BJ, Tabet S. Prospective study of particulated juvenile allograft cartilage to treat knee femoral cartilage lesions. *Arthroscopy* 2013;**29**(Suppl. 1):e27	No comparison group

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TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Farrag TY, Boahene KD, Agrawal N, Turner L, Byrne PJ, Earnest L, *et al.* Use of fibrin sealant in closing mucocutaneous fistulas following head and neck cancer surgery. *Otolaryngol Head Neck Surg* 2007;**137**:159–61	No adverse effects related to fibrin reported
Faust A, Aguillard R, Finch C. Use of fibrin glue administered during bronchoscopy to seal a persistent bronchopleural fistula: a case report. *Crit Care Med* 2010;**38**:A266	No comparison group
Fava MA, Choi CJ, El Mollayess G, Melki SA. Sandwich fibrin glue technique for attachment of conjunctival autograft during pterygium surgery. *Can J Ophthalmol* 2013;**48**:516–20	Not a relevant comparison
Federici AB, Sacco R, Stabile F, Carpenedo M, Zingaro E, Mannucci PM. Optimising local therapy during oral surgery in patients with von Willebrand disease: effective results from a retrospective analysis of 63 cases. *Haemophilia* 2000;**6**:71–7	Included children
Fékété *et al.* 1992[91]	RCT
Felipetto R, Vigano L, Cecchi M, Florentini L, Minervini R. Use of fibrin sealant in the treatment of prostatic cutaneous fistula in a case of *Pseudomonas prostatitis*. *Int Urol Nephrol* 1995;**27**:563–5	No comparison group
Feng JX, Lu QS, Jing ZP, Yang Y, Nie B, Bao JM, *et al.* [Fibrin glue embolization treating intra-operative type I endoleak of endovascular repair of abdominal aortic aneurysm: long-term result.] *Zhonghua Wai Ke Za Zhi* 2011;**49**:883–7	No comparison group
Ferlitsch A, Puspok A, Wewalka F, Schoefl R, Brownstone E, Madl C, *et al.* A multi-centre proof of concept study to assess efficacy and safety of a new liquid endoscopic hemostatic agent (Seraseal/Fastact) in patients with active gastrointestinal bleeding. *Gastrointest Endosc* 2014;**79**(Suppl. 1):AB151–2	Not fibrin sealant
Fernández Lobato R, García Septiem J, Ortega Deballon P, Martín Lucas FJ, Ruíz de Adana JC, Limones Esteban M. Tissucol application in dermolipectomy and incisional hernia repair. *Int Surg* 2001;**86**:240–5	RCT
Fernandez-Esparrach G, Lautz DB, Thompson CC. Peroral endoscopic anastomotic reduction improves intractable dumping syndrome in Roux-en-Y gastric bypass patients. *Surg Obes Relat Dis* 2010;**6**:36–40	No comparison group
Fernandez-Lobato R, Angulo-Morales F, Garcia-Septiem J, Hernandez-Matias A, Marin-Lucas J, Limones-Esteban M. Ten years of experience about laparoscopic ventral hernia repair. *Surg Endosc* 2011;**25**:S56	No comparison group
Fernandez-Lobato R, Bagot D'Arc M, Krishnan S. An economic evaluation of fibrin sealants used during incisional hernia with dermolipectomy procedures in Spain. *Value Health* 2010;**13**:A103	Not a comparative observational study
Ferrarese A, Marola S, Surace A, Borello A, Bindi M, Cumbo J, *et al.* Fibrin glue versus stapler fixation in laparoscopic transabdominal inguinal hernia repair: a single center 5-year experience and analysis of the results in the elderly. *Int J Surg* 2014;**12**(Suppl. 2):94–8	No adverse effects related to fibrin reported
Ferrer-Puchol MD, Gil-Romero J, Laso-Pablos S, Guijarro-Rosaleny J. Treatment of oesophago-cutaneous fistula with covered stent and percutaneous fibrin tissue sealant. *J Intervent Radiol* 1999;**14**:222–5	No comparison group
Figueras *et al.* 2007[71]	RCT
Filosso *et al.* 2013[136]	RCT
Finch CK, Pittman AL. Use of fibrin glue to treat a persistent pneumothorax with bronchopleural fistula. *Am J Health Syst Pharm* 2008;**65**:322–4	No comparison group
Finck C, Lefebvre P. Implantation of esterified hyaluronic acid in microdissected Reinke's space after vocal fold microsurgery: first clinical experiences. *Laryngoscope* 2005;**115**:1841–7	No comparison group
Fine AP. Laparoscopic repair of inguinal hernia using Surgisis mesh and fibrin sealant. *JSLS* 2006;**10**:461–5	No comparison group
Fink D, Klein JJ, Kang H, Ergin MA. Application of biological glue in repair of intracardiac structural defects. *Ann Thorac Surg* 2004;**77**:506–11	No comparison group

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Fiore A, Grandmougin D, Maureira JP, Elfarra M, Laurent N, Andronache M, *et al.* Efficacy of TachoSil® as a sutureless hemostatic patch to repair a perforation of the interventricular groove during endocardial radiofrequency ablation. *J Cardiovasc Surg* 2014;**55**:295–8	No comparison group
Fischer A, Benz S, Baier P, Hopt UT. Endoscopic management of pancreatic fistulas secondary to intraabdominal operation. *Surg Endosc* 2004;**18**:706–8	No comparison group
Fischer *et al.* 2013[241]	RCT
Fischer CP, Wood CG, Shen J, Batiller J, Hart JC, Patel B, *et al.* A randomized trial of aprotinin-free fibrin sealant versus absorbable hemostat. *Clin Appl Thromb Hemost* 2011;**17**:572–7	RCT
Fischer *et al.* 2011[72]	RCT
Fleisher AG, Evans KG, Nelems B, Finley RJ. Effect of routine fibrin glue use on the duration of air leaks after lobectomy. *Ann Thorac Surg* 1990;**49**:133–4	RCT
Flemming I. Fibrin glue in face lifts. *Facial Plast Surg* 1992;**8**:79–88	RCT
Fortelny RH, Petter-Puchner AH, Glaser KS. Fibrin sealant (Tissucol) for the fixation of hiatal mesh in the repair of giant paraesophageal hernia: a case report. *Surg Laparosc Endosc Percutan Tech* 2009;**19**:e91–4	No comparison group
Fortelny RH, Petter-Puchner AH, Khakpour Z, May C, Mika K, Glaser KS, *et al.* Spray application of fibrin sealant with an angled spray tip device in laparoscopic inguinal hernia repair. *Eur Surg* 2010;**42**:171–6	No comparison group
Fortelny RH, Petter-Puchner AH, May C, Jaksch W, Benesch T, Khakpour Z, *et al.* The impact of atraumatic fibrin sealant vs. staple mesh fixation in TAPP hernia repair on chronic pain and quality of life: results of a randomized controlled study. *Surg Endosc* 2012;**26**:249–54	RCT
Fortunato G, Bonucci E. Two cases of reconstruction of large defects of the facial skeleton with hydroxyapatite-fibrin glue. *Rivista Italiana di Chirurgia Plastica* 1996;**28**:17–29	No comparison group
Foster JA, Holck DE, Perry JD, Wulc AE, Burns JA, Cahill KV, *et al.* Fibrin sealant for Müller muscle-conjunctiva resection ptosis repair. *Ophthal Plast Reconstr Surg* 2006;**22**:184–7	No comparison group
Foster K, Greenhalgh D, Gamelli RL, Mozingo D, Gibran N, Neumeister M, *et al.* Efficacy and safety of a fibrin sealant for adherence of autologous skin grafts to burn wounds: results of a phase 3 clinical study. *J Burn Care Res* 2008;**29**:293–303	RCT
Fountas KN, Kapsalaki EZ, Johnston KW. Cerebrospinal fluid fistula secondary to dural tear in anterior cervical discectomy and fusion: case report. *Spine* 2005;**30**:E277–80	No comparison group
Fraioli RE, Hirsch BE, Kassam AB. Fibrin sealant for control of cerebrospinal fluid otorrhea. *Am J Otolaryngol* 2008;**29**:135–7	No comparison group
Franco-Vidal V, Daculsi G, Bagot d'Arc M, Sterkers O, Smail M, Robier A, *et al.* Tolerance and osteointegration of TricOs(TM)/MBCP in association with fibrin sealant in mastoid obliteration after canal wall-down technique for cholesteatoma. *Acta Oto-Laryngologica* 2014;**134**:358–65	No comparison group
Frena A, Martin F. How to improve bilio-stasis in liver surgery. *Chir Ital* 2006;**58**:793–5	No comparison group
French DB, Marcovich R. Fibrin sealant for retrograde ureteroscopic closure of urine leak after partial nephrectomy. *Urology* 2006;**67**:1085.e1–3	No comparison group
Frilling *et al.* 2005[73]	RCT
Fu *et al.* 2009[78]	RCT
Fuks D, Bréhant O, Dumont F, Viart L, Manaouil D, Bartoli E, *et al.* [Tissue adhesive treatment of persistent recto-cutaneous fistula following Hartmann procedure.] *J Chir* 2007;**144**:35–8	No comparison group
Fuks D, Bréhant O, Dumont F, Viart L, Manaouil D, Bartoli E, *et al.* [Tissue adhesive treatment of persistent recto-cutaneous fistula following Hartmann procedure.] *J Chir* 2007;**144**:35–8	Duplicate
Fuks D, Verhaeghe P, Brehant O, Sabbagh C, Dumont F, Riboulot M, *et al.* Results of laparoscopic sleeve gastrectomy: a prospective study in 135 patients with morbid obesity. *Surgery* 2009;**145**:106–13	No comparison group

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TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Fullarton G, Galloway D, Albillos A, Calleja JL, Rutgeerts P, Wara P, *et al.* Randomised trial of fibrin glue versus polidocanol for bleeding peptic ulcer (multiple letters). *Lancet* 1997;**350**:1397–8	Letter/commentary/reply
Fuller CW, Gillespie MB, Nguyen SA, Jones T, Hornig JD. A double-blind, randomized, placebo-controlled clinical trial evaluating fibrin sealant in thyroidectomy closure. *Otolaryngol Head Neck Surg* 2014;**151**(Suppl. 1):P160–1	RCT
Fullum TM, Aluka KJ, Turner PL. Decreasing anastomotic and staple line leaks after laparoscopic Roux-en-Y gastric bypass. *Surg Endosc* 2009;**23**:1403–8	RCT
Furey CG, Sadowski K, Ahn NU. Recurrent CSF leak following repair of incidental durotomy. *Spine J* 2014;**14**(Suppl. 1):113	Abstract
Furrer *et al.* 1993[116]	RCT
Furuse M, Ishikawa M, Nishida N, Aoki T, Takahashi JA. Transposition of the vertebral artery with fibrin glue adhesive in microvascular decompression: a case report. *Neurosurg Q* 2010;**20**:170–2	No comparison group
Gaertner WB, Madoff RD, Spencer MP, Mellgren A, Goldberg SM, Lowry AC. Results of combined medical and surgical treatment of recto-vaginal fistula in Crohn's disease. *Colorectal Dis* 2011;**13**:678–83	No comparison group
Gagarine A, Urschel JD, Miller JD, Bennett WF, Young JE. Effect of fibrin glue on air leak and length of hospital stay after pulmonary lobectomy. *J Cardiovasc Surg* 2003;**44**:771–3	No adverse effects related to fibrin reported
Gage EA, Jones GE, Powelson JA, Johnson MS, Goggins WC, Fridell JA. Treatment of enterocutaneous fistula in pancreas transplant recipients using percutaneous drainage and fibrin sealant: three case reports. *Transplantation* 2006;**82**:1238–40	No comparison group
Galajda Z, Fulop T, Peterffy A, Alamanni F, Parolari A, Biglioli P. Subacute left ventricular rupture complicated by free wall rupture: repair with a TachoComb sheet and Tissucol glue (multiple letters). *J Thorac Cardiovasc Surg* 2002;**123**:1014–6	Letter/commentary/reply
Gallego JM, Barcia JA, Barcia-Mariño C. Fatal outcome related to carmustine implants in glioblastoma multiforme. *Acta Neurochir* 2007;**149**:261–5	No comparison group
Galor A, Yoo SH, Piccoli FV, Schmitt AJ, Chang V, Perez VL. Phase I study of subconjunctival ranibizumab in patients with primary pterygium undergoing pterygium surgery. *Am J Ophthalmol* 2010;**149**:926–31.e2	RCT
Galosi AB, Lacetera V, Tiroli M, Conti A, Muzzonigro G. Haemostatic sponge application on Denonvillier fascia after open nerve-sparing prostatectomy. *Anticancer Res* 2010;**30**:1430	No comparison group
Gammon RR, Prum BE Jr, Avery N, Mintz PD. Rapid preparation of small-volume autologous fibrinogen concentrate and its same day use in bleb leaks after glaucoma filtration surgery. *Ophthalmic Surg Lasers* 1998;**29**:1010–12	No comparison group
Ganekal S, Venkataratnam S, Dorairaj S, Jhanji V. Comparative evaluation of suture-assisted and fibrin glue-assisted scleral fixated intraocular lens implantation. *J Refract Surg* 2012;**28**:249–52	No adverse effects related to fibrin reported
Garcia-Caballero M, Carbajo M, Martinez-Moreno JM, Sarria M, Osorio D, Carmona JA. Drain erosion and gastro-jejunal fistula after one-anastomosis gastric bypass: endoscopic occlusion by fibrin sealant. *Obes Surg* 2005;**15**:719–22	No comparison group
Garcia-Olmo D, Herreros M, Guadalajara H, DeLaQuintana P, Trebol J, Georgiev-Hristov T, *et al.* Expanded adipose derived autologous stem cells for the treatment of complex cryptoglandular fistulas. A phase III clinical trial (fatt1: Fistulaadvanced therapy trial 1) and longterm evaluation (LTE). *Dis Colon Rectum* 2011;**54**:e68–9	RCT
Garcia-Villarreal OA, Casillas-Covarrubias LE. Fibrin sealant for left ventricular rupture after mitral valve replacement. *Asian Cardiovasc Thorac Ann* 2008;**16**:152–3	No comparison group
Garçon C, Cavaillon JP, Girard P. [The use of Tissucol in oral surgery in problems of hemostasis.] *Chir Dent Fr* 1986;**56**:49–55	Included children
Gatti MAN, Vieira LM, Barraviera B, Barraviera S. Treatment of venous ulcers with fibrin sealant derived from snake venom. *J Venom Anim Toxins* 2011;**17**:226–9	RCT

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Gauthier L, Lagoutte F. [Use of a fibrin glue (Tissucol) for treating perforated or pre-perforated corneal ulcer.] *J Fr Opthalmol* 1989;**12**:469–76	No comparison group
Gazzeri R, Fiore C, Galarza M. (EVICEL) for augmentation of dural closure: results of a preliminary clinical study. *Surg Technol Int* 2014;**25**:265–70	No adverse effects related to fibrin reported
Gazzeri R, Galarza M, Alfieri A, Neroni M, Roperto R. Simple intraoperative technique for minor dural gap repair using fibrin glue and oxidized cellulose. *World Neurosurg* 2011;**76**:173–5	No comparison group
Gazzeri R, Galarza M, Fiore C, Callovini G, Alfieri A. Use of tissue-glue-coated collagen sponge (TachoSil) to repair minor cerebral dural venous sinus lacerations: technical note. *Neurosurgery* 2015;**11**(Suppl. 2):32–6	No comparison group
Gazzeri R, Neroni M, Alfieri A, Galarza M, Faiola A, Esposito S, *et al.* Transparent equine collagen biomatrix as dural repair. A prospective clinical study. *Acta Neurochir* 2009;**151**:537–43	No comparison group
Gentili ME. Epidural fibrin glue injection stops postdural puncture headache in patient with long-term intrathecal catheterization. *Reg Anesth Pain Med* 2003;**28**:70	No comparison group
Genyk Y, Kato T, Pomposelli JJ, Lophaven KW, Chapman WC. Tachosil versus surgicel original for the secondary treatment of local bleeding in adult patients undergoing hepatic resection. *HPB* 2014;**16**:27	RCT
Germanidis G, Papavramidis TS, Mantzoukis K, Sapalidis K, Divanis D, Kalevrosoglou I, *et al.* Fibrin glue as a protective biomembrane for a duodenal ulcer vessel. *Endoscopy* 2010;**42**(Suppl. 2):E348–9	No comparison group
Gerritse BM, van Dongen RT, Crul BJ. Epidural fibrin glue injection stops persistent cerebrospinal fluid leak during long-term intrathecal catheterization. *Anesth Analg* 1997;**84**:1140–1	No comparison group
Ghavanini AA, Scott CA, Chan DK, Tang-Wai DF. Management of patients with spontaneous intracranial hypotension causing altered level of consciousness: report of two cases and review of literature. *Cephalalgia* 2013;**33**:43–51	No comparison group
Ghelardi A, di Stefano C, Galante L, Guelfi F, Migliorini P. Inguinofemoral lymphadenectomy in patients undergoing radical vulvectomy for vulvar cancer. A new patch is able to reduce lymphatic complications. *Ital J Gynaecol Obstet* 2011;**23**:139–46	No adverse effects related to fibrin reported
Ghotb A, Shah JN, Binmoeller KF, Weilert F, Bhat YM. Efficacy of endoscopic treatment of symptomatic upper gastrointestinal leaks and fistulas post-bariatric surgery: report of 25 cases. *Gastrointest Endosc* 2011;**73**(Suppl. 1):AB395	No comparison group
Giampapa VC, Bitar GJ. Use of fibrin sealant in neck contouring. *Aesthet Surg J* 2002;**22**:519–25	No comparison group
Gibran N, Luterman A, Herndon D, Lozano D, Greenhalgh DG, Grubbs L, *et al.* Comparison of fibrin sealant and staples for attaching split-thickness autologous sheet grafts in patients with deep partial- or full-thickness burn wounds: a phase 1/2 clinical study. *J Burn Care Res* 2007;**28**:401–8	RCT
Gidaro S, Cindolo L, Lipsky K, Zigeuner R, Schips L. Efficacy and safety of the haemostasis achieved by Vivostat system during laparoscopic partial nephrectomy. *Arch Ital Urol Androl* 2009;**81**:223–7	No comparison group
Gilat H, Rappaport Z, Yaniv E. Endoscopic transnasal cerebrospinal fluid leak repair: a 10 year experience. *Isr Med Assoc J* 2011;**13**:597–600	Included children
Gille J, Schuseil E, Wimmer J, Gellissen J, Schulz AP, Behrens P. Mid-term results of autologous matrix-induced chondrogenesis for treatment of focal cartilage defects in the knee. *Knee Surg Sports Traumatol Arthrosc* 2010;**18**:1456–64	No comparison group
Gilly *et al.* 1998[108]	RCT
Gioffrè Florio MA, Mezzasalma F, Manganaro T, Pakravanan H, Cogliandolo A. [The use of fibrin glue in the surgery of breast carcinoma.] *G Chir* 1993;**14**:239–41	RCT
Giovannacci L, Eugster T, Stierli P, Hess P, Gürke L. Does fibrin glue reduce complications after femoral artery surgery? A randomised trial. *Eur J Vasc Endovasc Surg* 2002;**24**:196–201	RCT

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TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Giovannacci L, Renggli JC, Eugster T, Stierli P, Hess P, Gürke L. Reduction of groin lymphatic complications by application of fibrin glue: preliminary results of a randomized study. *Ann Vasc Surg* 2001;**15**:182–5	RCT
Girard S, Sideman M, Spain DA. A novel approach to the problem of intestinal fistulization arising in patients managed with open peritoneal cavities. *Am J Surg* 2002;**184**:166–7	No comparison group
Gisbertz SS, Sosef MN, Festen S, Gerhards MF. Treatment of fistulas in ano with fibrin glue. *Dig Surg* 2005;**22**:91–4	No comparison group
Giugno A, Maugeri R, D'Arpa S, Visocchi M, Iacopino DG. Complex reconstructive surgery following removal of extra-intracranial meningiomas, including the use of autologous fibrin glue and a pedicled muscle flap. *Interdisc Neurosurg* 2014;**1**:84–7	No comparison group
Giuliani G, Coletta D, Farina A, Guerra F, Velluti F, Iaquinandi F, *et al.* Perineal surgical approach to treat rectourethral fistula with Tachosil© patch apposition: a case report. *Tech Coloproctol* 2013;**17**:138	No comparison group
Glimåker H, Björck CG, Hallstensson S, Ohlsén L, Westman B. Avoiding blow-out of the aortic stump by reinforcement with fibrin glue. A report of two cases. *Eur J Vasc Surg* 1993;**7**:346–8	No comparison group
Glitsch A, von Bernstorff W, Seltrecht U, Partecke I, Paul H, Heidecke CD. Endoscopic transanal vacuum-assisted rectal drainage (ETVARD): an optimized therapy for major leaks from extraperitoneal rectal anastomoses. *Endoscopy* 2008;**40**:192–9	No comparison group
Glover W, Chavis TV, Daniel TM. Fibrin glue application through the flexible fiberoptic bronchoscope: closure of bronchopleural fistulas. *J Thorac Cardiovasc Surg* 1987;**93**:470–2	No comparison group
Godeberge P, Blain A, Christidis C, Denet C, Levard H, Mal F, *et al.* Biological glue in the treatment of postoperative fistula in colorectal surgery. *Acta Endoscopica* 2009;**39**:424–8	No comparison group
Goerler H, Oppelt P, Abel U, Haverich A. Safety of the use of Tissucol Duo S in cardiovascular surgery: retrospective analysis of 2149 patients after coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2007;**32**:560–6	Includes emergency surgery; overall 9.3% of patients
Gonfiotti *et al.* 2011[130]	RCT
González-Ojeda A, Avalos-González J, Muciño-Hernández MI, López-Ortega A, Fuentes-Orozco C, Sánchez-Hochoa M, *et al.* Fibrin glue as adjuvant treatment for gastrocutaneous fistula after gastrostomy tube removal. *Endoscopy* 2004;**36**:337–41	No adverse effects related to fibrin reported
Gopal SC, Gangopadhyay AN, Mohan TV, Upadhyaya VD, Pandey A, Upadhyaya A, *et al.* Use of fibrin glue in preventing urethrocutaneous fistula after hypospadias repair. *J Pediatr Surg* 2008;**43**:1869–72	RCT
Grau AE, Durán JA. Treatment of a large corneal perforation with a multilayer of amniotic membrane and TachoSil. *Cornea* 2012;**31**:98–100	No comparison group
Graziano F, Certo F, Basile L, Maugeri R, Grasso G, Meccio F, *et al.* Autologous fibrin sealant (Vivostat) in the neurosurgical practice: part I: intracranial surgical procedure. *Surg Neurol Int* 2015;**6**:77	No comparison group
Greco DP, Fei L, Guerriero L, Pradella P, Mazzola M, Magistro C, *et al.* Feasibility and effectiveness of primary umbilical hernia repair with biologic graft: preliminary study. *Acta Chir Belg* 2014;**114**:125–30	No comparison group
Greco S, Tringali A, Familiari P, Boskoski I, Perri V, Costamagna G. A rescue therapy for refractory post-sphincterotomy and post-papillectomy bleeding: fibrin glue injection. *Dig Liver Dis* 2015;**47**:e153	Not a relevant comparison
Greenberg R, Kashtan H, Skornik Y, Werbin N. Treatment of pilonidal sinus disease using fibrin glue as a sealant. *Tech Coloproctol* 2004;**8**:95–8	No comparison group
Greenberg R, Werbin N, Skornik Y, Kaplan O. [Repair of anorectal fistulas using fibrin glue tissue adhesive – preliminary experience in 15 patients.] *Harefuah* 2002;**141**:1021–4, 1091	No comparison group
Greenhalgh DG, Gamelli RL, Lee M, Delavari M, Lynch JB, Hansbrough JF, *et al.* Multicenter trial to evaluate the safety and potential efficacy of pooled human fibrin sealant for the treatment of burn wounds. *J Trauma* 1999;**46**:433–40	RCT

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Grewing R, Mester U. Fibrin sealant in the management of complicated hypotony after trabeculectomy. *Ophthalmic Surg Lasers* 1997;**28**:124–7	No comparison group
Grimaud JC, Munoz-Bongrand N, Siproudhis L, Abramowitz L, Sénéjoux A, Vitton V, *et al.* Fibrin glue is effective healing perianal fistulas in patients with Crohn's disease. *Gastroenterology* 2010;**138**:2275–81	RCT
Groitl H, Scheele J. Initial experience with the endoscopic application of fibrin tissue adhesive in the upper gastrointestinal tract. *Surg Endosc* 1987;**1**:93–7	No comparison group
Grossman JA, Capraro PA, Atagi T. A prospective, randomized, double-blind trial of the use of fibrin sealant for face lifts. *Plast Reconstr Surg* 2002;**110**:1371–2	RCT
Gubitosi A, Docimo G, Parmeggiani D, Pirozzi R, Vitiello C, Schettino P, *et al.* Acellular bovine pericardium dermal matrix in immediate breast reconstruction after skin sparing mastectomy. *Int J Surg* 2014;**12**(Suppl. 1):205–8	No comparison group
Gubitosi A, Ruggiero R, Docimo G, Avenia N, Villaccio G, Esposito A, *et al.* Hepatic cirrhosis and groin hernia: binomial or dichotomy? Our experience with a safe surgical treatment protocol. *Ann Ital Chir* 2011;**82**:197–204	No comparison group
Gugenheim J, Bredt LC, Iannelli A. A randomized controlled trial comparing fibrin glue and PlasmaJet on the raw surface of the liver after hepatic resection. *Hepatogastroenterology* 2011;**58**:922–5	RCT
Guilmet D, Bachet J, Goudot B, Laurian C, Gigou F, Bical O, *et al.* Use of biological glue in acute aortic dissection. Preliminary clinical results with a new surgical technique. *J Thorac Cardiovasc Surg* 1979;**77**:516–21	Emergency surgery
Gündoğdu AG, Yazicioğlu A, Kara M, Kanbak M, Doğan R. [The use of tissue glue and its effect on hospital cost in patients undergoing pulmonary surgery.] *Tuberk Toraks* 2006;**54**:157–60	No adverse effects related to fibrin reported
Guo S, Wagner RS, Forbes BJ, DeRespinis PA, Caputo AR. Cut and paste: sutureless conjunctival closure in strabismus surgery. *J Pediatr Ophthalmol Strabismus* 2010;**47**:228–30	No comparison group
Gürer B, Kertmen H, Akturk UD, Kalan M, Sekerci Z. Use of the bovine pericardial patch and fibrin sealant in meningomyelocele closure. *Acta Neurochir* 2014;**156**:1345–50	No comparison group
Gursoy S, Yapucu MU, Ucvet A, Yazgan S, Basok O, Ermete S. Fibrin glue administration to support bronchial stump line. *Asian Cardiovasc Thorac Ann* 2008;**16**:450–3	No comparison group
Gutierrez C, Barrios JE, Lluna J, Vila JJ, Garcia-Sala C, Roca A, *et al.* Recurrent tracheoesophageal fistula treated with fibrin glue. *J Pediatr Surg* 1994;**29**:1567–9	Not fibrin sealant
Gutiérrez Calzada JL, Burgos Rodríguez R. [Partial transplantectomy combined with substitution of the urinary tract, in the treatment of segmental renal infarction after transplantation.] *Arch Esp Urol* 1996;**49**:1093–9	No comparison group
Gutiérrez San Román C, Barrios JE, Lluna J, Ibañez V, Hernández E, Ayuso L, *et al.* Long-term assessment of the treatment of recurrent tracheoesophageal fistula with fibrin glue associated with diathermy. *J Pediatr Surg* 2006;**41**:1870–3	No comparison group
Gutiérrez-Calzada JL, Ramos-Titos J, González-Bonilla JA, Garcia-Vaquero AS, Martin-Morales A, Burgos-Rodríguez R. Caliceal fistula formation following renal transplantation: management with partial nephrectomy and ureteral replacement. *J Urol* 1995;**153**:612–14	No comparison group
Haas S. The use of a surgical patch coated with human coagulation factors in surgical routine: a multicenter postauthorization surveillance. *Clin Appl Thromb Hemost* 2006;**12**:445–50	No comparison group
Habesoglu TE, Kulekci S, Habesoglu M, Deveci I, Deveci S, Toros S, *et al.* Comparative outcomes of using fibrin glue in septoplasty and its effect on mucociliary activity. *Otolaryngol Head Neck Surg* 2010;**142**:394–9	No adverse effects related to fibrin reported
Hadzhiev B. [Treatment of chronic anorectal fistulas by fibrin sealant.] *Khirurgiia* 2008;**3**:41–5	No comparison group
Haga T, Kurihara M, Kataoka H. Spontaneous pneumothorax with persistent air leakage and invasive procedures. *Intern Med* 2013;**52**:2189–92	No comparison group

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TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Haim N, Neufeld D, Ziv Y, Tulchinsky H, Koller M, Khaikin M, *et al.* Long term success of fibrin glue in the treatment of perianal fistulae – a multicenter study. *Colorectal Dis* 2010;**12**:52	No comparison group
Haim N, Neufeld D, Ziv Y, Tulchinsky H, Koller M, Khaikin M, *et al.* Long-term success of fibrin glue in the treatment of perianal fistulas – a multicenter study. *Dis Colon Rectum* 2010;**53**:576	No comparison group
Haim N, Neufeld D, Ziv Y, Tulchinsky H, Koller M, Khaikin M, *et al.* Long-term results of fibrin glue treatment for cryptogenic perianal fistulas: a multicenter study. *Dis Colon Rectum* 2011;**54**:1279–83	No comparison group
Haim N, Neufeld D, Ziv Y, Tulchinsky H, Koller M, Khaikin M, *et al.* Long-term results of fibrin glue in the treatment of perianal fistulas: a multicenter study. *Tech Coloproctol* 2011;**15**:240	No comparison group
Haim N, Neufeld D, Ziv Y, Tulchinsky H, Koller M, Khaikin M, *et al.* Long-term success of fibrin glue in the treatment of perianal fistulas-a multicenter study. *Tech Coloproctol* 2011;**15**:121	Duplicate
Halfpenny W, Fraser JS, Adlam DM. Comparison of 2 hemostatic agents for the prevention of postextraction hemorrhage in patients on anticoagulants. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001;**92**:257–9	RCT
Hall *et al.* 2009[160]	RCT
Halverson AL, Hull TL, Fazio VW, Church J, Hammel J, Floruta C. Repair of recurrent rectovaginal fistulas. *Surgery* 2001;**130**:753–7	No comparison group
Hammond *et al.* 2011[219]	RCT
Hanai M, Kobayashi Y, Miyata K, Yoneyama F, Hattori T, Yuas N. Gastric tube-pulmonary fistula after esophageal reconstruction treated by endoscopic fibrin glue injection: a case report. *Nihon Shokaki Geka Gakkai Zasshi* 2001;**34**:329–33	No comparison group
Harries K, Masoud A, Brown TH, Richards DG. Endoscopic placement of fibrin sealant as a treatment for a long-standing Boerhaave's fistula. *Dis Esophagus* 2004;**17**:348–50	No comparison group
Hashimoto K, Shirakashi M, Watanabe J, Fukuchi T, Sawaguchi S, Kushiro M, *et al.* A case of the use of fibrin glue in leaking filtering bleb. *Nihon Ganka Kiyo* 1997;**48**:357–61	No comparison group
Hata N, Hisada K, Torisu R, Suzuki SO, Kameda K, Sasaki T. Foreign body granuloma associated with dura-cranioplasty after resection of convexity meningioma with extracranial extension: case report. *Neurol Med Chir* 2011;**51**:236–8	No comparison group
Hatzichristodoulou G, Fiechtner S, Gschwend JE, Lahme S. Long-term results after partial plaque excision and grafting with collagen fleece in Peyronie's disease. *Eur Urol Suppl* 2015;**14**:e133	No comparison group
Hatzichristodoulou G, Gschwend JE, Lahme S. Surgical correction of Peyronie's curvature by partial plaque excision or incision and grafting with collagen fleece – first results of a prospective, multicenter study. *Eur Urol Suppl* 2011;**10**:317	No comparison group
Hausmann M, Keller R. [Thoracoscopic pleurodesis in spontaneous pneumothorax.] *Schweiz Med Wochenschr* 1994;**124**:97–104	No comparison group
Hayashi K, Nagano J, Hattori S. Adhesive arachnoiditis after percutaneous fibrin glue treatment of a sacral meningeal cyst. *J Neurosurg Spine* 2014;**20**:763–6	No comparison group
Hayward PJ, Mackay IS. Fibrin glue in nasal septal surgery. *J Laryngol Otol* 1987;**101**:133–8	No comparison group
Heldwein W, Avenhaus W, Schönekäs H, Kaess H, Müller-Lissner S, Hasford B, *et al.* Injection of fibrin tissue adhesive versus laser photocoagulation in the treatment of high-risk bleeding peptic ulcers: a controlled randomized study. *Endoscopy* 1996;**28**:756–60	RCT
Helvind NM, Andresen K, Rosenberg J. Lower reoperation rates with the use of fibrin sealant versus tacks for mesh fixation. *Surg Endosc* 2013;**27**:4184–91	Emergency surgery
Hennis HL, Stewart WC, Jeter EK. Infectious disease risks of fibrin glue. *Ophthalmic Surg* 1992;**23**:640	Letter/commentary/reply
Herbrig K, Pistrosch F, Gross P, Palm C. Resumption of peritoneal dialysis after transcutaneous treatment of a peritoneal leakage using fibrin glue. *Nephrol Dial Transplant* 2006;**21**:2037–8	Letter/commentary/reply

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Hernandez C, Romero RJ, Lamoureux J, Seetharamaiah R, Garcia PE, Gallas M, *et al.* Gastric bypass postoperative clinical parameters using fibrin sealant. *Bariatr Surg Pract Patient Care* 2014;**9**:102–5	No comparison group
Herold G, Danz B. Endoscopic (-ERC) fibrin sealing and histoacryl sealing of an abscess induced bilio-hepatico-cutaneous and a bilio-hepatico-phrenico-bronchial fistulous system. *Z Gastroenterol* 1995;**33**:605–9	No comparison group
Herold G, Preclik G, Stange F. Gastroduodenal ulcer hemorrhage: endoscopic injection therapy using a fibrin sealant. *Hepatogastroenterology* 1994;**41**:116–19	No comparison group
Hester TR Jr, Gerut ZE, Shire JR, Nguyen DB, Chen AH, Diamond J, *et al.* Exploratory, randomized, controlled, phase 2 study to evaluate the safety and efficacy of adjuvant fibrin sealant VH S/D 4 S-Apr (ARTISS) in patients undergoing rhytidectomy. *Aesthet Surg J* 2013;**33**:323–33	RCT
Hester *et al.* 2013[231]	RCT
Heusse JL, Hivelin M, Lepage C, Santini C, Lantieri L. [Fibrin sealant significantly decrease postoperative drainage in breast reconstruction by deep inferior epigastric perforator (DIEP) flap.] *Ann Chir Plast Esthet* 2012;**57**:50–8	No adverse effects related to fibrin reported
Hevia M, Abascal-Junquera JM, Sacristan R, Suarez J, Lobo B, Mendez S, *et al.* [Haemostasis control during laparoscopic partial nephrectomy without parenchymal renorrhaphy: the VIVOSTAT experience.] *Actas Urol Esp* 2013;**37**:47–53	No comparison group
Hick EJ, Morey AF. Initial experience with fibrin sealant in pendulous urethral reconstruction. Is early catheter removal possible? *J Urol* 2004;**171**:1547–9	No adverse effects related to fibrin reported
Hick S, Demers PE, Brunette I, La C, Mabon M, Duchesne B. Amniotic membrane transplantation and fibrin glue in the management of corneal ulcers and perforations: a review of 33 cases. *Cornea* 2005;**24**:369–77	Not a relevant comparison
Hickey NC. Randomized clinical trial of tranexamic acid-free fibrin sealant during vascular surgical procedures. *Br J Surg* 2010;**97**:1790	RCT
Hida K, Yamaguchi S, Seki T, Yano S, Akino M, Terasaka S, *et al.* Nonsuture dural repair using polyglycolic acid mesh and fibrin glue: clinical application to spinal surgery. *Surg Neurol* 2006;**65**:136–42	No comparison group
Hidalgo M, Castillo MJ, Eymar JL, Hidalgo A. Lichtenstein inguinal hernioplasty: sutures versus glue. *Hernia* 2005;**9**:242–4	RCT
Hidalgo MP, Ferrero EH, Ortiz MA, Castillo JM, Hidalgo AG. Incisional hernia in patients at risk: can it be prevented? *Hernia* 2011;**15**:371–5	No comparison group
Higashiyama M, Takami K, Higaki N, Kodama K. Pulmonary middle lobe fixation using TachoComb in patients undergoing right upper lobectomy with complete oblique fissure. *Interact Cardiovasc Thorac Surg* 2004;**3**:107–9	No comparison group
Hillerdal G, Gustafsson G, Wegenius G, Englesson S, Hedenström H, Hedenstierna G. Large emphysematous bullae. Successful treatment with thoracoscopic technique using fibrin glue in poor-risk patients. *Chest* 1995;**107**:1450–3	No comparison group
Hino M, Ishiko O, Honda KI, Yamane T, Ohta K, Takubo T, *et al.* Transmission of symptomatic parvovirus B19 infection by fibrin sealant used during surgery. *Br J Haematol* 2000;**108**:194–5	No comparison group
Hino M, Yamamura R, Nishiki S, Ohta K, Yamane T, Takubo T, *et al.* [Human parvovirus B19-induced aplastic crisis in a patient treated with fibrin sealant.] *Rinsho Ketsueki* 1999;**40**:145–9	No comparison group
Hivelin M, Heusse JL, Matar N, Lepage C, Lantieri L. Fibrin sealant decreases postoperative drainage in immediate breast reconstruction by deep inferior epigastric perforator flap after mastectomy with axillary dissection. *Microsurgery* 2011;**31**:18–25	No comparison group
Hjortrup A, Moesgaard F, Kjaergård J. Fibrin adhesive in the treatment of perineal fistulas. *Dis Colon Rectum* 1991;**34**:752–4	No comparison group
Höckel M, Klose KJ. Treatment of non-neoplastic nipple discharge with fibrin adhesive. *Lancet* 1987;**2**:331–2	Letter/commentary/reply

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TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Hodges SD, Humphreys SC, Eck JC, Covington LA. Management of incidental durotomy without mandatory bed rest. A retrospective review of 20 cases. *Spine* 1999;**24**:2062–4	No comparison group
Hofmann HS, Rettig G, Radke J, Neef H, Silber RE. Iatrogenic ruptures of the tracheobronchial tree. *Eur J Cardiothorac Surg* 2002;**21**:649–52	No comparison group
Hofstetter C, Segovia E, Vara-Thorbeck R. Treatment of uncomplicated hydatid cyst of the liver by closed marsupialization and fibrin glue obliteration. *World J Surg* 2004;**28**:173–8	No comparison group
Hohendorff B, Siepen W, Spiering L, Staub L, Schmuck T, Boss A. Long-term results after operatively treated Achilles tendon rupture: fibrin glue versus suture. *J Foot Ankle Surg* 2008;**47**:392–9	Included children
Hölscher AH, Schröder W, Bollschweiler E, Beckurts KT, Schneider PM. [How safe is high intrathoracic esophagogastrostomy?] *Chirurg* 2003;**74**:726–33	No comparison group
Holub Z, Kliment Jr L. The effectiveness of collagen fleece combined with a fibrin glue in hemostasis during laparoscopic surgery. *J Gynecol Surg* 1999;**15**:185–91	No adverse effects related to fibrin reported
Honda K, Asato R, Tsuji J, Kanda T, Ushiro K, Watanabe Y. Extended application of polyglycolic acid sheet combined with sprayed fibrin glue to advanced oral cancers. *Oral Oncol* 2011;**47**:S151	No comparison group
Honda K, Ishiko O, Tsujimura A, Hino M, Hirai K, Itoh F, *et al.* Neutropenia accompanying parvovirus B19 infection after gynecologic surgery. *Acta Haematol* 2000;**103**:186–90	No comparison group
Hong CK, Kim YB, Hong JB, Lee KS. Sealing of cerebrospinal fluid leakage during conventional transsphenoidal surgery using a fibrin-coated collagen fleece. *J Clin Neurosci* 2015;**22**:696–9	No adverse effects related to fibrin reported
Huang and Qian 2014[93]	RCT
Huang *et al.* 2015[64]	RCT
Huguier M, Barrier A, Gouillat C, Suc B, Jaeck D, Launois B. [Pancreaticoduodenectomy for cancer of the head of the pancreas.] *J Chir* 2008;**145**:9–15	Not a comparative observational study
Huh JW, Kim HR, Kim YJ. Anastomotic leakage after laparoscopic resection of rectal cancer: the impact of fibrin glue. *Am J Surg* 2010;**199**:435–41	No adverse effects related to fibrin reported
Hurtgen M, Linder A, Friedel G, Toomes H. Video-assisted thoracoscopic pleurodesis. A survey conducted by the German Society for Thoracic Surgery. *Thorac Cardiovasc Surg* 1996;**44**:199–203	Emergency surgery
Hutter *et al.* 2014[237]	RCT
Hvass U, Chatel D, Assayag P, Juliard JM, Caliani J, Oroudji M, *et al.* [Repair of post-infarction left ventricular wall ruptures by biological glue and a flap from the pericardium. Results from 2 to 10 years.] *Arch Mal Coeur Vaiss* 1996;**89**:1255–8	No comparison group
Hvass U, Chatel D, Assayag P, Juliard JM, Caliani J, Oroudji M, *et al.* [Repair of post-infarction left ventricular wall ruptures by biological glue and a flap from the pericardium. Results from 2 to 10 years.] *Arch Mal Coeur Vaiss* 1996;**89**:1255–8	Duplicate
Iankin AV. [Tachocomb plates efficacy in prevention of lymphorrhea in radical operations for gastric cancer.] *Khirurgiia* 2006;**11**:44–6	Unobtainable
Ikeda T, Sasaki M, Yamada N, Takamori A, Tanabe S, Okada A, *et al.* Controlling air leaks using free pericardial fat pads as surgical sealant in pulmonary resection. *Ann Thorac Surg* 2015;**99**:1170–5	Not a relevant comparison
Imai K, Taniguchi M, Watanabe K, Einama T, Karasaki H, Kono T, *et al.* Efficacy of fibrin glue spray and polyglycolic acid sheet for the protection of transection surface after liver resection. *HPB (Oxford)* 2012;**14**:517–18	Abstract
Imhof M, Ohmann C, Roher HD, Glutig H, Duesuc study g. Endoscopic versus operative treatment in high-risk ulcer bleeding patients – results of a randomised study. *Langenbecks Arch Surg* 2003;**387**:327–36	RCT
Inderbitzi RG, Krebs T, Stirneman T, Ulrich A. Treatment of postoperative chylothorax by fibrin glue application under thoracoscopic view with use of local anesthesia. *J Thorac Cardiovasc Surg* 1992;**104**:209–10	Letter/commentary/reply

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Inghilleri G, Santoleri L, Cristallo A, Aloni A, Mancini L, Rondinara G, *et al.* Homemade vs commercial fibrin glue in liver surgery. *Blood Transfus* 2006;**4**:81–91	Fibrin was used in both groups
Ishikura Y, Odagiri S, Shimazu A, Yoshimatsu H. Left ventricular rupture following mitral valve replacement – a report of two cases. *Jpn J Surg* 1990;**20**:699–703	No comparison group
Ishio K. Delayed postoperative labyrinthine fistula. *Otolaryngol Head Neck Surg (Tokyo)* 1995;**67**:1024–9	No comparison group
Ito H, Kimura T, Sameshima T, Aiyama H, Nishimura K, Ochiai C, *et al.* Reinforcement of pericranium as a dural substitute by fibrin sealant. *Acta Neurochir* 2011;**153**:2251–4	No comparison group
Ito H, Nakayama H, Arai H, Karita S, Shotsu A, Fujita A. [Prevention of parenchymal air leakage after lung resection; comparison of effectiveness in drug formation of fibrin adhesive.] *Kyobu Geka* 2003;**56**:1014–16	Fibrin was used in both groups
Izzo F, Palaia R, Albino V, Amore A, di Giacomo R, Piccirillo M, *et al.* Hepatocellular carcinoma and liver metastases: clinical data on a new dual-lumen catheter kit for surgical sealant infusion to prevent perihepatic bleeding and dissemination of cancer cells following biopsy and loco-regional treatments. *Infectious Agents Cancer* 2015;**10**:11	No comparison group
Jabłoński S, Brocki M, Klejszmit P, Kutwin L, Wawrzycki M, Śmigielski J. Repair of postpneumonectomy bronchopleural fistula using pedicled pericardial flap supported by fibrin glue. *Int Wound J* 2015;**12**:154–9	Not a relevant comparison
Jackson *et al.* 1999[193]	RCT
Jain *et al.* 2004[99]	RCT
Johnsen S, Ermuth T, Tanczos E, Bannasch H, Horch RE, Zschocke I, *et al.* Treatment of therapy-refractive ulcera cruris of various origins with autologous keratinocytes in fibrin sealant. *VASA* 2005;**34**:25–9	No comparison group
Johnson *et al.* 2005[100]	RCT
Johnston WK, Montgomery JS, Seifman BD, Hollenbeck BK, Wolf JS. Fibrin glue v sutured bolster: lessons learned during 100 laparoscopic partial nephrectomies. *J Urol* 2005;**174**:47–52	No adverse effects related to fibrin reported
Jones BM, Grover R. Avoiding hematoma in cervicofacial rhytidectomy: a personal 8-year quest. Reviewing 910 patients. *Plast Reconstr Surg* 2004;**113**:381–7	Not a relevant comparison
Jones BM, Grover R. Early postoperative efficacy of fibrin glue in face lifts: a prospective randomized trial. *Plast Reconstr Surg* 2007;**119**:433–4	RCT
Jonk A, van Dongen JA, Kroon BB. Prevention of seroma following axillary lymph node dissection or radical mastectomy; ineffectiveness of fibrin glue sealing technique. *Neth J Surg* 1987;**39**:135	Unobtainable
Joseph *et al.* 2004[200]	RCT
Jurczak F, Laridon JY, Raffaitin P, Redon Y, Pousset JP. [Long-term follow-up of the treatment of high anal fistulas using fibrin glue.] *J Chir* 2009;**146**:382–6	No comparison group
Kahook MY, Noecker RJ. Fibrin glue-assisted glaucoma drainage device surgery. *Br J Ophthalmol* 2006;**90**:1486–9	No adverse effects related to fibrin reported
Kamal HM, Goda HAEB. Epidural fibrin glue for treatment of post-dural puncture headache (PDPH): comparative study with epidural blood patch. *Egypt J Anaesth* 2009;**25**:41–7	RCT
Kamer FM, Nguyen DB. Experience with fibrin glue in rhytidectomy. *Plast Reconstr Surg* 2007;**120**:1045–51	RCT
Kanazawa R, Sato S, Iwamoto N, Teramoto A. Allergic reaction following arachnoid plasty with a fibrin sealant. *Neurol Med Chir* 2010;**50**:608–10	No comparison group
Kanemaru S, Umeda H, Kitani Y, Nakamura T, Hirano S, Ito J. Regenerative treatment for tympanic membrane perforation. *Otol Neurotol* 2011;**32**:1218–23	RCT
Kang GC, Sng KW, Tay AG. Modified technique for frontal sinus obliteration using calvarial bone and Tisseel glue. *J Craniofac Surg* 2009;**20**:528–31	No comparison group

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TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Kaplonyi G, Zimmerman I, Frenyo AD, Farkas T, Nemes G. The use of fibrin adhesive in the repair of chondral and osteochondral injuries. *Injury* 1988;**19**:267–72	No comparison group
Karim MA, Ali A. Simple technique to manage redundant skin after laparoscopic ventral hernia repair. *Asian J Endosc Surg* 2013;**6**:137–9	No comparison group
Karlikaya C, Ucan E, Oto O, Akkoclu A, Cimrin A, Akpinar O. Successful fibrin glue repair of iatrogenic bronchial rupture. *Respir Med* 1993;**87**:397–8	Letter/commentary/reply
Karvonen JA, Gronroos JM, Nikulainen V, Gullichsen R, Salminen P. Endoscopic treatment of internal gastrointestinal fistulas with fibrin glue. *Surg Laparosc Endosc Percutan Tech* 2013;**23**:37–40	No comparison group
Kaseda S, Aoki T, Hangai N, Omoto T, Yamamoto S, Sugiura H. Treating bullous lung disease with Holmium YAG laser in conjunction with fibrin glue and DEXON mesh. *Lasers Surg Med* 1998;**22**:219–22	No comparison group
Kaseda S, Aoki T, Hangai N, Shimizu K, Kiguchi H. One hundred consecutive treatments with holmium: YAG laser for pulmonary bullae: especially in conjunction with gelatin-resorcinol formaldehyde-glutaraldehyde glue adhesion. *Lasers Surg Med* 2001;**28**:255–8	Not fibrin sealant
Kassam A, Horowitz M, Carrau R, Snyderman C, Welch W, Hirsch B, *et al.* Use of tisseel fibrin sealant in neurosurgical procedures: incidence of cerebrospinal fluid leaks and cost-benefit analysis in a retrospective study. *Neurosurgery* 2003;**52**:1102–5	Included children
Katkhouda N. Application of fibrin glue after hepatectomy might still be justified. *Ann Surg* 2008;**247**:399-400	RCT
Katoch CD, Chandran VM, Bhattacharyya D, Barthwal MS. Closure of bronchopleural fistula by interventional bronchoscopy using sealants and endobronchial devices. *Med J Armed Forces India* 2013;**69**:326–9	No comparison group
Kauer WKH, Stein HJ, Dittler HJ, Siewert JR. Stent implantation as a treatment option in patients with thoracic anastomotic leaks after esophagectomy. *Surg Endosc* 2008;**22**:50–3	No comparison group
Kavanagh MC, Ohr MP, Czyz CN, Cahill KV, Perry JD, Holck DE, *et al.* Comparison of fibrin sealant versus suture for wound closure in Muller muscle-conjunctiva resection ptosis repair. *Ophthal Plast Reconstr Surg* 2009;**25**:99–102	No adverse effects related to fibrin reported
Kawamura M, Kase K, Sawafuji M, Watanabe M, Horinouchi H, Kobayashi K. Staple-line reinforcement with a new type of polyglycolic acid felt. *Surg Laparosc Endosc Percutan Tech* 2001;**11**:43–6	No comparison group
Kawamura M, Sawafuji M, Watanabe M, Horinouchi H, Kobayashi K. Frequency of transmission of human parvovirus B19 infection by fibrin sealant used during thoracic surgery. *Ann Thorac Surg* 2002;**73**:1098–100	No comparison group
Keller R. [Thoracoscopic pleurodesis in persistent and recurrent pneumothorax.] *Zentralbl Chir* 1992;**117**:267–9	No comparison group
Khafagy W, Zedan S, Setiet A, El-Awady S, El-Shobaky MT. Autologous fibrin glue in treatment of fistula in ano. *Coloproctology* 2001;**23**:17–21	No adverse effects related to fibrin reported
Khaleal F, Berney C. The role of fibrin glue in decreasing chronic pain in laparoscopic totally extraperitoneal (TEP) inguinal hernia repair: a single surgeon's experience. *ANZ J Surg* 2011;**81**:154–8	No comparison group
Kheirkhah A, Casas V, Blanco G, Li W, Hayashida Y, Chen YT, *et al.* Amniotic membrane transplantation with fibrin glue for conjunctivochalasis. *Am J Ophthalmol* 2007;**144**:311–13	No comparison group
Kheirkhah A, Casas V, Sheha H, Raju VK, Tseng SC. Role of conjunctival inflammation in surgical outcome after amniotic membrane transplantation with or without fibrin glue for pterygium. *Cornea* 2008;**27**:56–63	No adverse effects related to fibrin reported
Kheirkhah A, Ghaffari R, Kaghazkanani R, Hashemi H, Behrouz MJ, Raju VK. A combined approach of amniotic membrane and oral mucosa transplantation for fornix reconstruction in severe symblepharon. *Cornea* 2013;**32**:155–60	No comparison group

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Kiejna N, Lubocki M, Wegrzyn K, Rzepecki P. Laparoscopic nephron sparing surgery (LNSS) using a clamp on the renal parenchyma and haemostatic material on the loge of the tumor. *Eur Urol Suppl* 2011;**10**:653	No comparison group
Kilic B, Turna A, Demirkaya A, Kaynak K. A prospective randomized trial comparing heterologous and autologous fibrin sealants for the control of alveolar air leak. *Interact Cardiovasc Thorac Surg* 2013;**17**(Suppl. 1):1–62	RCT
Kim HH, Mun HJ, Park YJ, Lee KW, Shin JP. Conjunctivolimbal autograft using a fibrin adhesive in pterygium surgery. *Korean J Ophthalmol* 2008;**22**:147–54	No comparison group
Kim HJ, Huh JW, Kim HR, Kim YJ. Oncologic impact of anastomotic leakage in rectal cancer surgery according to the use of fibrin glue: case-control study using propensity score matching method. *Am J Surg* 2014;**207**:840–6	No comparison group
Kim HK, Park HS. Fibrin glue-assisted augmented amniotic membrane transplantation for the treatment of large noninfectious corneal perforations. *Cornea* 2009;**28**:170–6	No comparison group
Kim TS, Oh JH, Rhew HY. 'Off-clamp, non-renorrhaphy' laparoscopic partial nephrectomy with perirenal fat and gerota's fascia reapproximation: initial experience and perioperative outcomes. *J Laparoendosc Adv Surg Tech A* 2014;**24**:339–44	No comparison group
Kim YA, Steinbacher DM. Demineralized bone-fibrin sandwich for genioplasty. *Aesthetic Plast Surg* 2014;**38**:755–8	RCT
Kim YA, Steinbacher DM. Demineralized bone-fibrin sandwich for genioplasty. *Aesthet Plast Surg* 2014;**38**:755–8	No comparison group
Kimura N, Kawahito K, Murata S, Yamaguchi A, Adachi H, Ino T. Pitfalls of sutureless repair of a blow-out type left ventricular free wall rupture. *Jpn J Thorac Cardiovasc Surg* 2005;**53**:382–5	No comparison group
Kinahan TJ, Johnson HW. Tisseel in hypospadias repair. *Can J Surg* 1992;**35**:75–7	No adverse effects related to fibrin reported
Kingsnorth AN, Shahid MK, Valliattu AJ, Hadden RA, Porter CS. Open onlay mesh repair for major abdominal wall hernias with selective use of components separation and fibrin sealant. *World J Surg* 2008;**32**:26–30	Fibrin data not shown separately from control
Kinoshita T. Usefulness of intrapleural administration of a large amount of diluted fibrin glue for intractable pneumothoraces. *J Wakayama Med Soc* 1998;**49**:289–96	No comparison group
Kinoshita T, Miyoshi S, Suzuma T, Sakurai T, Enomoto K, Yoshimasu T, *et al.* Intrapleural administration of a large amount of diluted fibrin glue for intractable pneumothorax. A clinical study based on 57 cases: including 2 unsuccessful cases. *Jpn J Thorac Cardiovasc Surg* 2003;**51**:41–7	No comparison group
Kirkegaard P, Madsen PV. [Closure of fistula with fibrin-glue.] *Ugeskr Laeg* 1982;**144**:3832–4	Unobtainable
Kirkegaard P, Madsen PV. Perineal sinus after removal of the rectum. Occlusion with fibrin adhesive. *Am J Surg* 1983;**145**:791–4	No comparison group
Kitago M, Matsui J, Tanabe M, Kawachi S, Itano O, Shinoda M, *et al.* Pylorus-preserving pancreatoduodenectomy with gastrointestinal reconstruction by the imanaga method enable the endoscopic examination of pancreatojejunostomy or choledochojejunostomy anastomosis. *HPB (Oxford)* 2012;**14**:672	No comparison group
Kjaergard and Trumbull 1998[138]	RCT
Kjølhede P, Rydén G, Hewardt P. Abdominal urethrocystopexy using fibrin sealant. A prospective study of long-term efficacy. *Int Urogynecol J Pelvic Floor Dysfunct* 2000;**11**:93–6	No comparison group
Kluba *et al.* 2012[145]	RCT
Knox Cartwright NE, Tole DM. Potential complication of fibrin sealant. *J Cataract Refract Surg* 2008;**34**:881–2	Letter/commentary/reply
Kobayashi M, Suzuki K, Ichinose Y, Hashimoto K, Matsumoto K, Yamanaka H. Intractable fecal fistula cured by a combination of conservative therapy using fibrin adhesive agent and complicating. *Jpn J Clin Urol* 1989;**43**:815–17	No comparison group

continued

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Kobayashi S, Nagano H, Marubashi S, Wada H, Eguchi H, Takeda Y, *et al.* Fibrin sealant with PGA felt for prevention of bile leakage after liver resection. *Hepatogastroenterology* 2012;**59**:2564–8	Fibrin was used in both groups
Kohno *et al.* 1992[75]	RCT
Kon NF, Masumo H, Nakajima S, Tozawa R, Kimura M, Maeda S. [Anaphylactic reaction to aprotinin following topical use of biological tissue sealant.] *Masui* 1994;**43**:1606–10	No comparison group
Konety BR. Fibrin glue v sutured bolster: lessons learned during 100 laparoscopic partial nephrectomies. *Urol Oncol* 2006;**24**:88	Letter/commentary/reply
Koranyi *et al.* 2005[162]	No adverse effects related to fibrin reported
Korotin DP, Pavlunin AV, Artifexova AA. Surgical prevention technique of the primary bronchus stump insufficiency using a fibrin-collagenic plate. *Sovrem Tekhnologii Med* 2011;**2011**:61–6	No adverse effects related to fibrin reported
Kosmidis C, Efthimiadis C, Anthimidis G, Levva S, Prousalidis J, Papapolychroniadis K, *et al.* Combined left hepatectomy with fenestration and using a harmonic scalpel, fibrin glue and closed suction drainage to prevent bile leakage and ascites in the management of symptomatic polycystic liver disease: a case report. *J Med Case Rep* 2009;**3**:7442	No comparison group
Kowalski C, Kastuar S, Mehta V, Brolin RE. Endoscopic injection of fibrin sealant in repair of gastrojejunostomy leak after laparoscopic Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2007;**3**:438–42	No adverse effects related to fibrin reported
Kram HB, Nathan RC, Stafford FJ, Fleming AW, Shoemaker WC. Fibrin glue achieves hemostasis in patients with coagulation disorders. *Arch Surg* 1989;**124**:385–7	No comparison group
Kram HB, Ocampo HP, Yamaguchi MP, Nathan RC, Shoemaker WC. Fibrin glue in renal and ureteral trauma. *Urology* 1989;**33**:215–18	No comparison group
Krämer SC, Görich J, Rilinger N, Siech M, Aschoff AJ, Vogel J, *et al.* Embolization for gastrointestinal hemorrhages. *Eur Radiol* 2000;**10**:802–5	No comparison group
Kruger T, Lisy M, Kalhil M, Nagy C, Stock UA, Wildhirt SM. Matrix-based repair of acute type-a aortic dissections as an alternative to conventional glue repair. *Innovations* 2012;**7**:105	No comparison group
Kudo H, Sakagami Y, Kawamura A, Tamaki N. Delayed cerebrospinal fluid rhinorrhea seven months after transsphenoidal surgery for pituitary adenoma – case report. *Neurol Med Chir* 2000;**40**:160–3	No comparison group
Kumar A, Maartens NF, Kaye AH. Evaluation of the use of BioGlue in neurosurgical procedures. *J Clin Neurosci* 2003;**10**:661–4	No comparison group
Kurian A, Reghunadhan I, Nair KG. Autologous blood versus fibrin glue for conjunctival autograft adherence in sutureless pterygium surgery: a randomised controlled trial. *Br J Ophthalmol* 2015;**99**:464–70	RCT
Lalos O, Berglund AL, Bjerle P. The long-term outcome of retropubic urethrocystopexy (sutures and fibrin sealant) and pubococcygeal repair. *Acta Obstet Gynecol Scand* 2000;**79**:135–9	No comparison group
Lam FC, Kasper E. Augmented autologous pericranium duraplasty in 100 posterior fossa surgeries – a retrospective case series. *Neurosurgery* 2012;**71**(Suppl. 2):ons302–7	No comparison group
Lam FC, Penumaka A, Chen CC, Fischer EG, Kasper EM. Fibrin sealant augmentation with autologous pericranium for duraplasty after suboccipital decompression in Chiari 1 patients: a case series. *Surg Neurol Int* 2013;**4**:6	No comparison group
Lamm P, Adelhard K, Juchem G, Weitkunat R, Milz S, Kilger E, *et al.* Fibrin glue in coronary artery bypass grafting operations: casting out the Devil with Beelzebub? *Eur J Cardiothorac Surg* 2007;**32**:567–72	No valid comparison
Lamont JP, Hooker G, Espenschied JR, Lichliter WE, Franko E. Closure of proximal colorectal fistulas using fibrin sealant. *Am Surg* 2002;**68**:615–18	No comparison group
Lang *et al.* 2004[134]	RCT

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Lange V, Meyer G, Wenk H, Schildberg FW. Fistuloscopy – an adjuvant technique for sealing gastrointestinal fistulae. *Surg Endosc* 1990;**4**:212–16	RCT
Lassen *et al.* 2006[141]	RCT
Lau 2005[172]	RCT
Laws ER. Sellar repair with fibrin sealant and collagen fleece after endoscopic endonasal transsphenoidal surgery. Commentary. *Surg Neurol* 2004;**62**:233	Letter/commentary/reply
Lebowitz RA, Hoffman RA, Roland JT, Cohen NL. Autologous fibrin glue in the prevention of cerebrospinal fluid leak following acoustic neuroma surgery. *Am J Otol* 1995;**16**:172–4	Fibrin was used in both groups
Lee FY, Leung KL, Lai PB, Lau JW. Selection of patients for laparoscopic repair of perforated peptic ulcer. *Br J Surg* 2001;**88**:133–6	Emergency surgery
Lee S, Kim HR, Cho S, Huh DM, Lee EB, Ryu KM, *et al.* Staple line coverage after bullectomy for primary spontaneous pneumothorax: a randomized trial. *Ann Thorac Surg* 2014;**98**:2005–11	RCT
Lee JH, Kang NY. Comparison of fibrin glue and sutures for conjunctival wound closure in strabismus surgery. *Korean J Ophthalmol* 2011;**25**:178–84	RCT
Lee *et al.* 2009[227]	RCT
Lehnhardt M, Hauser J, Daigeler A, Fredersdorf S, Dragieva G, Ploder B, *et al.* A variant PDGF incorporated into fibrin sealant for treatment of burn patients undergoing autologous mesh skin grafting. *Burns* 2009;**35**:S43	RCT
Lei QF, Cai W. Clinical observation on fibrin glue application during pterygium surgery. *Int Eye Sci* 2015;**15**:364–6	RCT
Leonardo C, De Mayo E, Franco G, Zampelli A, Tiesi A, Tartaglia N, *et al.* Modified 'pluck' technique with tissucol for the management of distal ureter during nephroureterectomy. *Eur Urol Suppl* 2009;**8**:347	No comparison group
Levy O, Martinowitz U, Oran A, Tauber C, Horoszowski H. The use of fibrin tissue adhesive to reduce blood loss and the need for blood transfusion after total knee arthroplasty. A prospective, randomized, multicenter study. *J Bone Joint Surg* 1999;**81**:1580–8	RCT
Lewandowski B. [Topical treatment of bleeding post removed teeth in patients with prosthetic heart valves whose receiving long-term of oral anticoagulant therapy.] *Pol Merkur Lekarski* 2002;**12**:20–4	No comparison group
Liang HS, Hu M, Zhu XS, Zhao HB. Fibrin glue plus danshen injection in the prevention of postoperative lower back pain due to epidural adhesion: a synchronous controlled study. *Chin J Clin Rehabil* 2005;**9**:16–17	RCT
Lillemoe *et al.* 2004[83]	RCT
Lin JM, Brolin RE. Treatment of gastric leaks after roux-en-y gastric bypass: a paradigm shift. *Surg Obes Relat Dis* 2011;**7**:373–4	No comparison group
Lin R, Zhang FJ, Yu BW. Fibrin sealant and anaphylactic shock. *Chin J New Drugs* 2010;**19**:203–6	Review
Lippert E, Klebl FH, Schweller F, Ott C, Gelbmann CM, Scholmerich J, *et al.* Fibrin glue in the endoscopic treatment of fistulae and anastomotic leakages of the gastrointestinal tract. *Int J Colorectal Dis* 2011;**26**:303–11	No comparison group
Liu H, Wei RH, Huang Y, Yang RB, Zhang C, Zhao SZ. Clinical observation on fibrin glue technique in pterygium surgery performed with limbal autograft transplantation. *Int Eye Sci* 2013;**13**:1498–9	RCT
Liu *et al.* 2014[13]	Not a comparative observational study
Liu W, Zhang YP, Xie MF, Liu Y. Application of fibrin glue with bandage contact lens in pterygium surgery. *Int Eye Sci* 2014;**14**:879–81	RCT
Llewellyn-Bennett *et al.* 2012[101]	RCT

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TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Lobel B, Ordonez O, Olivo JF, Cipolla B, Milon D, Leveque JM, *et al.* [Radical prostatectomy and biologic glue.] *Prog Urol* 1991;**1**:440–4	No adverse effects related to fibrin reported
Locatelli D, Vitali M, Custodi VM, Scagnelli P, Castelnuovo P, Canevari FR. Endonasal approaches to the sellar and parasellar regions: closure techniques using biomaterials. *Acta Neurochir* 2009;**151**:1431–7	No adverse effects related to fibrin reported
Lopez *et al.* 2013[129]	RCT
Lovisetto *et al.* 2007[180]	RCT
Low JC, von Niederhäusern B, Rutherford SA, King AT. Pilot study of perioperative accidental durotomy: does the period of postoperative bed rest reduce the incidence of complication? *Br J Neurosurg* 2013;**27**:800–2	No comparison group
Lowe J, Luber J, Levitsky S, Hantak E, Montgomery J, Schiestl N, *et al.* Evaluation of the topical hemostatic efficacy and safety of TiSSEEL VH S/D fibrin sealant compared with currently licensed TISSEEL VH in patients undergoing cardiac surgery: a phase 3, randomized, double-blind clinical study. *J Cardiovasc Surg* 2007;**48**:323–31	RCT
Lu Q, Feng J, Yang Y, Nie B, Bao J, Zhao Z, *et al.* Treatment of type I endoleak after endovascular repair of infrarenal abdominal aortic aneurysm: success of fibrin glue sac embolization. *J Endovasc Ther* 2010;**17**:687–93	No comparison group
Lund JN, Leveson SH. Fibrin glue in the treatment of pilonidal sinus: results of a pilot study. *Dis Colon Rectum* 2005;**48**:1094–6	No comparison group
Mabrouk *et al.* 2013[214]	RCT
Macias CA, Sandler B, Barajas-Gamboa JS, Valero M, Cheverie J, Talamini MA, *et al.* Standardized protocol utilization decreases rate of complications: A study of laparoscopic sleeve gastrectomy in 189 consecutive patients. *Surg Endosc* 2013;**27**:S489	No comparison group
Maharaj *et al.* 2006[230]	RCT
Mahdy RA, Wagieh MM. Safety and efficacy of fibrin glue versus vicryl sutures in recurrent pterygium with amniotic membrane grafting. *Ophthalmic Res* 2012;**47**:23–6	RCT
Maisano *et al.* 2009[140]	RCT
Makiyama K, Sakata R, Sano F, Yamanaka H, Nakaigawa N, Yao M, *et al.* Clinical comparison between microporrus polysaccharide hemispheres (MPH) and fibrin glue during laparoscopic partial nephrectomy. *J Endourol* 2012;**26**:A258–9	Abstract
Malik and Kumar 2010[171]	RCT
Mammis A, Agarwal N, Mogilner AY. Alternative treatment of intracranial hypotension presenting as postdural puncture headaches using epidural fibrin glue patches: two case reports. *Int J Neurosci* 2014;**124**:863–6	No comparison group
Maralcan G, Başkonuş I, Aybasti N, Gökalp A. The use of fibrin glue in the treatment of fistula-in-ano: a prospective study. *Surg Today* 2006;**36**:166–70	No comparison group
Maralcan G, Başkonuş I, Gökalp A, Borazan E, Balk A. Long-term results in the treatment of fistula-in-ano with fibrin glue: a prospective study. *J Korean Surg Soc* 2011;**81**:169–75	No comparison group
Marangos IP, Rosok BI, Kazaryan AM, Rosseland AR, Edwin B. Effect of TachoSil patch in prevention of postoperative pancreatic fistula. *J Gastrointest Surg* 2011;**15**:1625–9	No comparison group
Marchac and Greensmith 2005[226]	RCT
Marta *et al.* 2010[135]	RCT
Martin and Au 2013[86]	RCT
Martin II, Yuen L, Au K. Does fibrin glue sealant decrease the rate of anastomotic leak following pancreaticoduodenectomy? Results of a prospective randomized trial. *HPB* 2012;**14**:84	RCT

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Martin-Mateos RM, Lopez-San Roman A, García-Sánchez C, Garcia-Hoz F, Gil-Grande LA, Gómez EG, *et al.* Fibrin-glue-sealed liver biopsy: indications, complications and results. *J Gastrointestin Liver Dis* 2014;**23**:100–1	Letter/commentary/reply
Matsuse S, Maruyama A, Hara Y. Nitrogenous subcutaneous emphysema caused by spray application of fibrin glue during retroperitoneal laparoscopic surgery. *J Anesth* 2011;**25**:426–30	No comparison group
Matthews TW, Briant TD. The use of fibrin tissue glue in thyroid surgery: resource utilization implications. *J Otolaryngol* 1991;**20**:276–8	No adverse effects related to fibrin reported
McConnell *et al.* 2012[146]	RCT
McGoldrick JP, White RW. Fibrin sealant in coronary artery surgery – the devil is always in the detail! *Eur J Cardiothorac Surg* 2008;**33**:949–50	Letter/commentary/reply
Meister T, Kuhlgatz J, Floer M. Over-the-Scope Clip (OTSC) application as rescue therapy for postoperative enterocutaneous fistula closure. *Acta Chir Belg* 2014;**114**:87–9	No comparison group
Melissa CS, Bun TAY, Wing CK, Chung TY, Wai NEK, Tat LH. Randomized double-blinded prospective trial of fibrin sealant spray versus mechanical stapling in laparoscopic total extraperitoneal hernioplasty. *Ann Surg* 2014;**259**:432–7	RCT
Menegolo M, Frigatti P, Antonello M, Lepidi S, Morelli I, Scrivere P, *et al.* Prevention of type ii endoleaks by coils and fibrin glue embolization of the aneurysmatic sac. *Interact Cardiovasc Thorac Surg* 2011;**12**:S52–3	Abstract
Menovsky T. Editorial note on: the clinical study of repairing cauda equina fibres with fibrin glue after lumbar fracture and dislocation. *Spinal Cord* 2010;**48**:638	Letter/commentary/reply
Mentens R, Stalmans P. Comparison of fibrin glue and sutures for conjunctival closure in pars plana vitrectomy. *Am J Ophthalmol* 2007;**144**:128–31	No adverse effects related to fibrin reported
Mentens R, Stalmans P. Comparison of postoperative comfort in 20 gauge versus 23 gauge pars plana vitrectomy. *Bull Soc Belge Ophtalmol* 2009;**311**:5–10	Not a relevant comparison
Messmann H, Schaller P, Andus T, Lock G, Vogt W, Gross V, *et al.* Effect of programmed endoscopic follow-up examinations on the rebleeding rate of gastric or duodenal peptic ulcers treated by injection therapy: a prospective, randomized controlled trial. *Endoscopy* 1998;**30**:583–9	RCT
Mikhail AA, Kaptein JS, Bellman GC. Use of fibrin glue in percutaneous nephrolithotomy. *Urology* 2003;**61**:910–14	Included children
Mikulas J, Laurinc P, Kazik P, Mraz R. Haemostatic use of Tachosil in partial nephrectomy – initial experience. *Eur Urol Suppl* 2010;**9**:636	No comparison group
Milde LN. An anaphylactic reaction to fibrin glue. *Anesth Analg* 1989;**69**:684–6	No comparison group
Milic DJ, Perisic ZD, Zivic SS, Stanojkovic ZA, Stojkovic AM, Karanovic ND, *et al.* Prevention of pocket related complications with fibrin sealant in patients undergoing pacemaker implantation who are receiving anticoagulant treatment. *Europace* 2005;**7**:374–9	RCT
Milne *et al.* 1995[201]	RCT
Milne *et al.* 1996[203]	RCT
Minami K, Saito Y, Shomura Y, Imamura H. [A device to prevent an air-leakage after a thoracoscopic surgery for spontaneous pneumothorax.] *Kyobu Geka* 2003;**56**:904–7	Emergency surgery
MiriBonjar *et al.* 2012[103]	RCT
Miscusi M, Polli FM, Forcato S, Coman MA, Ricciardi L, Ramieri A, *et al.* The use of surgical sealants in the repair of dural tears during non-instrumented spinal surgery. *Eur Spine J* 2014;**23**:1761–6	No adverse effects related to fibrin reported
Mishra A, Shah S, Nar AS, Bawa A. The role of fibrin glue in the treatment of high and low fistulas in ano. *J Clin Diagn Res* 2013;**7**:876–9	Not a relevant comparison

continued

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Mita K, Ito H, Fukumoto M, Murabayashi R, Koizumi K, Hayashi T, *et al.* Pancreaticojejunostomy using a fibrin adhesive sealant (TachoComb) for the prevention of pancreatic fistula after pancreaticoduodenectomy. *Hepatogastroenterology* 2011;**58**:187–91	No comparison group
Mita K, Ito H, Fukumoto M, Murabayashi R, Koizumi K, Hayashi T, *et al.* A fibrin adhesive sealing method for the prevention of pancreatic fistula following distal pancreatectomy. *Hepatogastroenterology* 2011;**58**:604–8	No comparison group
Mithal C, Agarwal P, Mithal N. Pterygium surgery with conjunctival limbal autograft with fibrin glue under topical anaesthesia with lignocaine 2% jelly. *Nepal J Ophthalmol* 2011;**3**:151–4	No comparison group
Mitsuhata H, Horiguchi Y, Saitoh J, Saitoh K, Fukuda H, Hirabayasi Y, *et al.* An anaphylactic reaction to topical fibrin glue. *Anesthesiology* 1994;**81**:1074–7	No comparison group
Miyamoto H, Futagawa T, Wang Z, Yamazaki A, Morio A, Sonobe S, *et al.* Fibrin glue and bioabsorbable felt patch for intraoperative intractable air leaks. *Jpn J Thorac Cardiovasc Surg* 2003;**51**:232–6	No comparison group
Mizuno H, Hitomi S, Nakamura T, Shimizu Y. [Clinical experience of the combined use of polyglycolide non-woven felt with fibrin glue to prevent postoperative pulmonary fistula.] *Nihon Kyobu Geka Gakkai Zasshi* 1995;**43**:1559–64	Not a relevant comparison
Moench *et al.* 2010[250]	RCT
Molloy *et al.* 2007[147]	RCT
Montorsi *et al.* 2012[84]	RCT
Moore *et al.* 2001[111]	RCT
Moralee SJ, Carney AS, Cash MP, Murray JA. The effect of fibrin sealant haemostasis on post-operative pain in tonsillectomy. *Clin Otolaryngol Allied Sci* 1994;**19**:526–8	RCT
Morita Y, Nishii O, Kido M, Tsutsumi O. Parvovirus infection after laparoscopic hysterectomy using fibrin glue hemostasis. *Obstet Gynecol* 2000;**95**:1026	No comparison group
Morris MS, Morey AF, Stackhouse DA, Santucci RA. Fibrin sealant as tissue glue: preliminary experience in complex genital reconstructive surgery. *Urology* 2006;**67**:688–91	No comparison group
Mortenson *et al.* 2008[120]	RCT
Moser *et al.* 2008[126]	RCT
Mueller TJ, DaJusta DG, Cha DY, Kim IY, Ankem MK. Ureteral fibrin sealant injection of the distal ureter during laparoscopic nephroureterectomy – a novel and simple modification of the pluck technique. *Urology* 2010;**75**:187–92	No comparison group
Muntean W, Zenz W, Edlinger G, Beitzke A. Severe bleeding due to factor V inhibitor after repeated operations using fibrin sealant containing bovine thrombin. *Thromb Haemost* 1997;**77**:1223	Letter/commentary/reply
Muramatsu T, Ohmori K, Shimamura M, Furuichi M, Takeshita S, Negishi N. Staple line reinforcement with fleece-coated fibrin glue (TachoComb) after thoracoscopic bullectomy for the treatment of spontaneous pneumothorax. *Surg Today* 2007;**37**:745–9	Emergency surgery
Murphy WG, Milne AA, Ruckley CV, Kubba AK, Palmer KR. Fibrin sealant: update on clinical studies. *Transfus Sci* 1996;**17**:341–2	Review
Mustonen *et al.* 2004[104]	RCT
Nakahira J, Ishii H, Sawai T, Minami T. Fibrin glue on an aortic cusp detected by transesophageal echocardiography after valve-sparing aortic valve replacement: a case report. *J Med Case Rep* 2015;**9**:53	No comparison group
Nakamura *et al.* 2005[236]	RCT
Narotam PK, José S, Nathoo N, Taylon C, Vora Y. Collagen matrix (DuraGen) in dural repair: analysis of a new modified technique. *Spine* 2004;**29**:2861–7	No comparison group
Nativ *et al.* 2012[59]	RCT

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Navarro-Rodriguez E, Gomez-Luque I, Diaz-Jimenez N, Rioja-Torres P, Bascunana-Estudillo G, Ruiz-Rabelo JF, *et al.* Effectiveness of an absorbable fibrin sealant patch to reduce lymphoceles formation after axillary lymphadenectomy for breast cancer: a matched-pair analysis. *Am J Surg* 2014;**208**:824–30	No adverse effects related to fibrin reported
Nelson RL, Cintron J, Abcarian H. Dermal island-flap anoplasty for transsphincteric fistula-in-ano: assessment of treatment failures. *Dis Colon Rectum* 2000;**43**:681–4	No comparison group
Nervi C, Gamelli RL, Greenhalgh DG, Luterman A, Hansbrough JF, Achauer BM, *et al.* A multicenter clinical trial to evaluate the topical hemostatic efficacy of fibrin sealant in burn patients. *J Burn Care Rehabil* 2001;**22**:99–103	RCT
Neuss H, Raue W, Koplin G, Schwenk W, Reetz C, Mall JW. Intraoperative application of fibrin sealant does not reduce the duration of closed suction drainage following radical axillary lymph node dissection in melanoma patients: a prospective randomized trial in 58 patients. *World J Surg* 2008;**32**:1450–5	RCT
Neuss *et al.* 2009[118]	RCT
Nieuwendaal CP, van der Meulen IJ, Mourits M, Lapid-Gortzak R. Long-term follow-up of pterygium surgery using a conjunctival autograft and Tissucol. *Cornea* 2011;**30**:34–6	No comparison group
Nishizawa S, Yokota N, Yokoyama T, Mukodaka H, Watanabe T, Hoshino T, *et al.* Prevention of postoperative complications in skull base surgery for nasal or paranasal sinus carcinoma invading the skull base. *J Clin Neurosci* 2001;**8**(Suppl. 1):67–70	No comparison group
Nistor RF. Fibrin sealant in coronary artery bypass grafting surgery; reflection on risk and benefit. *Eur J Cardiothorac Surg* 2008;**33**:317	Letter/commentary/reply
Notarnicola A, Moretti L, Martucci A, Spinarelli A, Tafuri S, Pesce V, *et al.* Comparative efficacy of different doses of fibrin sealant to reduce bleeding after total knee arthroplasty. *Blood Coagul Fibrinolysis* 2012;**23**:278–84	RCT
Novik B, Hagedorn S, Mörk UB, Dahlin K, Skullman S, Dalenbäck J. Fibrin glue for securing the mesh in laparoscopic totally extraperitoneal inguinal hernia repair: a study with a 40-month prospective follow-up period. *Surg Endosc* 2006;**20**:462–7	No comparison group
Ochiai T, Sonoyama T, Soga K, Inoue K, Ikoma H, Shiozaki A, *et al.* Application of polyethylene glycolic acid felt with fibrin sealant to prevent postoperative pancreatic fistula in pancreatic surgery. *J Gastrointest Surg* 2010;**14**:884–90	No comparison group
Ochsner MG, Maniscalco-Theberge ME, Champion HR. Fibrin glue as a hemostatic agent in hepatic and splenic trauma. *J Trauma* 1990;**30**:884–7	No comparison group
Ofikwu GI, Sarhan M, Ahmed L. EVICEL glue-induced small bowel obstruction after laparoscopic gastric bypass. *Surg Laparosc Endosc Percutan Tech* 2013;**23**:e38–40	No comparison group
Ohta M, Komatsu F, Abe H, Sakamoto S, Tsugu H, Oshiro S, *et al.* Complication caused by use of fibrin glue in vessel transposition for trigeminal neuralgia. *Neurol Med Chir* 2008;**48**:30–2	No comparison group
Ohwada *et al.* 1998[8]	Not a relevant comparison
Oliver *et al.* 2001[228]	RCT
Oliver *et al.* 2002[215]	RCT
Öllinger R, Mihaljevic AL, Schuhmacher C, Bektas H, Vondran F, Kleine M, *et al.* A multicentre, randomized clinical trial comparing the Veriset™ haemostatic patch with fibrin sealant for the management of bleeding during hepatic surgery. *HPB* 2013;**15**:548–58	RCT
Olmi S, Erba L, Bertolini A, Scaini A, Croce E. Fibrin glue for mesh fixation in laparoscopic transabdominal preperitoneal (TAPP) hernia repair: indications, technique, and outcomes. *Surg Endosc* 2006;**20**:1846–50	No comparison group
Olmi S, Erba L, Bertolini A, Scaini A, Mastropasqua E, Conti M, *et al.* [Use of fibrin glue (Tissucol) for mesh fixation in laparoscopic transabdominal hernia repair.] *Chir Ital* 2005;**57**:753–9	No comparison group
Olmi *et al.* 2007[259]	No comparison group

continued

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Olmi S, Scaini A, Erba L, Croce E. Use of fibrin glue (Tissucol) in laparoscopic repair of abdominal wall defects: preliminary experience. *Surg Endosc* 2007;**21**:409–13	No comparison group
Olsen TW, Sternberg P Jr, Capone A Jr, Martin DF, Lim JI, Grossniklaus HE, *et al.* Macular hole surgery using thrombin-activated fibrinogen and selective removal of the internal limiting membrane. *Retina* 1998;**18**:322–9	No comparison group
Olsha O, Hadar T, Dalo RA, Verocherinsky N, Ashkenazi I. Fibrin sealant to reduce drainage after axillary dissection. *Ann Surg Oncol* 2014;**21**:92–3	Not a relevant comparison
Olsha O, Hadar T, Noy V, Verocherinsky N, Abu Dalo R, Ashkenazi I. Fibrin sealant to reduce lymphatic drainage after axillary dissection. *Eur J Cancer* 2014;**50**:S130–1	No comparison group
Omote Y, Kubo Y. [Effectiveness of fibrin glue in preventing postoperative pulmonary air leakage.] *Kyobu Geka* 1994;**47**:355–9	No adverse effects related to fibrin reported
Orsel I, Guillaume A, Feiss P. [Anaphylactic shock caused by fibrin glue.] *Ann Fr Anesth Reanim* 1997;**16**:292–3	No comparison group
Oswald AM, Joly LM, Gury C, Disdet M, Leduc V, Kanny G. Fatal intraoperative anaphylaxis related to aprotinin after local application of fibrin glue. *Anesthesiology* 2003;**99**:762–3	Letter/commentary/reply
Ozdamar Y, Mutevelli S, Han U, Ileri D, Onal B, Ilhan O, *et al.* A comparative study of tissue glue and vicryl suture for closing limbal-conjunctival autografts and histologic evaluation after pterygium excision. *Cornea* 2008;**27**:552–8	RCT
Ozeki M, Watanabe N, Miyamoto N, Takahashi M, Murakami S, Sekiya Y, *et al.* Prevention of postoperative meningitis in cochlear implantation: the advantage of the use of temporal muscles and fibrin glue for the shield of cochleostomy. *Cochlear Implants Int* 2004;**5**(Suppl. 1):73–5	Abstract
Palacios Jaraquemada JM, Pesaresi M, Nassif JC, Hermosid S. Anterior placenta percreta: surgical approach, hemostasis and uterine repair. *Acta Obstet Gynecol Scand* 2004;**83**:738–44	Not a relevant comparison
Parker MC, Pohlen U, Borel Rinkes IH, Delvin T. The application of TachoSil® for sealing colorectal anastomosis: a feasibility study. *Colorectal Dis* 2013;**15**:252–7	No comparison group
Pavlik Marangos I, Røsok BI, Kazaryan AM, Rosseland AR, Edwin B. Effect of TachoSil patch in prevention of postoperative pancreatic fistula. *J Gastrointest Surg* 2011;**15**:1625–9	No adverse effects related to fibrin reported
Pescatore P, Jornod P, Borovicka J, Pantoflickova D, Suter W, Meyenberger C, *et al.* Epinephrine versus epinephrine plus fibrin glue injection in peptic ulcer bleeding: a prospective randomized trial. *Gastrointest Endosc* 2002;**55**:348–53	RCT
Petersen B, Barkun A, Carpenter S, Chotiprasidhi P, Chuttani R, Silverman W, *et al.* Tissue adhesives and fibrin glues. *Gastrointest Endosc* 2004;**60**:327–33	Not a comparative observational study
Petsas T, Siamblis D, Giannakenas C, Tepetes K, Dougenis D, Spiropoulos K, *et al.* Fibrin glue for sealing the needle track in fine-needle percutaneous lung biopsy using a coaxial system: Part II – Clinical study. *Cardiovasc Intervent Radiol* 1995;**18**:378–82	RCT
Petter Puchner AH, Khakpour Z, May C, Mika K, Glaser KS, Redl H. The impact of atraumatic fibrin sealant vs. staple mesh fixation in tapp hernia repair on chronic pain and quality of life – results of a randomized controlled study. *Surg Endosc* 2010;**24**(Suppl. 1):618	RCT
Pfuhl JP, Rucker KJ, Schafer D, Baumann R. Extrauterine pregnancy after tubal anastomosis with fibrin glue-light microscopy. *Arch Gynecol Obstet* 1989;**245**:436–7	Abstract
Phillips AW, Viswanath YK, Burns JK, Hall CE, Horgan AF. Use of fibrin glue for fixation of mesh and approximation of Peritoneum in Transabdominal Preperitoneal (TAPP) inguinal hernia repair: technical feasibility and early surgical outcomes. *Surg Laparosc Endosc Percutan Tech* 2014;**24**:e43–5	No comparison group
Pilon F, Tosato F, Danieli D, Campanile F, Zaramella M, Milite D. Intrasac fibrin glue injection after platinum coils placement: the efficacy of a simple intraoperative procedure in preventing type II endoleak after endovascular aneurysm repair. *Interact Cardiovasc Thorac Surg* 2010;**11**:78–82	No adverse effects related to fibrin reported
Pilone *et al.* 2012[89]	RCT

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Por YM, Tan YL, Mehta JS, Tan DT. Intracameral fibrin tissue sealant as an adjunct in tectonic lamellar keratoplasty for large corneal perforations. *Cornea* 2009;**28**:451–5	No comparison group
Porpiglia F, Fiori C, Bertolo R, Mele F, Valentino F, Di Stasio A, *et al.* Complications after laparoscopic partial nephrectomy in a recent series. *J Urol* 2011;**185**:e314–15	No comparison group
Porpiglia F, Renard J, Billia M, Morra I, Terrone C, Scarpa RM. Biological glues and collagen fleece for hemostasis during laparoscopic partial nephrectomy: technique and results of prospective study. *J Endourol* 2007;**21**:423–8	No adverse effects related to fibrin reported
Porte RJ, Verhoef C, De Wilt JHW, Rijken AM, Klaase JM, Ayez N, *et al.* Fibrocaps™, a novel fibrin sealant, for bleeding during hepatic resection: results of a phase 2, randomized, controlled study. *HPB (OXFORD)* 2012;**14**:133	RCT
Powell BS, Wandrey D, Voeller GR. A technique for placement of a bioabsorbable prosthesis with fibrin glue fixation for reinforcement of the crural closure during hiatal hernia repair. *Hernia* 2013;**17**:81–4	No comparison group
Prado *et al.* 2006[187]	RCT
Probst EN, Grzyska U, Westphal M, Zeumer H. Preoperative embolization of intracranial meningiomas with a fibrin glue preparation. *Am J Neuroradiol* 1999;**20**:1695–702	No comparison group
Pruthi RS, Chun J, Richman M. The use of a fibrin tissue sealant during laparoscopic partial nephrectomy. *BJU Int* 2004;**93**:813–17	No comparison group
Pugao R, Perenack J. Delayed reaction to fibrin sealant after facelift surgery: a case report and literature review. *J Oral Maxillofac Surg* 2012;**70**:e44–5	No comparison group
Rábago LR, Ventosa N, Castro JL, Marco J, Herrera N, Gea F. Endoscopic treatment of postoperative fistulas resistant to conservative management using biological fibrin glue. *Endoscopy* 2002;**34**:632–8	No comparison group
Ramon Rabago L, Moral I, Delgado M, Guerra I, Quintanilla E, Castro JL, *et al.* [Endoscopic treatment of gastrointestinal fistulas with biological fibrin glue.] *Gastroenterologia y Hepatologia* 2006;**29**:390–6	No comparison group
Randelli F, Banci L, Ragone V, Pavesi M, Randelli G. Effectiveness of fibrin sealant after cementless total hip replacement: a double-blind randomized controlled trial. *Int J Immunopathol Pharmacol* 2013;**26**:189–97	RCT
Randelli *et al.* 2014[149]	RCT
Raquel SS, Gonzalez S, Nicolas R, Crego R, Tome C, Estevez S, *et al.* Staple line reinforcement with tissue glue sealant (Tissucol) during the learning curve of laparoscopic bariatric surgery. *Obes Surg* 2009;**19**:1045	No comparison group
Reddy M, Schöggl A, Reddy B, Saringer W, Weigel G, Matula C. A clinical study of a fibrinogen-based collagen fleece for dural repair in neurosurgery. *Acta Neurochir* 2002;**144**:265–9	No comparison group
Reppenhagen S, Reichert JC, Rackwitz L, Rudert M, Raab P, Daculsi G, *et al.* Biphasic bone substitute and fibrin sealant for treatment of benign bone tumours and tumour-like lesions. *Int Orthop* 2012;**36**:139–48	No comparison group
Richmon JD, Tian Y, Husseman J, Davidson TM. Use of a sprayed fibrin hemostatic sealant after laser therapy for hereditary hemorrhagic telangiectasia epistaxis. *Am J Rhinol* 2007;**21**:187–91	Included children
Romeo F, Pagano N, Carlino A, Rando G, Strangio G, Vitetta E, *et al.* Multimodal endoscopic approach to postsurgical gastro-esophageal anastomotic leaks. *Gastrointest Endosc* 2010;**71**:AB132	No comparison group
Rousou J, Levitsky S, Gonzalez-Lavin L, Cosgrove D, Magilligan D, Weldon C, *et al.* Randomized clinical trial of fibrin sealant in patients undergoing resternotomy or reoperation after cardiac operations. A multicenter study. *J Thorac Cardiovasc Surg* 1989;**97**:194–203	RCT
Rudelstorfer B, Loidl K, Heider R. [Wound closure of the fallopian tube with fibrin glue: endoscopic organ preserving therapy of extrauterine pregnancy.] *Gynakol Geburtshilfliche Rundsch* 1997;**37**:62–7	No comparison group

continued

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Ruggiero R, Procaccini E, Gili S, Cremone C, Parmeggiani D, Conzo G, *et al.* New trends on fibrin glue in seroma after axillary lymphadenectomy for breast cancer. *G Chir* 2009;**30**:306–10	RCT
Ruggiero R, Procaccini E, Piazza P, Docimo G, Iovino F, Antoniol G, *et al.* Effectiveness of fibrin glue in conjunction with collagen patches to reduce seroma formation after axillary lymphadenectomy for breast cancer. *Am J Surg* 2008;**196**:170–4	No adverse effects related to fibrin reported
Sabatini *et al.* 2012[148]	RCT
Sadik KW, Bonatti H, Schmitt T. Injection of fibrin glue for temporary treatment of an ascites leak from a ruptured umbilical hernia in a patient with liver cirrhosis. *Surgery* 2008;**143**:574	Letter/commentary/reply
Sadik KW, Laibstain S, Northup PG, Kashmer D, Schmitt TM, Bonatti HJR. Closure of ascites leaks with fibrin glue injection in patients with end-stage liver disease. *J Laparoendosc Adv Surg Tech A* 2011;**21**:609–14	No comparison group
Sáenz Medina J, Redondo González E, Hernández-Atance JM, Crespo Martínez L, Llanes González L, Rendón Sánchez D, *et al.* Renocolic fistula as a complication of radiofrequency in the treatment of renal cell carcinoma. *Arch Esp Urol* 2010;**63**:74–7	No comparison group
Safan *et al.* 2009[235]	RCT
Saha *et al.* 2011[204]	RCT
Saha *et al.* 2012[197]	RCT
Salgado W, Rosa GV, Nonino-Borges CB, Ceneviva R. Prospective and randomized comparison of two techniques of staple line reinforcement during open Roux-en-Y gastric bypass: oversewing and bioabsorbable Seamguard®. *J Laparoendosc Adv Surg Tech A* 2011;**21**:579–82	RCT
Samimi DB, Hamilton DR. Recalcitrant epithelial ingrowth in patients with compromised eyelid function. *J Refract Surg* 2008;**24**:544–6	No comparison group
Sanal M. Does fibrin glue cause foreign body reactions? *Eur J Pediatr Surg* 1993;**3**:190	Letter/commentary/reply
Sanchez-Mendez JI, Lopez-Rodriguez MJ, Sanchez-Martinez C, Martinez-Garcia MT, Iniesta Donate MD, Ordas Santotomas J. Fibrin sealant for the prevention of axillary seroma formation after axillary lymph node dissection. A prospective randomized study. *Cancer Res* 2009;**69**:4139	RCT
Santoro E, Agresta F, Buscaglia F, Mulieri G, Mazzarolo G, Bedin N, *et al.* Preliminary experience using fibrin glue for mesh fixation in 250 patients undergoing minilaparoscopic transabdominal preperitoneal hernia repair. *J Laparoendosc Adv Surg Tech A* 2007;**17**:12–15	No adverse effects related to fibrin reported
Santulli P, Marcellin L, Touboul C, Ballester M, Darai E, Rouzier R. Experience with TachoSil in obstetric and gynecologic surgery. *Int J Gynaecol Obstet* 2011;**113**:112–15	No comparison group
Sapala JA, Wood MH, Schuhknecht MP. Anastomotic leak prophylaxis using a vapor-heated fibrin sealant: report on 738 gastric bypass patients. *Obes Surg* 2004;**14**:35–42	No comparison group
Sarnicola V, Vannozzi L, Motolese PA. Recurrence rate using fibrin glue-assisted ipsilateral conjunctival autograft in pterygium surgery: 2-year follow-up. *Cornea* 2010;**29**:1211–14	No comparison group
Satoi S, Toyokawa H, Yanagimoto H, Yamamoto T, Hirooka S, Yui R, *et al.* Reinforcement of pancreticojejunostomy using polyglycolic acid mesh and fibrin glue sealant. *Pancreas* 2011;**40**:16–20	No adverse effects related to fibrin reported
Sautter NB, Batra PS, Citardi MJ. Endoscopic management of sphenoid sinus cerebrospinal fluid leaks. *Ann Otol Rhinol Laryngol* 2008;**117**:32–9	No comparison group
Savva A, Taylor MJ, Beatty CW. Management of cerebrospinal fluid leaks involving the temporal bone: report on 92 patients. *Laryngoscope* 2003;**113**:50–6	No adverse effects related to fibrin reported
Schaller B, Baumann A. Headache after removal of vestibular schwannoma via the retrosigmoid approach: a long-term follow-up-study. *Otolaryngol Head Neck Surg* 2003;**128**:387–95	No comparison group
Scheele J, Schricker KT, Goy RD, Lampe I, Panis R. [Risk of hepatitis in fibrin gluing in general surgery.] *Med Welt* 1981;**32**:783–8	Unobtainable
Schenk *et al.* 2003[195]	RCT

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Schenk *et al.* 2002[196]	RCT
Schettino AM, Franco D, Franco T, Filho JM, Vendramin FS. Use of autologous fibrin glue (platelet-poor plasma) in abdominal dermolipectomies. *Aesthetic Plast Surg* 2012;**36**:1296–301	Not fibrin sealant
Scheule AM, Beierlein W, Lorenz H, Ziemer G. Repeated anaphylactic reactions to aprotinin in fibrin sealant. *Gastrointest Endosc* 1998;**48**:83–5	No comparison group
Schlenker M, Ringelstein EB. Epidural fibrin clot for the prevention of post-lumbar puncture headache: a new method with risks. *J Neurol Neurosurg Psychiatr* 1987;**50**:1715	Letter/commentary/reply
Schmidt SC, Langrehr JM. Re: Spray application of fibrin glue as risk factor for subcutaneous emphysema in laparoscopic transabdominal inguinal hernia repair. *Surg Laparosc Endosc Percutan Tech* 2007;**17**:221–2	Letter/commentary/reply
Scholz *et al.* 2002[121]	RCT
Schopf SK, von Ahnen M, von Ahnen T, Schardey HM. [Observations on the use of TachoSil® in cholecystectomy – a multicentre, prospective, single-arm cohort study.] *Zentralbl Chir* 2012;**137**:55–60	No comparison group
Schwartz *et al.* 2004[77]	RCT
Segal N, Puterman M, Rotem E, Niv A, Kaplan D, Kraus M, *et al.* A prospective randomized double-blind trial of fibrin glue for reducing pain and bleeding after tonsillectomy. *Int J Pediatr Otorhinolaryngol* 2008;**72**:469–73	RCT
Séguin JR, Frapier JM, Colson P, Chaptal PA. Fibrin sealant improves surgical results of type A acute aortic dissections. *Ann Thorac Surg* 1991;**52**:745–8	Emergency surgery
Séguin JR, Picard E, Frapier JM, Chaptal PA. Repair of the aortic arch with fibrin glue in type A aortic dissection. *J Card Surg* 1994;**9**:734–8	No comparison group
Seiler RW, Mariani L. Sellar reconstruction with resorbable vicryl patches, gelatin foam, and fibrin glue in transsphenoidal surgery: a 10-year experience with 376 patients. *J Neurosurg* 2000;**93**:762–5	No comparison group
Sentovich SM. Fibrin glue for anal fistulas: long-term results. *Dis Colon Rectum* 2003;**46**:498–502	No comparison group
Seo JK, Kim HJ, Koh JK, Hong SK, Jung SY, Hwang SH, *et al.* The use of fibrin glue in osmidrosis surgery with a cartilage shaver: 18 patients. *J Am Acad Dermatol* 2013;**68**(Suppl. 1):AB223	No comparison group
Seok Y, Cho S, Lee E. Bronchial stump coverage with fibrin glue-coated collagen fleece in lung cancer patients who underwent pneumonectomy. *Ann Thorac Cardiovasc Surg* 2014;**20**:117–22	No adverse effects related to fibrin reported
Shah HN, Hegde S, Shah JN, Mohile PD, Yuvaraja TB, Bansal MB. A prospective, randomized trial evaluating the safety and efficacy of fibrin sealant in tubeless percutaneous nephrolithotomy. *J Urol* 2006;**176**:2488–92	RCT
Shah HN, Kausik V, Hedge S, Shah JN, Bansal MB. Initial experience with hemostatic fibrin glue as adjuvant during tubeless percutaneous nephrolithotomy. *J Endourol* 2006;**20**:194–8	No adverse effects related to fibrin reported
Sharma *et al.* 2003[164]	RCT
Sharma SK, Perry KT, Turk TM. Endoscopic injection of fibrin glue for the treatment of urinary-tract pathology. *J Endourol* 2005;**19**:419–23	No comparison group
Shehadeh-Mashor R, Srinivasan S, Boimer C, Lee K, Tomkins O, Slomovic AR. Management of recurrent pterygium with intraoperative mitomycin C and conjunctival autograft with fibrin glue. *Am J Ophthalmol* 2011;**152**:730–2	No comparison group
Shen L, Luo H, Tan S. Effect of fibrin glue on patients after high frequency electrocoagulatomy for gastrointestinal protuberant lesions. *Med J Wuhan Uni* 2003;**24**:377	RCT
Shimada Y, Hongo M, Miyakoshi N, Sugawara T, Kasukawa Y, Ando S, *et al.* Dural substitute with polyglycolic acid mesh and fibrin glue for dural repair: technical note and preliminary results. *J Orthop Sci* 2006;**11**:454–8	Fibrin was used in both groups

continued

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Shin IS, Lee DW, Lew DH. Efficacy of quilting sutures and fibrin sealant together for prevention of seroma in extended latissimus dorsi flap donor sites. *Arch Plast Surg* 2012;**39**:509–13	Fibrin was used in both groups
Shinohara H, Koizumi T, Aoki T, Yoshiya K, Koike T, Tsuchida M. Intrapleural administration of a combination of cisplatin and fibrin glue for pleural lavage cytology-positive patients with non-small cell lung cancer. *J Thorac Oncol* 2013;**8**:S508	Not a relevant comparison
Siemer *et al.* 2007[221]	RCT
Silas AM, Forauer AR, Perrich KD, Gemery JM. Sclerosis of postoperative lymphoceles: avoidance of prolonged catheter drainage with use of a fibrin sealant. *J Vasc Interv Radiol* 2006;**17**:1791–5	No comparison group
Silecchia *et al.* 2008[62]	RCT
Silecchia G, Boru CE, Mouiel J, Rossi M, Anselmino M, Tacchino RM, *et al.* Clinical evaluation of fibrin glue in the prevention of anastomotic leak and internal hernia after laparoscopic gastric bypass: preliminary results of a prospective, randomized multicenter trial. *Obes Surg* 2006;**16**:125–31	RCT
Silecchia G, Iossa A, Cavallaro G, Rizzello M, Longo F. Reinforcement of hiatal defect repair with absorbable mesh fixed with non-permanent devices. *Minim Invasive Ther Allied Technol* 2014;**23**:302–8	Not a comparative observational study
Singer M, Cintron J, Nelson R, Orsay C, Bastawrous A, Pearl R, *et al.* Treatment of fistulas-in-ano with fibrin sealant in combination with intra-adhesive antibiotics and/or surgical closure of the internal fistula opening. *Dis Colon Rectum* 2005;**48**:799–808	RCT
Sintler *et al.* 2005[202]	RCT
Skovgaard *et al.* 2013[150]	RCT
Slupski P, Jarzemski P, Listopadzki S, Wisniewski P. Suture-free laparoscopic partial nephrectomy - improvement of hemostasis with human fibrinogen and thrombin-coated collagen patch (TachoSil). *Eur Urol Suppl* 2010;**9**:636	Abstract
Sokullu O, Sanioglu S, Orhan G, Kut MS, Hastaoglu O, Karaca P, *et al.* New use of teflon to reduce bleeding in modified bentall operation. *Tex Heart Inst J* 2008;**35**:147–51	No comparison group
Soumian S, Al-Ani S, Sterne G. Randomized clinical trial on the effect of fibrin sealant on latissimus dorsi donor-site seroma formation after breast reconstruction (*Br J Surg* 2012;**99**:1381–8). *Br J Surg* 2013;**100**:1671	RCT
Sozen *et al.* 2011[212]	RCT
Sozen S, Topuz O, Keceli M, Tukenmez M, Onceken O, Tuna O. The use of fibrin glue in surgical treatment of pilonidal sinus disease: a prospective study in the limberg flap procedure. *Pak J Med Sci* 2011;**27**:537–40	RCT
Spotnitz WD, Dalton MS, Baker JW, Nolan SP. Successful use of fibrin glue during 2 years of surgery at a university medical center. *Am Surg* 1989;**55**:166–8	No comparison group
Srinivasan *et al.* 2009[167]	RCT
Stanojkovic Z, Milic D, Zivic S, Perisic Z. Application effect of fibrin sealant in patients undergoing pacemaker implantation. *Vox Sang* 2009;**96**:238	Abstract
Sterkers O, Becherel P, Sterkers JM. [Repair of the facial nerve exclusively by fibrin glue. 56 cases.] *Ann Otolaryngol Chir Cervicofac* 1989;**106**:176–81	No comparison group
Stoeckli SJ, Moe KS, Huber A, Schmid S. A prospective randomized double-blind trial of fibrin glue for pain and bleeding after tonsillectomy. *Laryngoscope* 1999;**109**:652–5	RCT
Sugg U. [Risk of transmission of hepatitis through human fibrin adhesives.] *Dtsch Med Wochenschr* 1985;**110**:1161–2	No adverse effects related to fibrin reported
Suzuki A, Amano J, Tanaka H, Sakamoto T, Sunamori M. Surgical consideration of aortitis involving the aortic root. *Circulation* 1989;**80**:I222–32	Not a relevant comparison
Swain BT, Ellis CN. Fibrin glue treatment of low rectal and pouch-anal anastomotic sinuses. *Dis Colon Rectum* 2004;**47**:253–5	No comparison group

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Swan *et al.* 2011[113]	RCT
Szczesny T, Kubiszewska I, Rybak A, Michalkiewicz J, Szymankiewicz M, Kowalewski J. The role of Tachosil in lymphostasis after mediastinal lymphadenectomy in lung cancer patients. *J Thorac Oncol* 2011;**6**(Suppl. 2):876–7	RCT
Tachibana *et al.* 2003[122]	RCT
Taguchi Y, Suzuki R, Okada M, Sekino H. Spinal arachnoid cyst developing after surgical treatment of a ruptured vertebral artery aneurysm: a possible complication of topical use of fibrin glue. Case report. *J Neurosurg* 1996;**84**:526–9	No comparison group
Takeuchi *et al.* 2005[234]	RCT
Tan LA, Takagi I, Straus D, O'Toole JE. Management of intended durotomy in minimally invasive intradural spine surgery: clinical article. *J Neurosurg Spine* 2014;**21**:279–85	No comparison group
Tan QT, Lee CM, Tan VKM, Ong KW. The use of Tisseel fibrin sealant in seroma reduction after mastectomy – a pilot study. *Breast* 2015;**24**:S133	Abstract
Târcoveanu E, Lupaşcu C, Moldovanu R, Vlad N, Bradea C, Vasilescu A. [Fibrin-collagen patch (TachoComb) in general surgery. Indications and results.] *Rev Med Chir Soc Med Nat Iasi* 2007;**111**:396–401	No comparison group
Terasaka S, Iwasaki Y, Kuroda S, Uchida T. [A novel method of dural repair using polyglycolic acid non-woven fabric and fibrin glue: clinical results of 140 cases.] *No Shinkei Geka* 2006;**34**:1109–17	No comparison group
Terashima M, Fujiwara S, Yaginuma GY, Takizawa K, Kaneko U, Meguro T. Outcome of percutaneous intrapericardial fibrin-glue injection therapy for left ventricular free wall rupture secondary to acute myocardial infarction. *Am J Cardiol* 2008;**101**:419–21	No comparison group
Than KD, Baird CJ, Olivi A. Polyethylene glycol hydrogel dural sealant may reduce incisional cerebrospinal fluid leak after posterior fossa surgery. *Neurosurgery* 2008;**63**(Suppl. 1):ON182–6	Not fibrin sealant
Tirindelli MC, Flammia G, Cudillo L, Dentamaro T, Picardi A, Annibali O, *et al.* Fibrin glue directly applied on damaged bladder mucosa during cystoscopy is highly effective to treat severe, refractory, haemorrhagic cystitis after allogeneic transplant. *Bone Marrow Transplant* 2010;**45**:S12	No comparison group
Tirindelli MC, Flammia G, Sergi F, Cerretti R, Cudillo L, Picardi A, *et al.* Fibrin glue for refractory hemorrhagic cystitis after unrelated marrow, cord blood, and haploidentical hematopoietic stem cell transplantation. *Transfusion* 2009;**49**:170–5	No comparison group
Tirindelli MC, Flammia GP, Bove P, Cerretti R, Cudillo L, de Angelis G, *et al.* Fibrin glue therapy for severe hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2014;**20**:1612–17	No comparison group
Tiscione D, Cicuto S, Luciani L, Vattovani V, Coccarelli F, Malossini G. Use of fibrin gel (Tissucol) as hemostatic agent during laparoscopic partial nephrectomy: our experience. *Anticancer Res* 2010;**30**:1520–1	No comparison group
Toman N, Buschmann A, Muehlberger T. [Fibrin glue and seroma formation following abdominoplasty.] *Chirurg* 2007;**78**:531–5	Fibrin was used in both groups
Tomizawa Y, Endo M, Kitamura M, Shiikawa A, Yagi Y, Koyanagi H. [Coronary artery bypass graft stenosis suspected to be due to hemostatic agents: a case report.] *Kyobu Geka* 1991;**44**:764–6	No comparison group
Topart P, Vandenbroucke F, Lozac'h P. Tisseel versus tack staples as mesh fixation in totally extraperitoneal laparoscopic repair of groin hernias: a retrospective analysis. *Surg Endosc* 2005;**19**:724–7	No adverse effects related to fibrin reported
Topgül K, Anadol AZ, Güngör B, Malazgirt Z. Laparoscopic bilateral hernia repair using fibrin sealant: technical report of two cases. *J Laparoendosc Adv Surg Tech A* 2005;**15**:638–41	No comparison group
Topiwala P, Bansal RK. Comparative evaluation of cyanoacrylate and fibrin glue for muscle recession in strabismus surgery. *J Pediatr Ophthalmol Strabismus* 2014;**51**:349–54	RCT

continued

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Tournoux F, Karila-Cohen D, Hvass U, Peytavin G, Phelippeau G, Vahanian A. [Neutropenia and fever after aorto-coronary bypasses.] *Ann Chir* 2004;**129**:174–6	No comparison group
Tredwell SJ, Sawatzky B. The use of fibrin sealant to reduce blood loss during Cotrel-Dubousset instrumentation for idiopathic scoliosis. *Spine* 1990;**15**:913–15	RCT
Tripoloni DE, Schierano MC. Comments about the article 'Open tension-free Lichtenstein repair of inguinal hernia: use of fibrin glue versus sutures for mesh fixation' by Negro *et al. Hernia* 2012;**16**:235–6	Letter/commentary/reply
Troisi RI, Bektas H, Pratschke J, Topal B, Buchler M, Schuhmacher CP, *et al.* A prospective, multi-center, randomized, single-blind study to compare the Veriset™ hemostatic patch to fibrin sealant (Tachosil) in subjects undergoing hepatic surgery. *HPB* 2012;**14**:104–5	RCT
Truong S, Bohm G, Klinge U, Stumpf M, Schumpelick V. Results after endoscopic treatment of postoperative upper gastrointestinal fistulas and leaks using combined Vicryl plug and fibrin glue. *Surg Endosc* 2004;**18**:1105–8	No comparison group
Tsuji Y, Fujishiro M, Kodashima S, Ono S, Niimi K, Mochizuki S, *et al.* Polyglycolic acid sheets and fibrin glue decrease the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms (with video). *Gastrointest Endosc* 2015;**81**:906–12	Not a comparative observational study
Tsuji Y, Ohata K, Gunji T, Shozushima M, Hamanaka J, Ohno A, *et al.* Endoscopic tissue shielding method with polyglycolic acid sheets and fibrin glue to cover wounds after colorectal endoscopic submucosal dissection (with video). *Gastrointest Endosc* 2014;**79**:151–5	No comparison group
Udén *et al.* 1993[98]	RCT
Ulusoy *et al.* 2003[96]	RCT
Ussat S, Lodes U, Wex C, Rapp L, Schulz HU, Meyer F. [Successful closure of a postoperative esophagobronchial fistula following esophageal resection using fibrin glue.] *Dtsch Med Wochenschr* 2013;**138**:1406–9	RCT
Uy HS, Reyes JMG, Flores JDG, Lim-Bon-Siong R. Comparison of fibrin glue and sutures for attaching conjunctival autografts after pterygium excision. *Ophthalmology* 2005;**112**:667–71	No comparison group
Vaiman M, Eviatar E. Lymphatic fistulae after neck dissection: the fibrin sealant treatment. *J Surg Oncol* 2008;**98**:467–71	RCT
Vaiman *et al.* 2002[188]	No comparison group
Vaiman M, Eviatar E, Shlamkovich N, Segal S. Effect of modern fibrin glue on bleeding after tonsillectomy and adenoidectomy. *Ann Otol Rhinol Laryngol* 2003;**112**:410–14	RCT
Vaiman *et al.* 2005[191]	RCT
Vaiman *et al.* 2005[189]	RCT
Vaiman M, Segal S, Eviatar E. Fibrin glue treatment for epistaxis. *Rhinology* 2002;**40**:88–91	RCT
Valenti A, Rivkin E, Carandina S, Steiger A, Polliand C, Rizk N, *et al.* Laparoscopy sleeve gastrectomy: 220 cases in a comparative study with three buttressing methods applied on stapler line. *Obes Surg* 2013;**23**:1053	Not a comparative observational study
Van Velthoven V, Clarici G, Auer LM. Fibrin tissue adhesive sealant for the prevention of CSF leakage following transsphenoidal microsurgery. *Acta Neurochir* 1991;**109**:26–9	No comparison group
Vaxman *et al.* 1995[112]	RCT
Vaxman *et al.* 1995[251]	RCT
Verhoef *et al.* 2015[240]	RCT
Vichare N, Choudhary T, Arora P. A comparison between fibrin sealant and sutures for attaching conjunctival autograft after pterygium excision. *Med J Armed Forces India* 2013;**69**:151–5	No adverse effects related to fibrin reported
Vitton V, Gasmi M, Barthet M, Desjeux A, Orsoni P, Grimaud JC. Long-term healing of Crohn's anal fistulas with fibrin glue injection. *Aliment Pharmacol Ther* 2005;**21**:1453–7	No comparison group

TABLE 39 Excluded observational studies (*continued*)

Study excluded	Reason for exclusion
Waclawiczek HW, Boeckl O. [Clinical experience with fibrin gluing in general and thoracic surgery.] *Zentralbl Chir* 1986;**111**:16–24	No comparison group
Wang *et al.* 2003[153]	RCT
Wang *et al.* 2001[144]	RCT
Wang X, Ren J, Zhu W, Li N, Li J. Fibrin sealant prevents gastrointestinal anastomosis dehiscence in intra-abdominal sepsis. *Int Surg* 2007;**92**:27–31	No comparison group
Watanabe G, Haverich A, Speier R, Dresler C, Borst HG. Surgical treatment of active infective endocarditis with paravalvular involvement. *J Thorac Cardiovasc Surg* 1994;**107**:171–7	No comparison group
White N, Carver ED, Rodrigues D, Dover S, Magdum S, Nishikawa H, *et al.* Calvarial remodelling for sagittal synostosis: does fibrin glue (Tisseel) reduce post-operative blood transfusion requirements? *Childs Nerv Syst* 2009;**25**:867–9	Included children
Willecocq C, Pizzoferrato AC, Fauconnier A, Bader G. [Use of glue in laparoscopic sacrocolpopexy. A comparative study about 32 cases.] *Gynecol Obstet Fertil* 2014;**42**:822–6	No adverse effects related to fibrin reported
Wong K, Goldstraw P. Effect of fibrin glue in the reduction of postthoracotomy alveolar air leak. *Ann Thorac Surg* 1997;**64**:979–81	RCT
Yeom JS, Buchowski JM, Shen HX, Liu G, Bunmaprasert T, Riew KD. Effect of fibrin sealant on drain output and duration of hospitalization after multilevel anterior cervical fusion: a retrospective matched pair analysis. *Spine* 2008;**33**:E543–7	No adverse effects related to fibrin reported
Yildirim AE, Dursun E, Ozdol C, Divanlioglu D, Nacar OA, Koyun OK, *et al.* Using an autologous fibrin sealant in the preventing of cerebrospinal fluid leak with large skull base defect following endoscopic endonasal transsphenoidal surgery. *Turk Neurosurg* 2013;**23**:736–41	No comparison group
Yin W, Pauza K, Olan W, Doerzbacher J. Long-term outcomes from a prospective, multicenter investigational device exemption (IDE) pilot study of intradiscal fibrin sealant for the treatment of discogenic pain. *Pain Med* 2011;**12**:1446–7	No comparison group
Yu L, Gu T, Song L, Shi E, Fang Q, Wang C, *et al.* Fibrin sealant provides superior hemostasis for sternotomy compared with bone wax. *Ann Thorac Surg* 2012;**93**:641–4	No comparison group
Yuan Q, Bai XM, Cheng L, Gu XS, Jin Y. Efficacy of fibrin glue in percutaneous transhepatic obliteration for the management of upper gastrointestinal bleeding in patients with portal hypertension. *Shijie Huaren Xiaohua Zazhi* 2012;**20**:3397–402	RCT
Yüksel *et al.* 2010[158]	No comparison group
Zacharias T, Ferreira N. Carrier-bound fibrin sealant compared to oxidized cellulose application after liver resection. *HPB* 2012;**14**:839–47	No adverse effects related to fibrin reported
Zhang YH, Gu TX, Zhang GW, Wang C, Liu Y, Yu Y. Injection of fibrin glue directly into the sternum for sternal bleeding in old patients with osteoporosis during coronary artery bypass. *J Clin Rehabil Tiss Engin Res* 2011;**15**:4735–8	RCT
Zhou D, Shen L, Jin Y, Bennet S, Wang W, McLennan G. Efficacy and safety of selective arterial embolization with fibrin glue in the treatment of primary postpartum hemorrhage: a prospective study of 61 cases. *J Vasc Interv Radiol* 2012;**23**(Suppl. 1):105–6	Abstract
Zmora O, Neufeld D, Ziv Y, Tulchinsky H, Scott D, Khaikin M, *et al.* Prospective, multicenter evaluation of highly concentrated fibrin glue in the treatment of complex cryptogenic perianal fistulas. *Dis Colon Rectum* 2005;**48**:2167–72	No comparison group
Zoumalan R, Rizk SS. Hematoma rates in drainless deep-plane face-lift surgery with and without the use of fibrin glue. *Arch Facial Plast Surg* 2008;**10**:103–7	No adverse effects related to fibrin reported

Appendix 8 Sensitivity analysis random-effects model (DerSimonian and Laird[55])

Primary outcomes

Seroma development

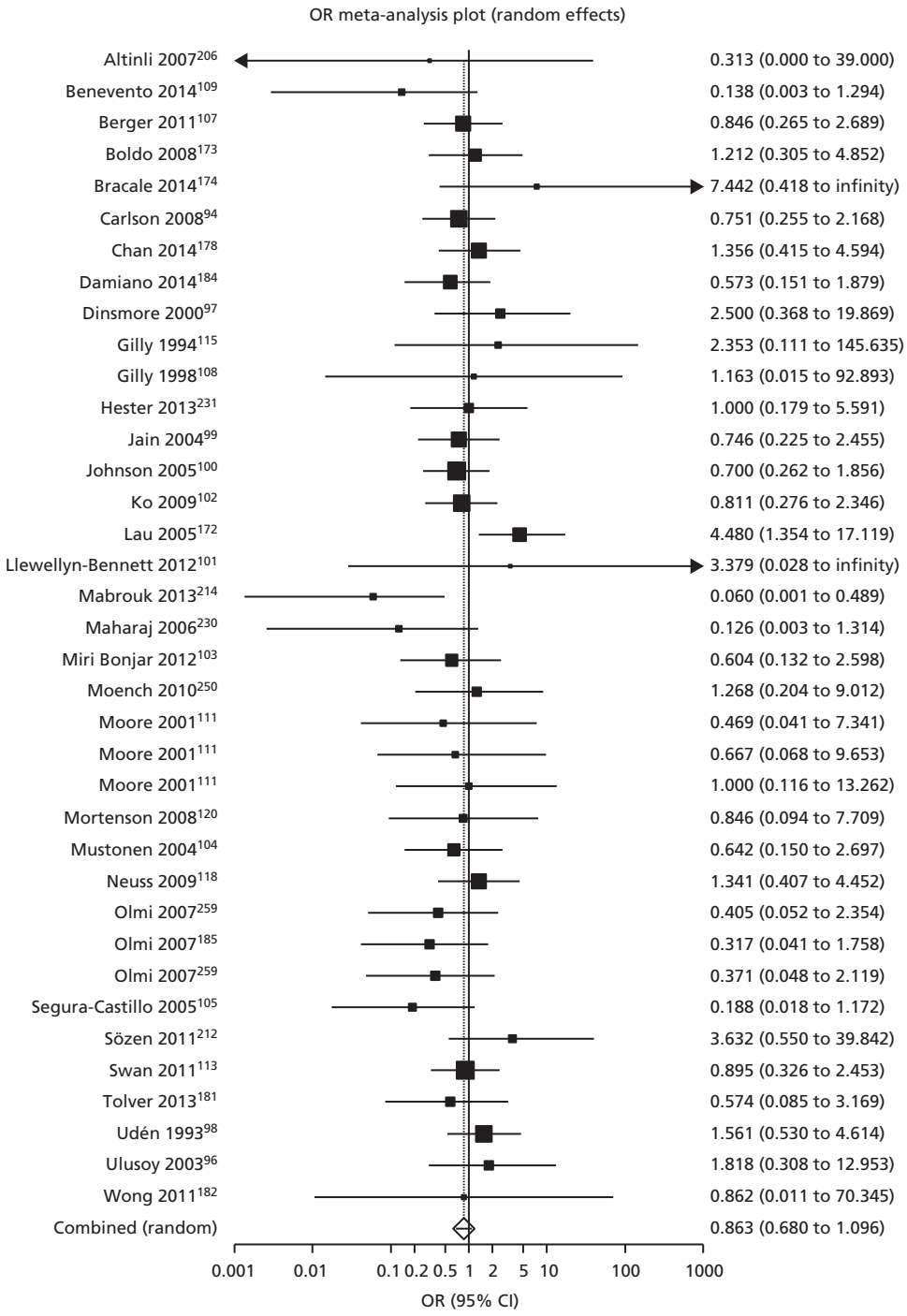

FIGURE 49 Seroma development in all surgical specialties: fibrin sealant vs. standard care. Pooled OR 0.86 (95% CI 0.68 to 1.10; $p = 0.23$).

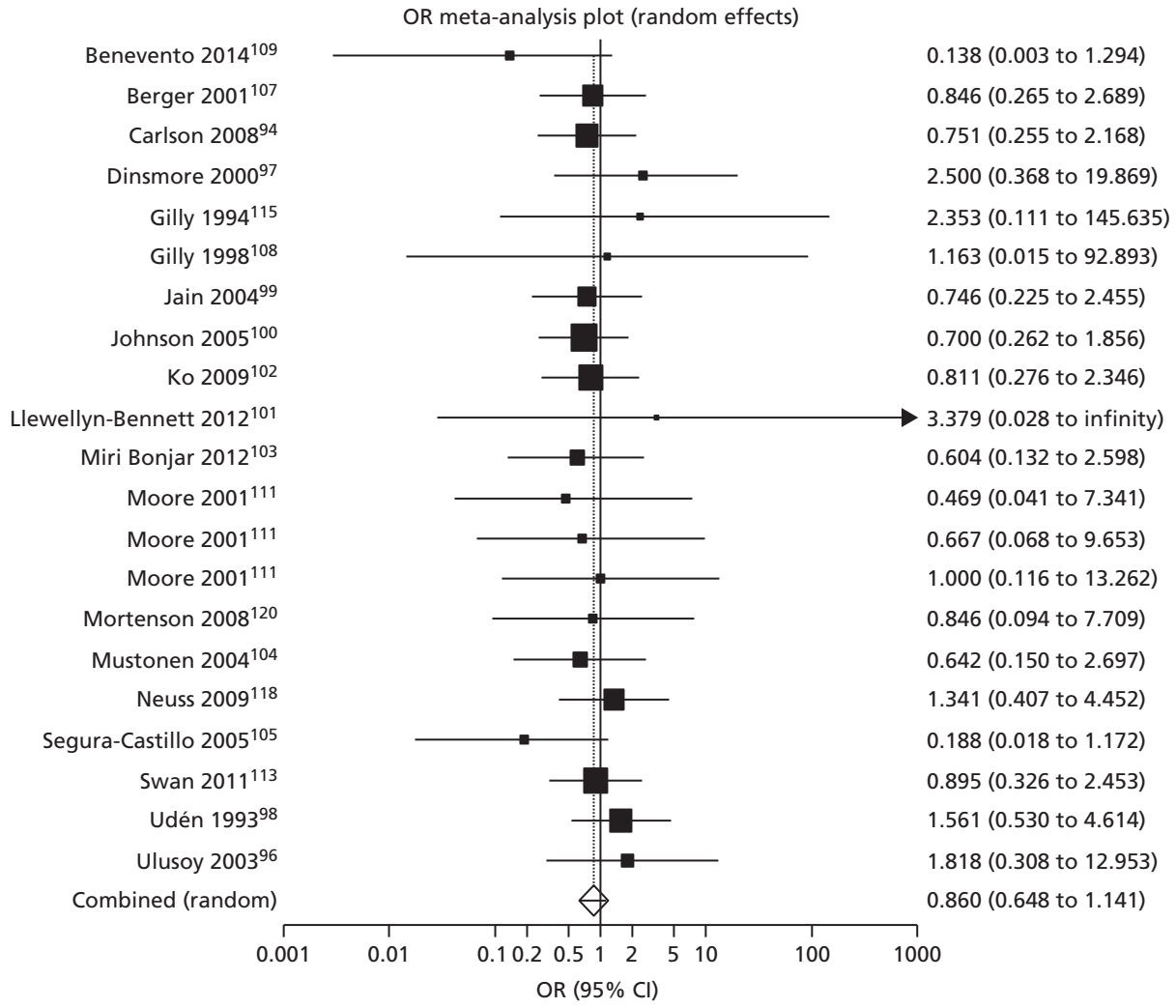

FIGURE 50 Seroma development in breast surgery: fibrin sealant vs. standard care. Pooled OR 0.86 (95% CI 0.65 to 1.14; $p = 0.30$).

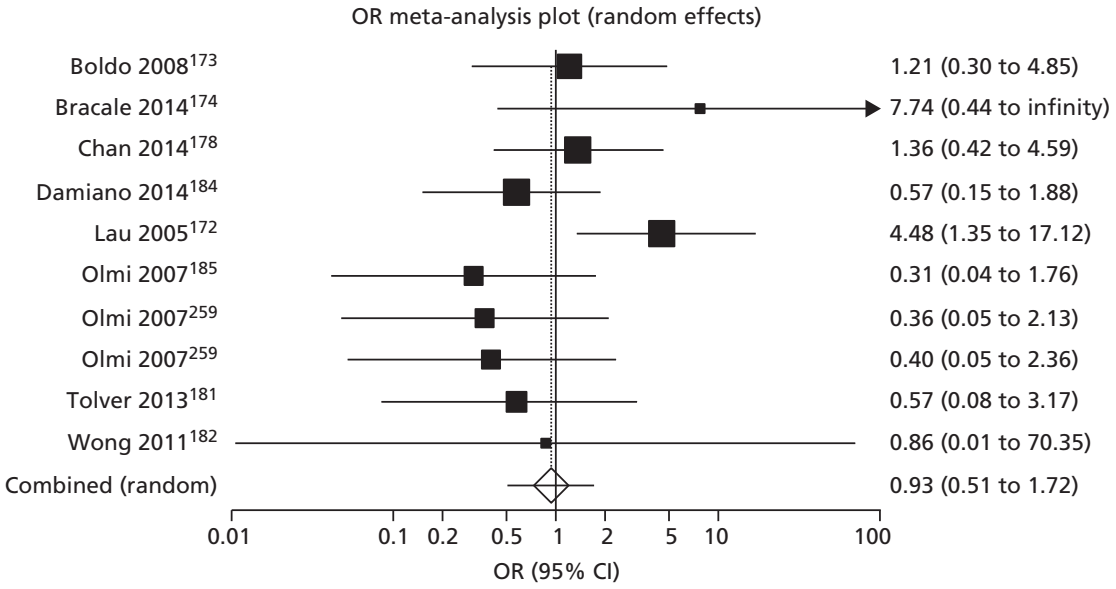

FIGURE 51 Seroma development in hernia surgery: fibrin sealant vs. standard care. Pooled OR 0.93 (95% CI 0.51 to 1.72; $p = 0.825$).

Haematoma development

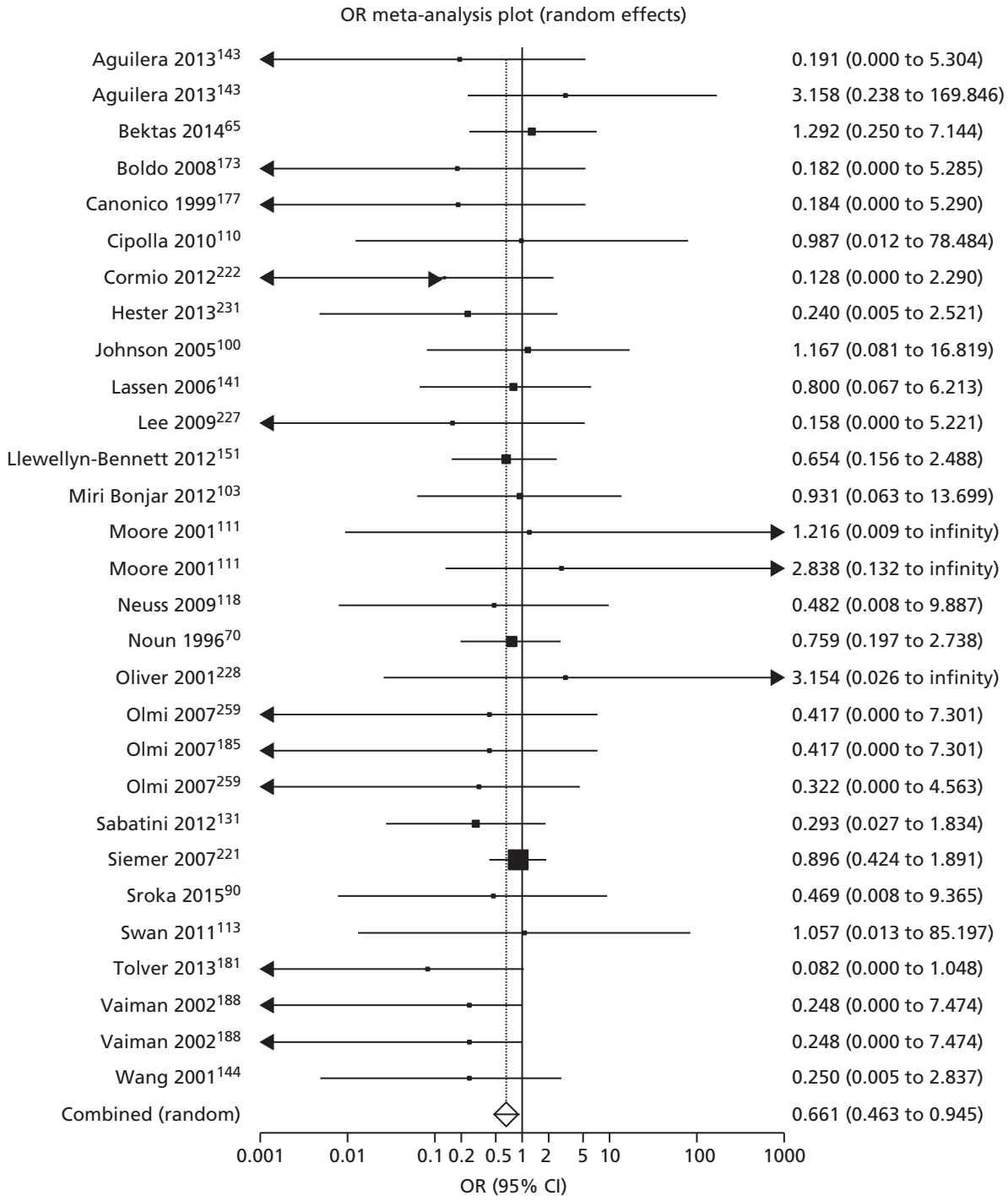

FIGURE 52 Haematoma development in all surgical specialties: fibrin sealant vs. standard care. Pooled OR 0.66 (95% CI 0.46 to 0.94; $p = 0.023$).

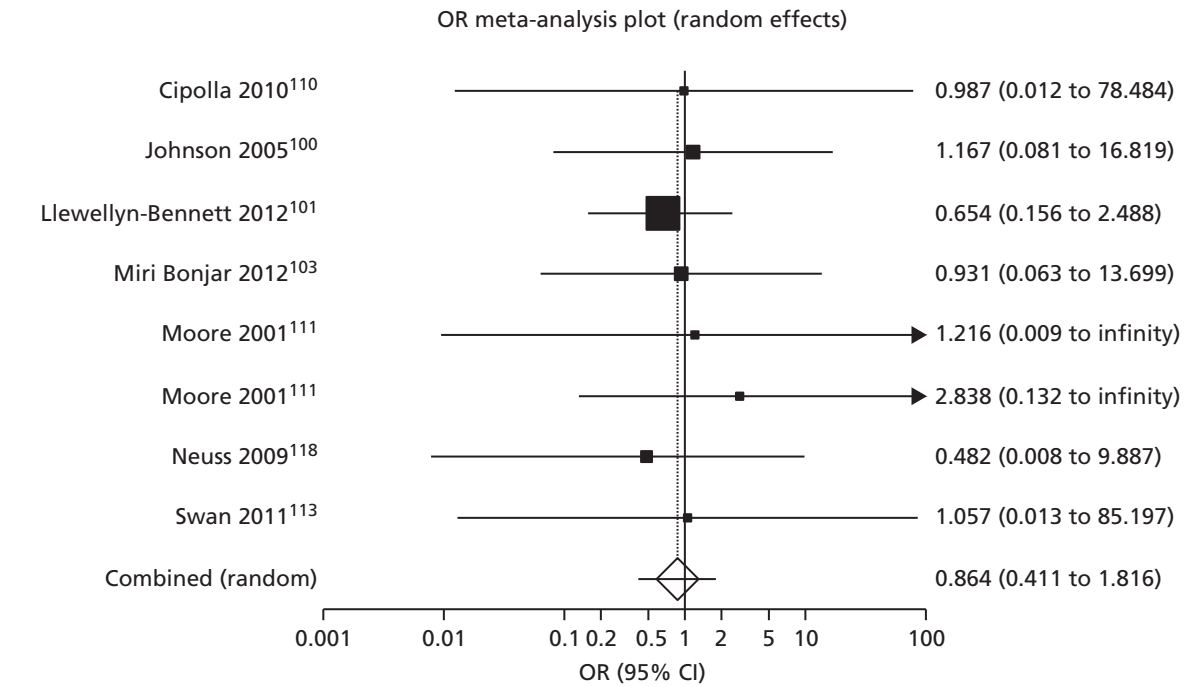

FIGURE 53 Haematoma development in breast surgery: fibrin sealant vs. standard care. Pooled OR 0.86 (95% CI 0.41 to 1.82; $p = 0.70$).

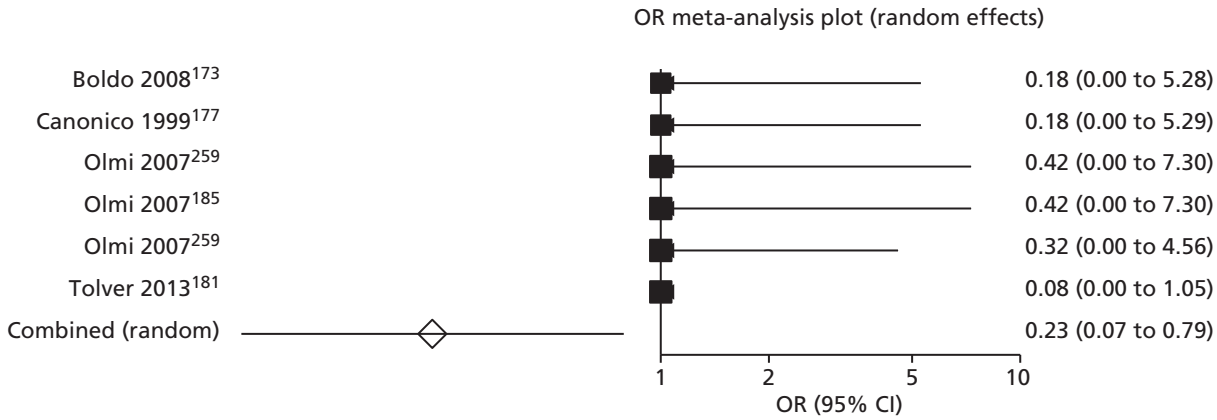

FIGURE 54 Haematoma development in hernia surgery: fibrin sealant vs. standard care. Pooled OR 0.23 (95% CI 0.07 to 0.79; $p = 0.02$).

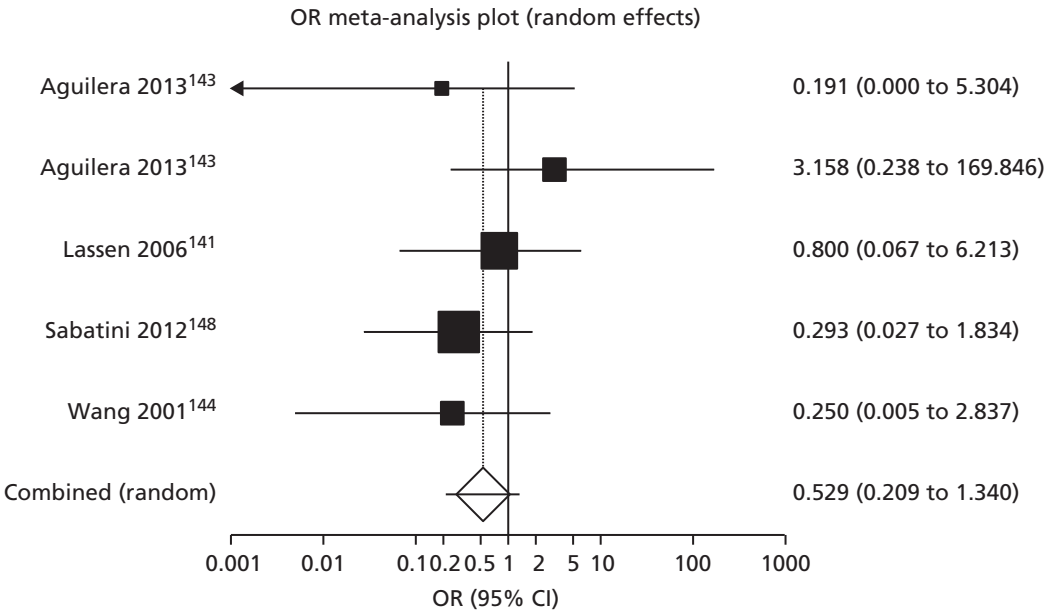

FIGURE 55 Haematoma development in orthopaedic surgery: fibrin sealant vs. standard care. Pooled OR 0.53 (95% CI 0.21 to 1.34; $p = 0.18$).

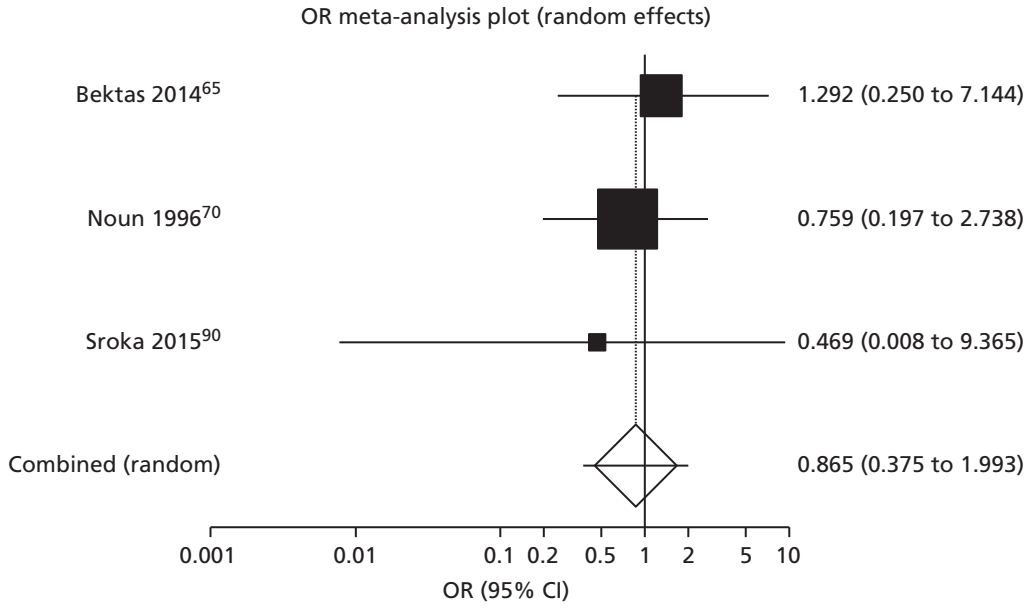

FIGURE 56 Haematoma development in upper GI tract surgery: fibrin sealant vs. standard care. Pooled OR 0.86 (95% CI 0.38 to 1.99; $p = 0.73$).

Seroma and haematoma combined

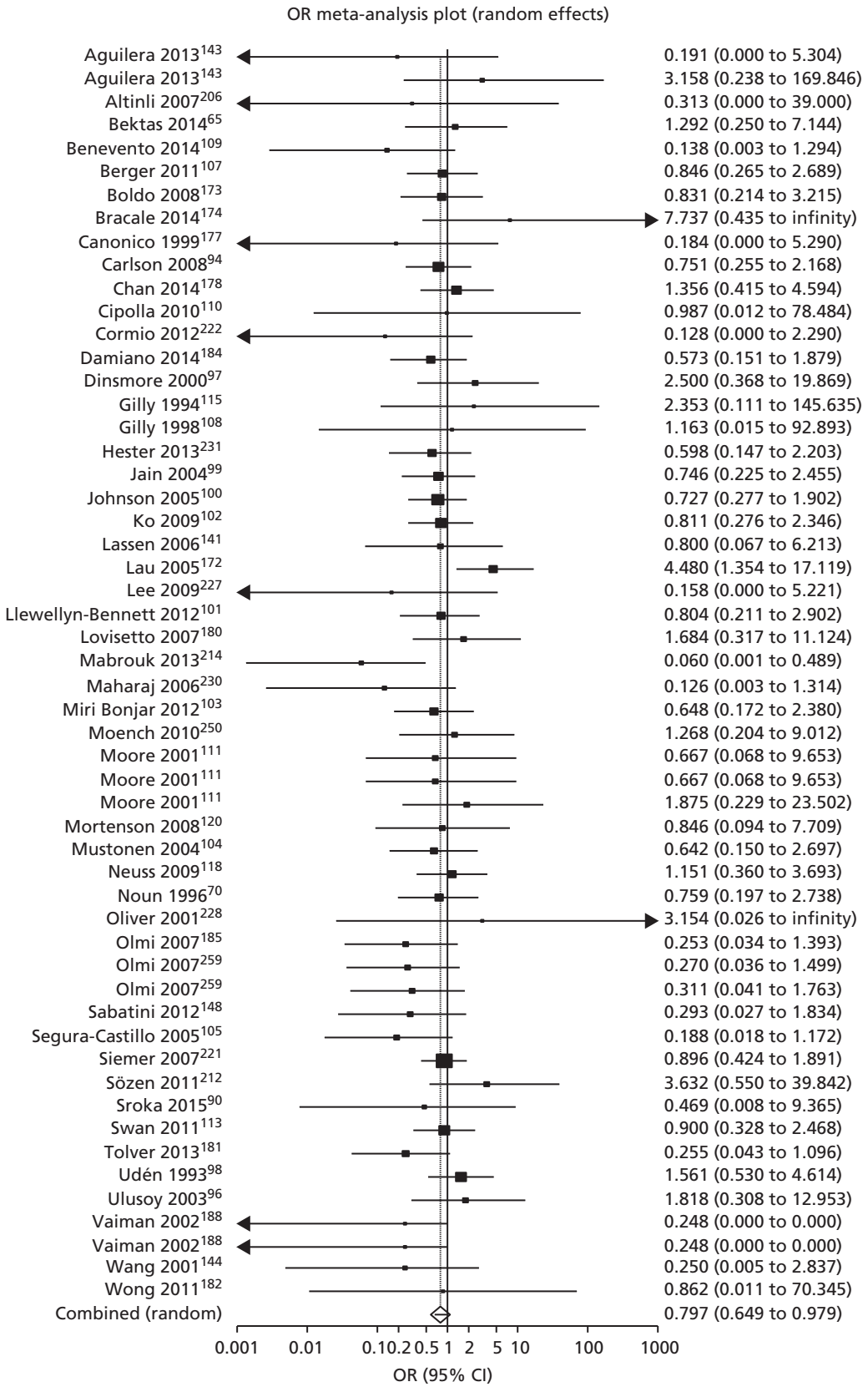

FIGURE 57 Seroma and haematoma development combined in all surgical specialties: fibrin sealant vs. standard care. Pooled OR 0.80 (95% CI 0.65 to 0.98; $p = 0.03$).

Secondary dichotomous outcomes

Haemorrhage (bleeding)

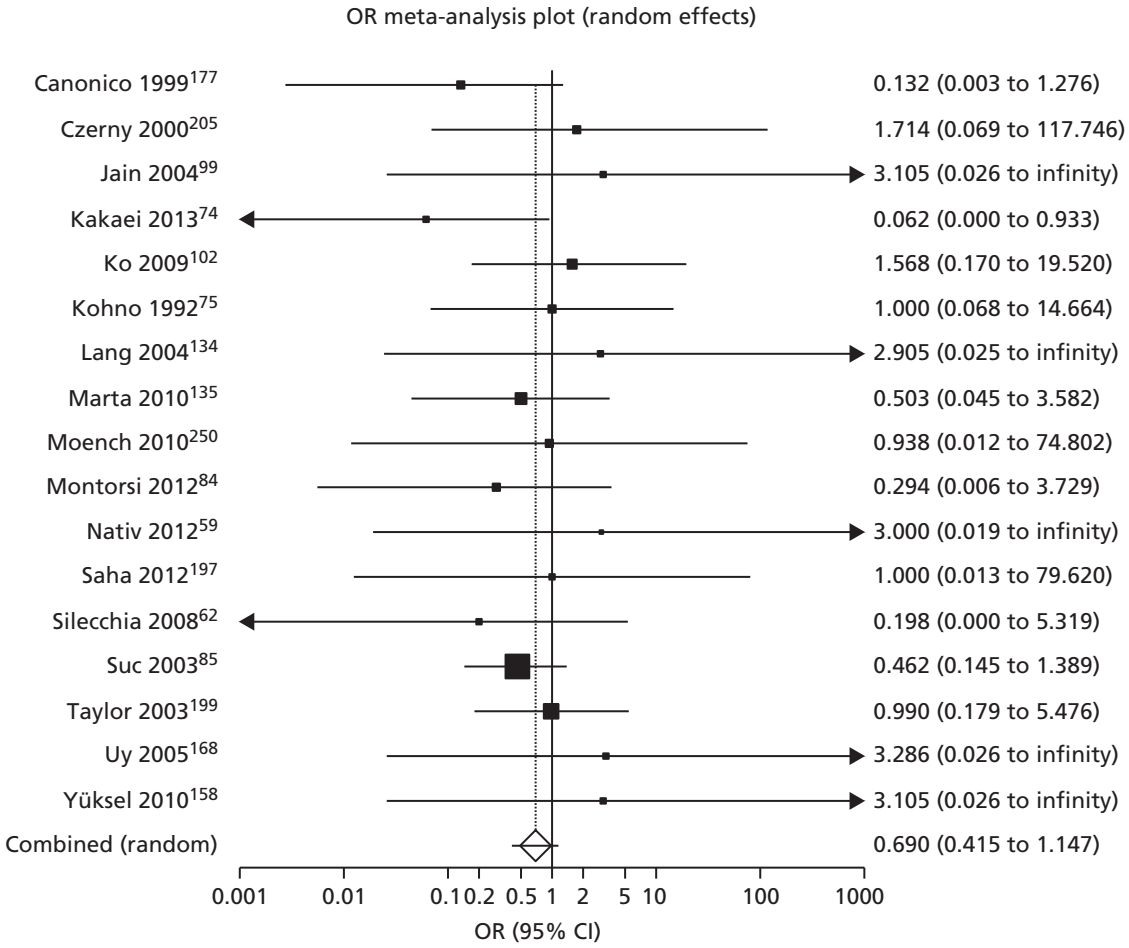

FIGURE 58 Haemorrhage (bleeding) in all surgical specialties: fibrin sealant vs. standard care. Pooled OR 0.69 (95% CI 0.41 to 1.15; $p = 0.15$).

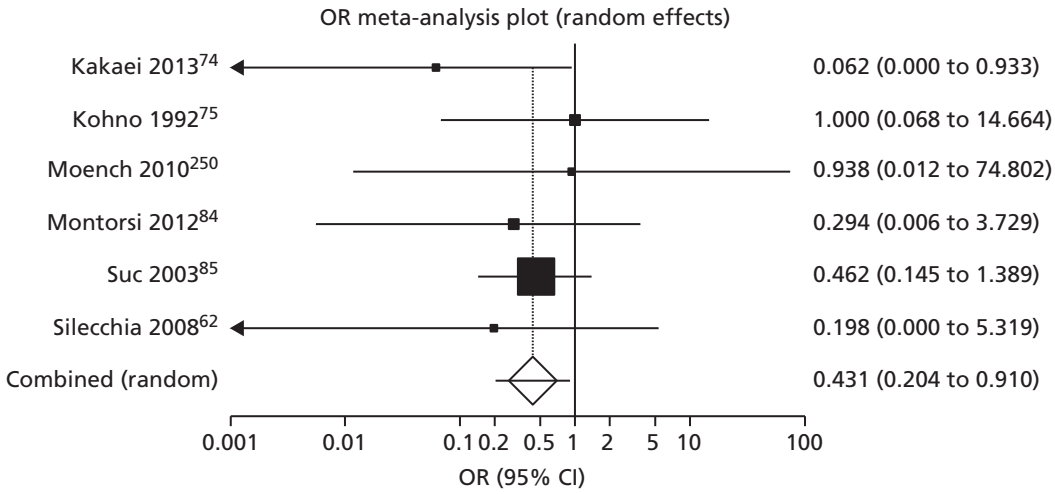

FIGURE 59 Haemorrhage (bleeding) in upper GI tract surgery: fibrin sealant vs. standard care. Pooled OR 0.43 (95% CI 0.20 to 0.91; $p = 0.03$).

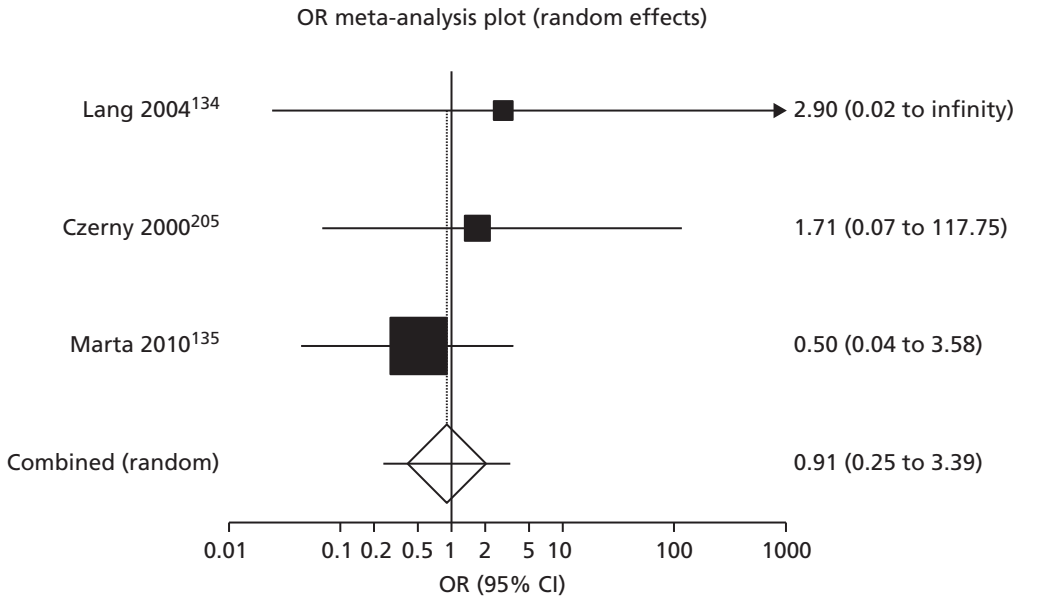

FIGURE 60 Haemorrhage (bleeding) in cardiothoracic surgery: fibrin sealant vs. standard care. Pooled OR 0.91 (95% CI 0.25 to 3.39; $p = 0.89$).

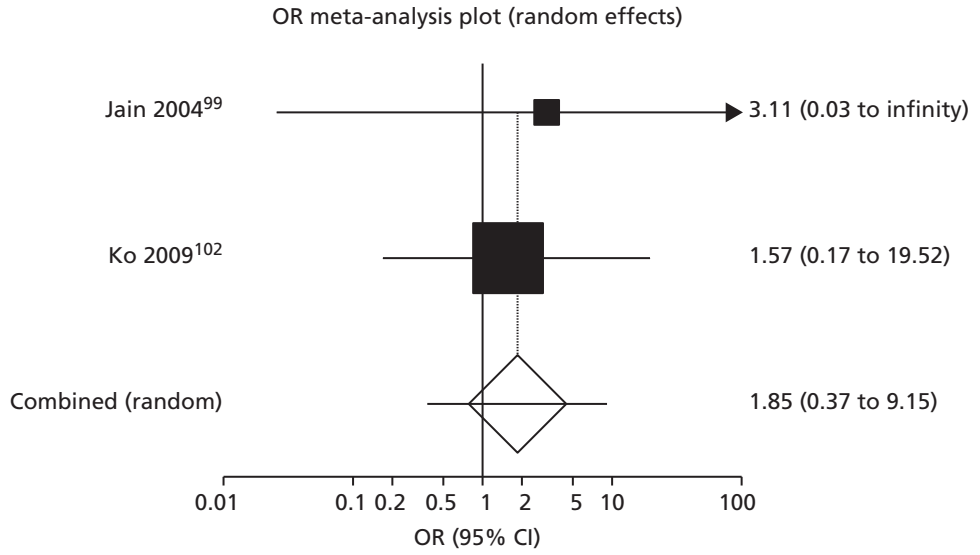

FIGURE 61 Haemorrhage (bleeding) in vascular surgery: fibrin sealant vs. standard care. Pooled OR 1.85 (95% CI 0.37 to 9.15; $p = 0.45$).

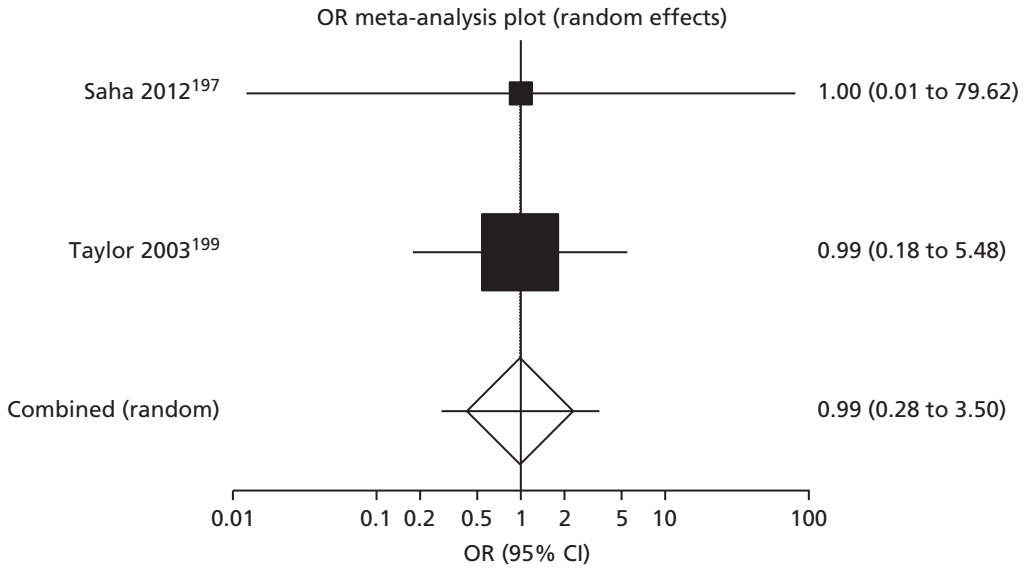

FIGURE 62 Haemorrhage (bleeding) in vascular surgery: fibrin sealant vs. standard care. Pooled OR 0.99 (95% CI 0.28 to 3.50; $p = 0.99$).

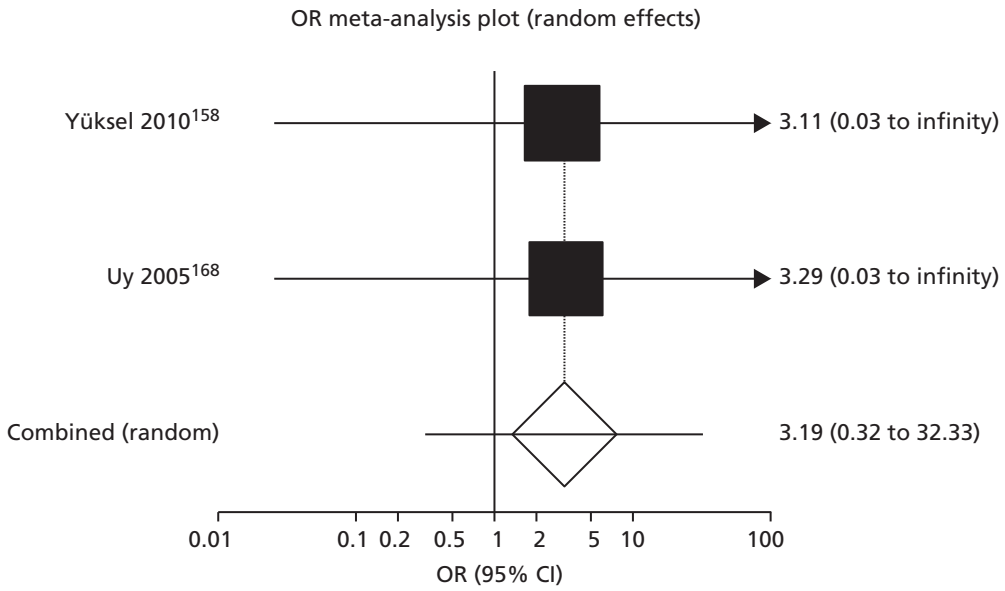

FIGURE 63 Haemorrhage (bleeding) in eye surgery: fibrin sealant vs. standard care. Pooled OR 3.19 (95% CI 0.32 to 32.33; $p = 0.33$).

Reoperation

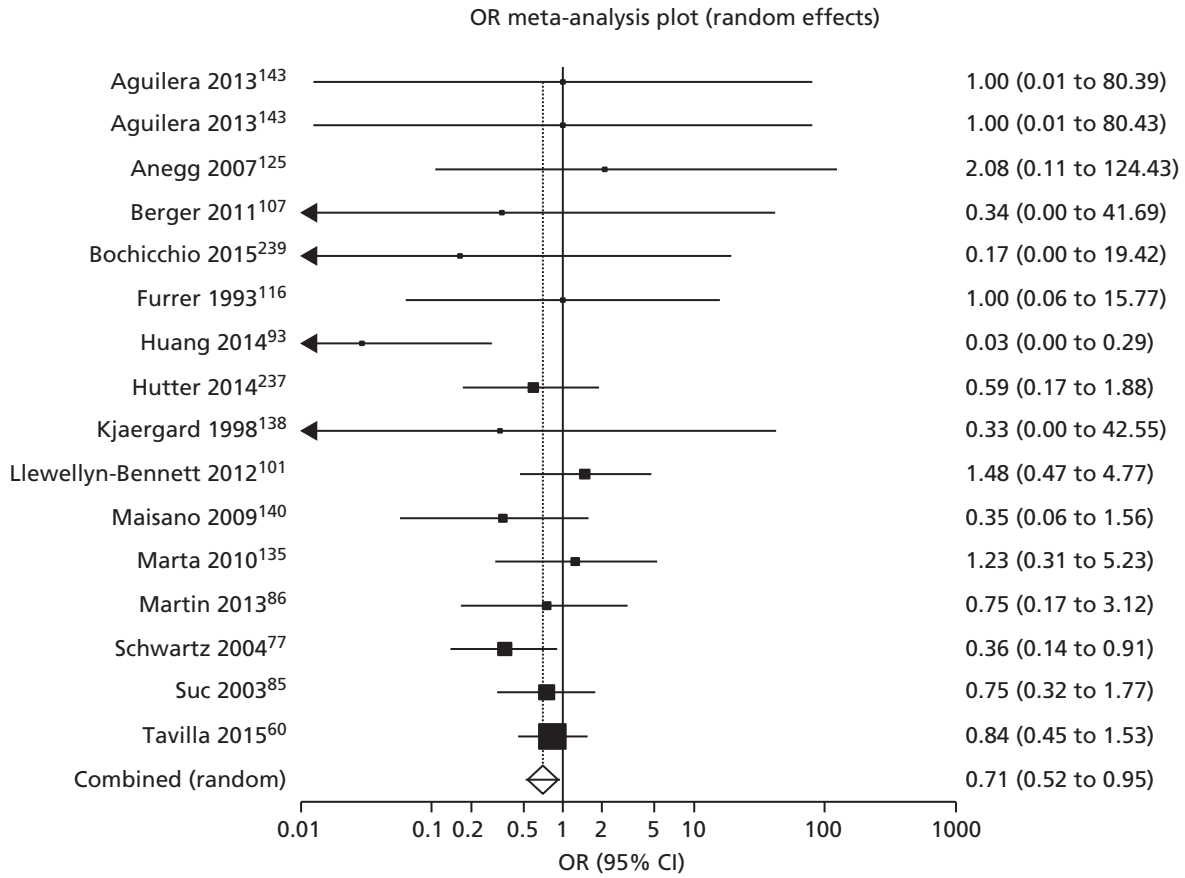

FIGURE 64 Reoperation in all surgical specialties: fibrin sealant vs. standard care. Pooled OR 0.71 (95% CI 0.52 to 0.95; $p = 0.02$).

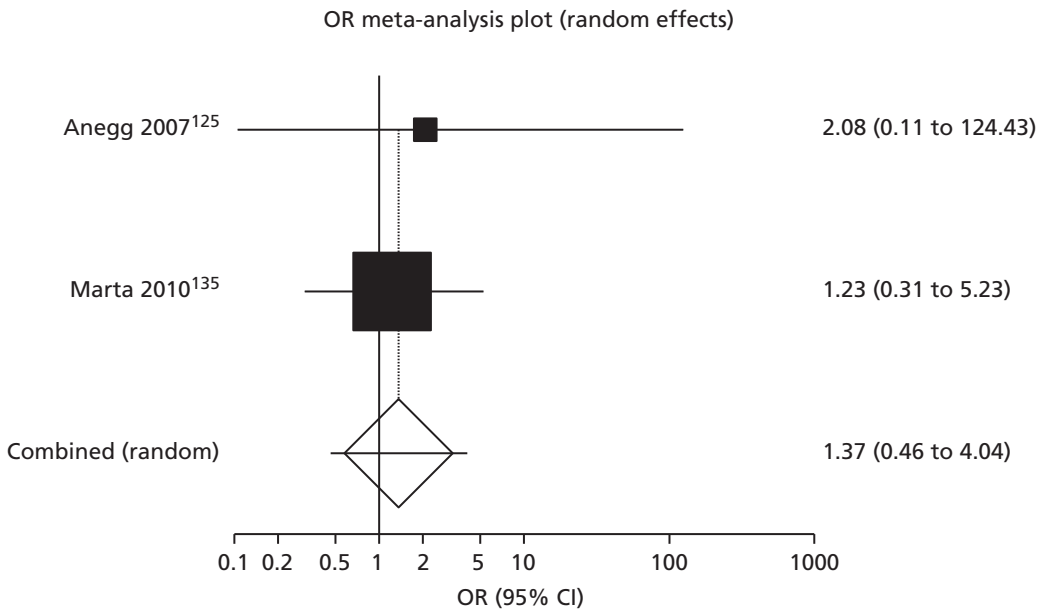

FIGURE 65 Reoperation in cardiothoracic lung surgery: fibrin sealant vs. standard care. Pooled OR 1.37 (95% CI 0.46 to 4.04; $p = 0.57$).

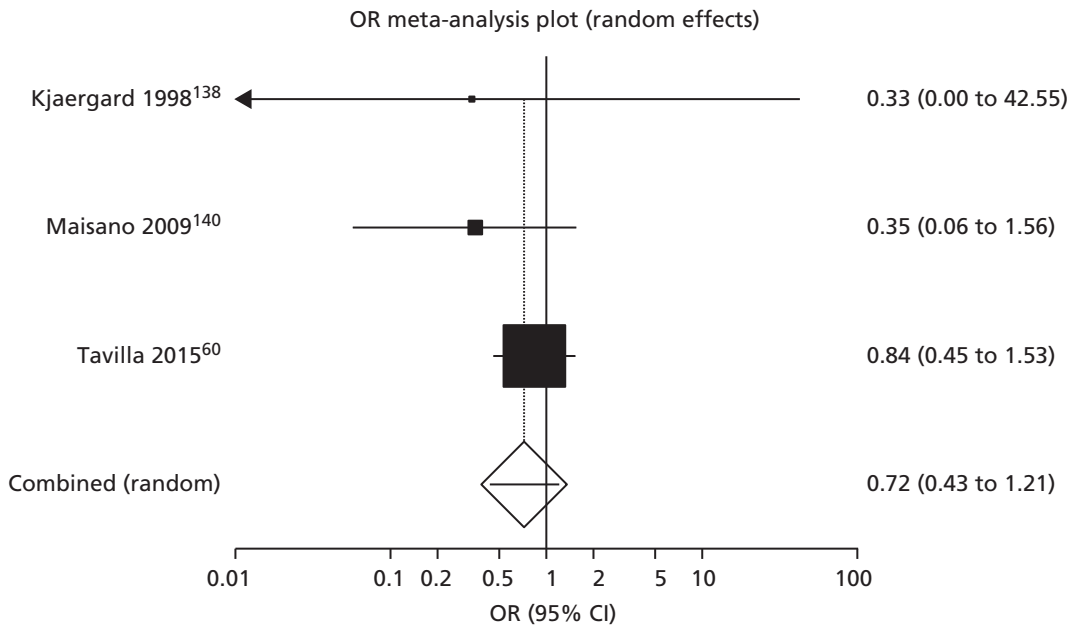

FIGURE 66 Reoperation in cardiothoracic heart surgery: fibrin sealant vs. standard care. Pooled OR 0.72 (95% CI 0.43 to 1.21; $p = 0.22$).

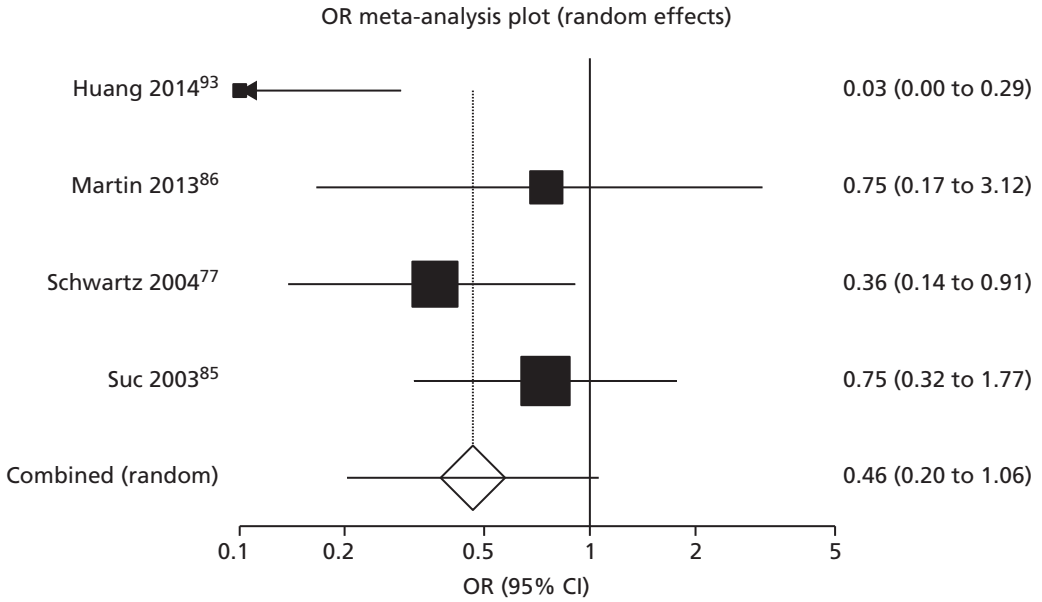

FIGURE 67 Reoperation in upper GI tract surgery: fibrin sealant vs. standard care. Pooled OR 0.46 (95% CI 0.20 to 1.06; $p = 0.07$).

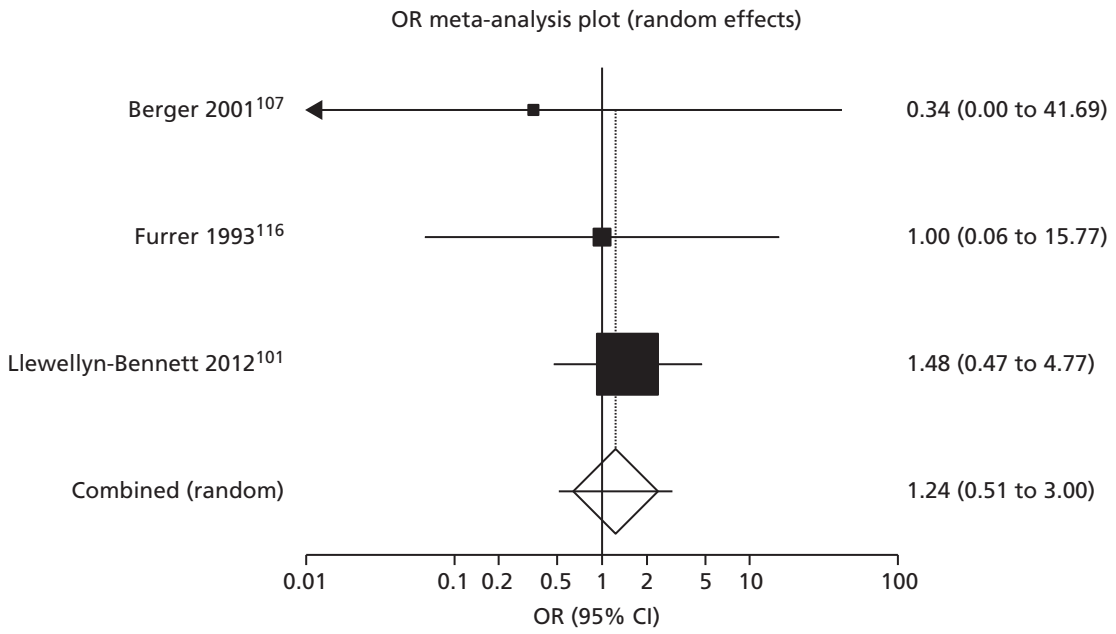

FIGURE 68 Reoperation in breast surgery: fibrin sealant vs. standard care. Pooled OR 1.24 (95% CI 0.51 to 3.00; $p = 0.64$).

Infections

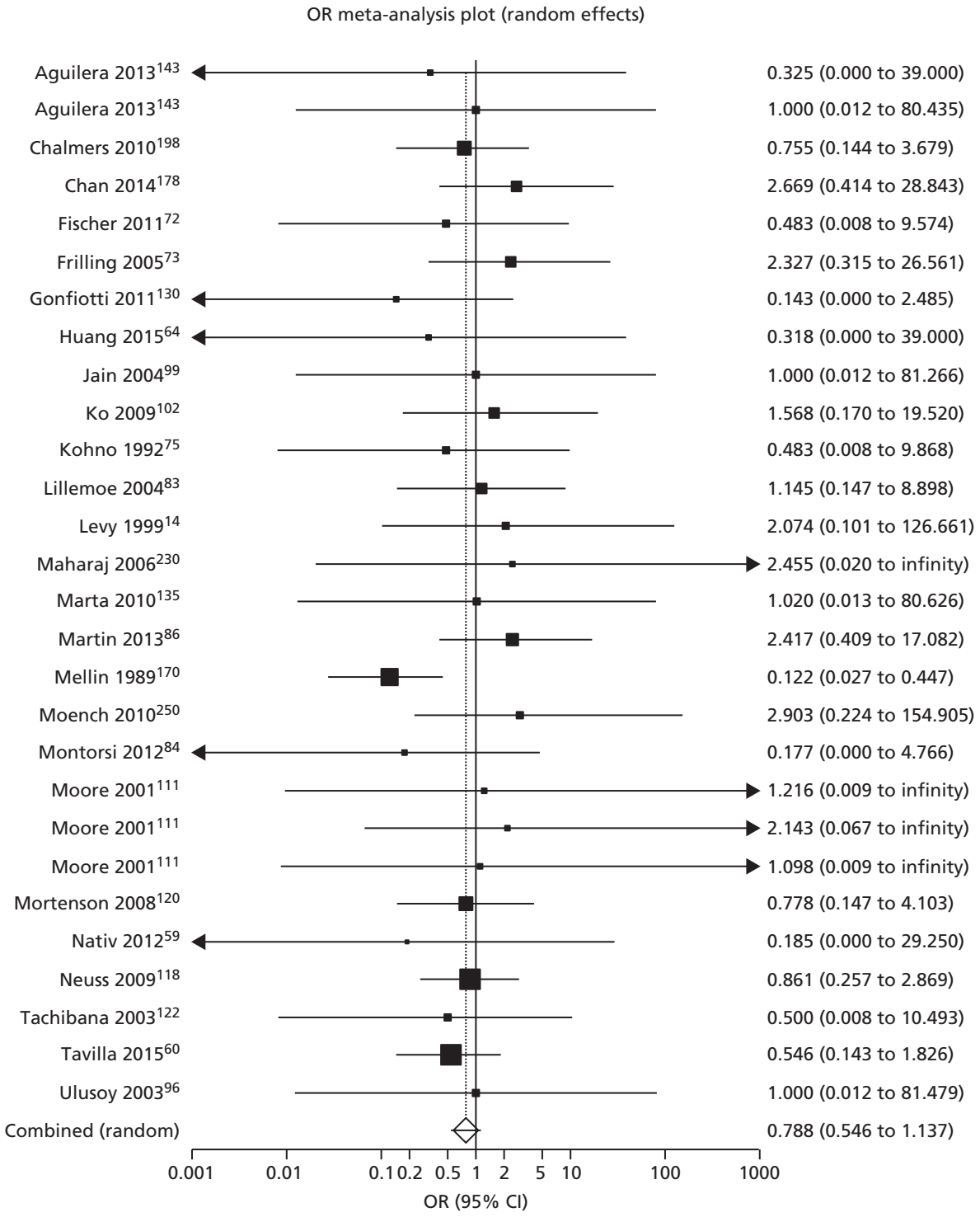

FIGURE 69 Infections in all surgeries: fibrin sealant vs. standard care. Pooled OR 0.79 (95% CI 0.55 to 1.14; $p = 0.20$).

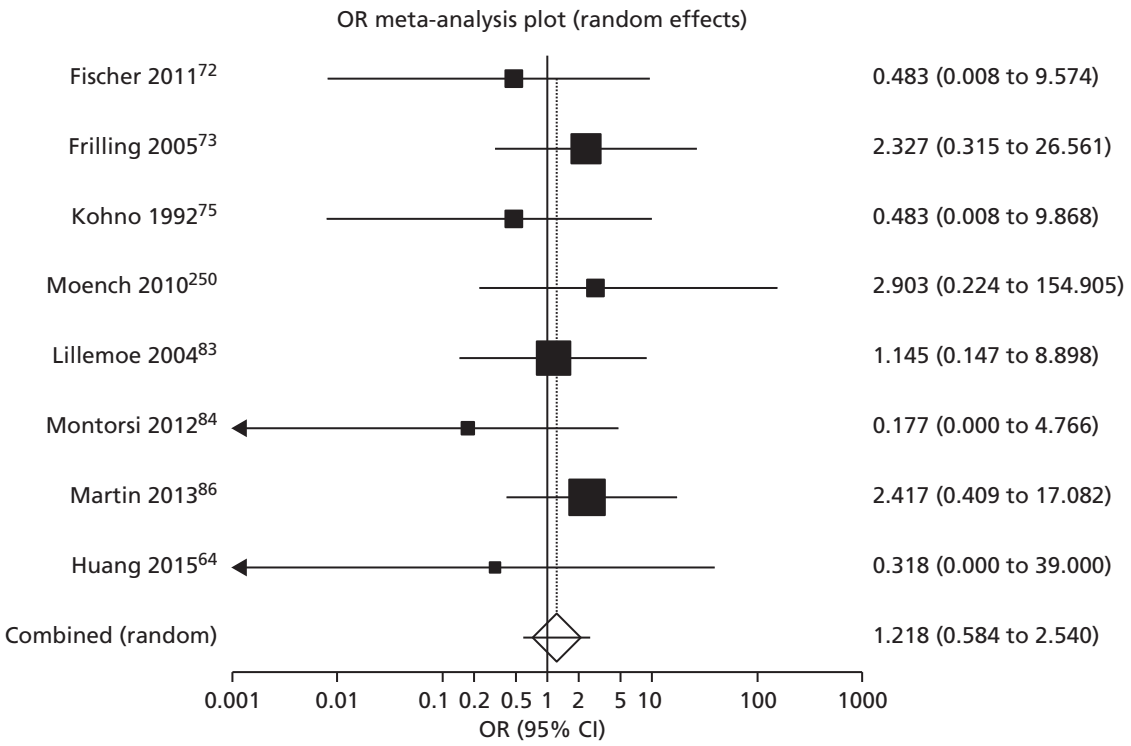

FIGURE 70 Infections in upper GI tract surgery: fibrin sealant vs. standard care. Pooled OR 1.22 (95% CI 0.58 to 2.54; $p = 0.60$).

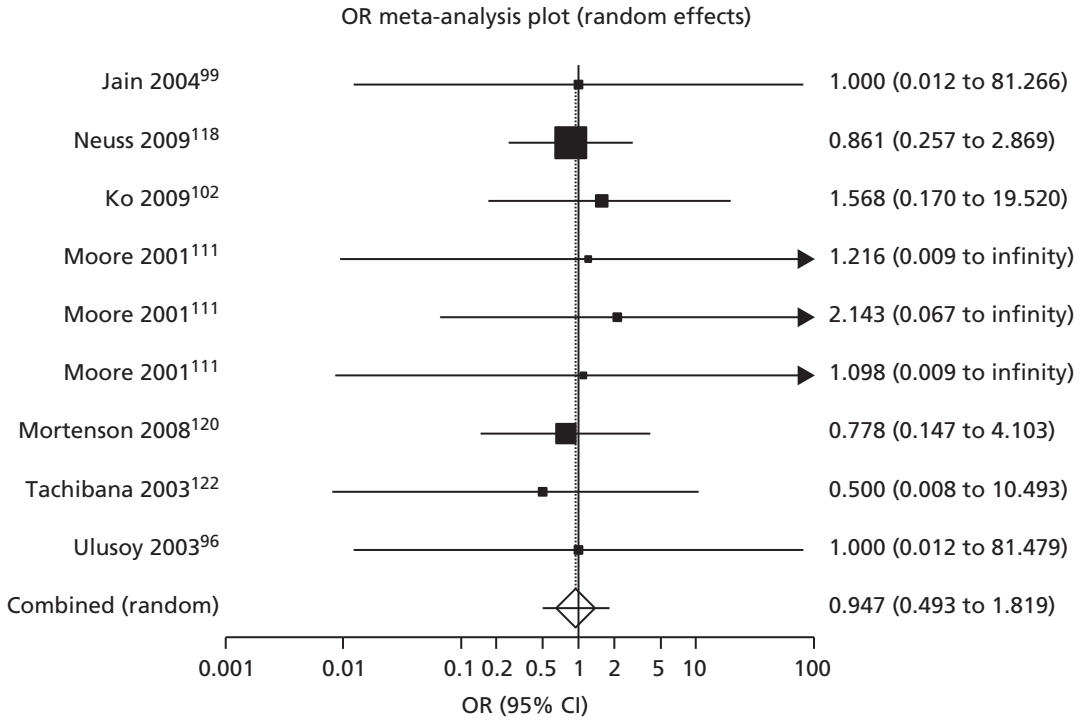

FIGURE 71 Infections in breast surgery: fibrin sealant vs. standard care. Pooled OR 0.95 (95% CI 0.49 to 1.82; $p = 0.87$).

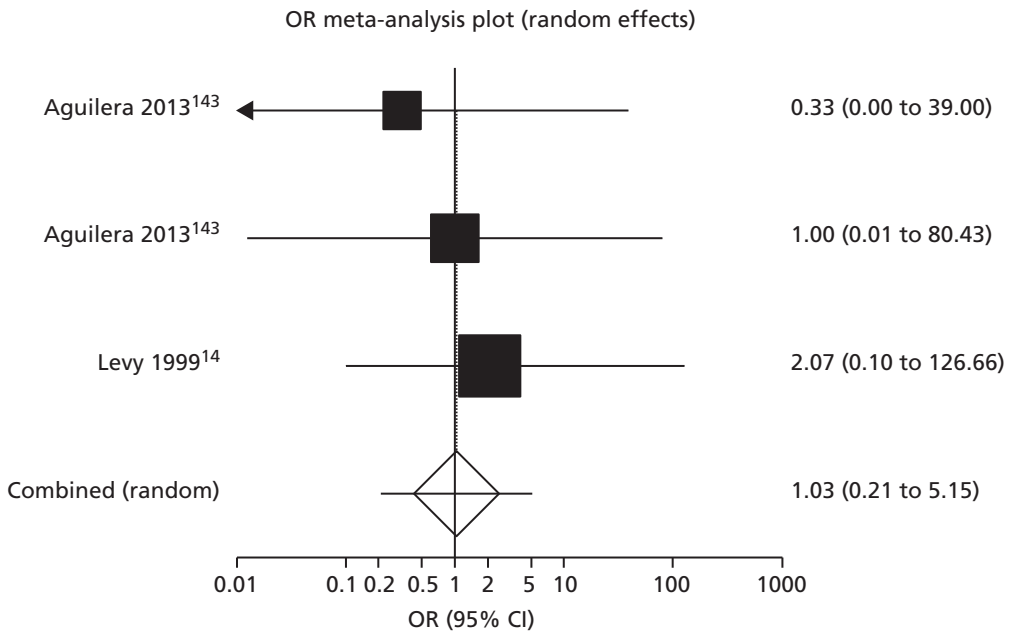

FIGURE 72 Infections in orthopaedic surgery: fibrin sealant vs. standard care. Pooled OR 1.034 (95% CI 0.21 to 5.15; $p = 0.97$).

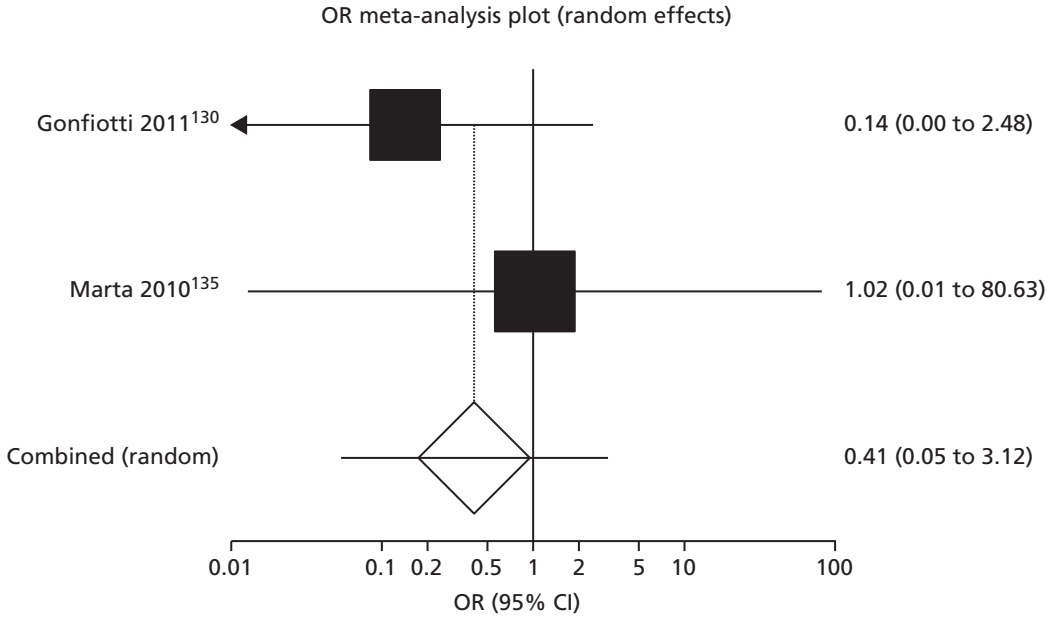

FIGURE 73 Infections in cardiothoracic lung surgery: fibrin sealant vs. standard care. Pooled OR 0.41 (95% CI 0.05 to 3.12; $p = 0.39$).

Secondary continuous outcomes

Duration of operation

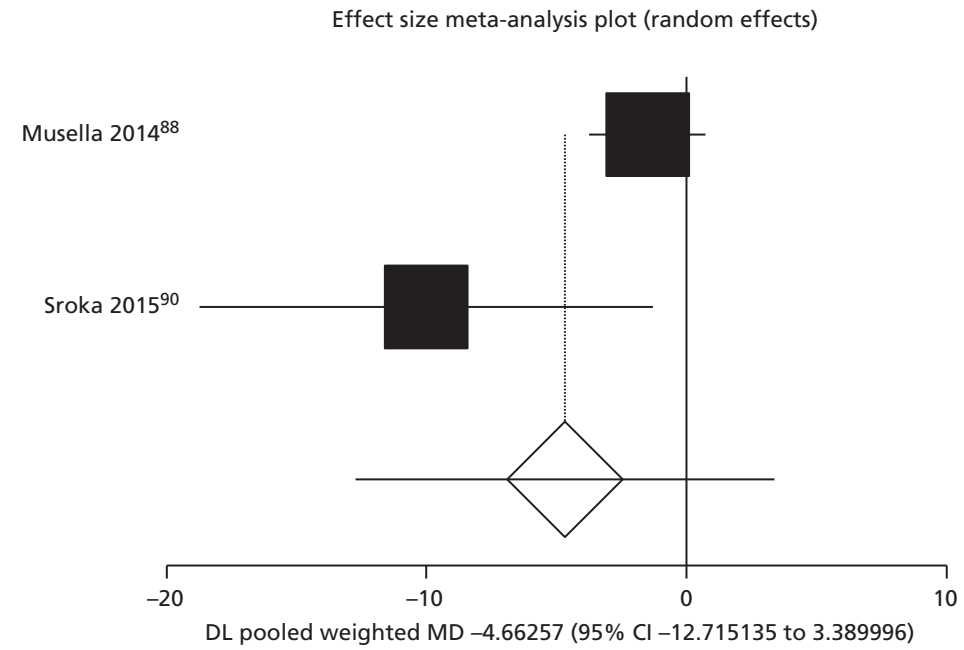

FIGURE 74 Mean duration of gastric surgery in minutes: fibrin sealant vs. no sealant. Pooled MD –4.66 (95% CI –12.71 to 3.39; $p = 0.26$). DL, DerSimonian and Laird.[55]

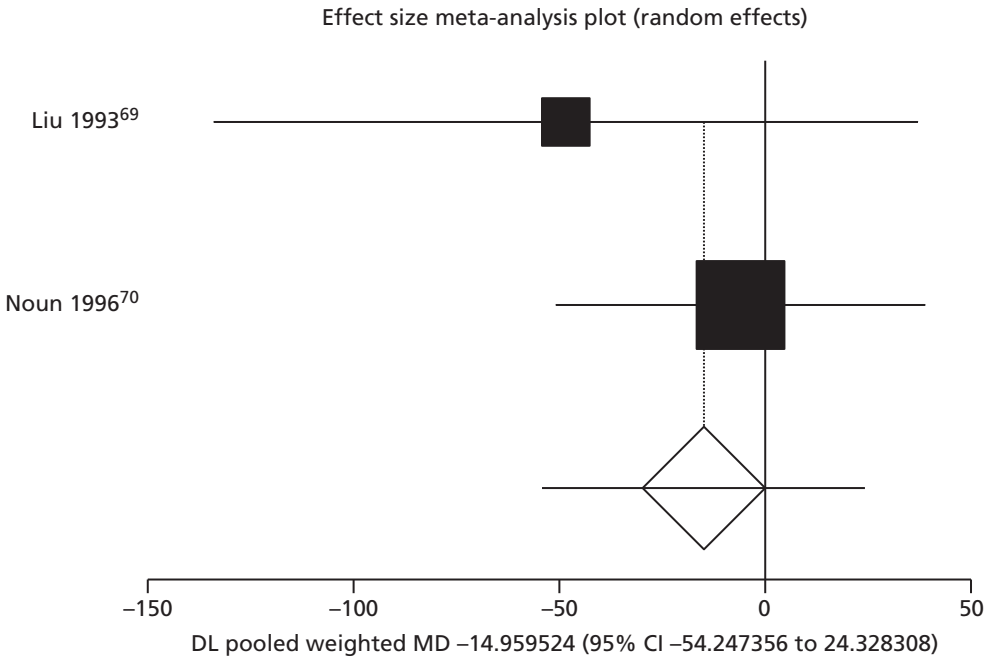

FIGURE 75 Mean duration of hepatic resection without liver mobilisation in minutes: fibrin sealant vs. standard care. Pooled MD –14.96 (95% CI –54.2 to 24.3; $p = 0.46$). DL, DerSimonian and Laird.[55]

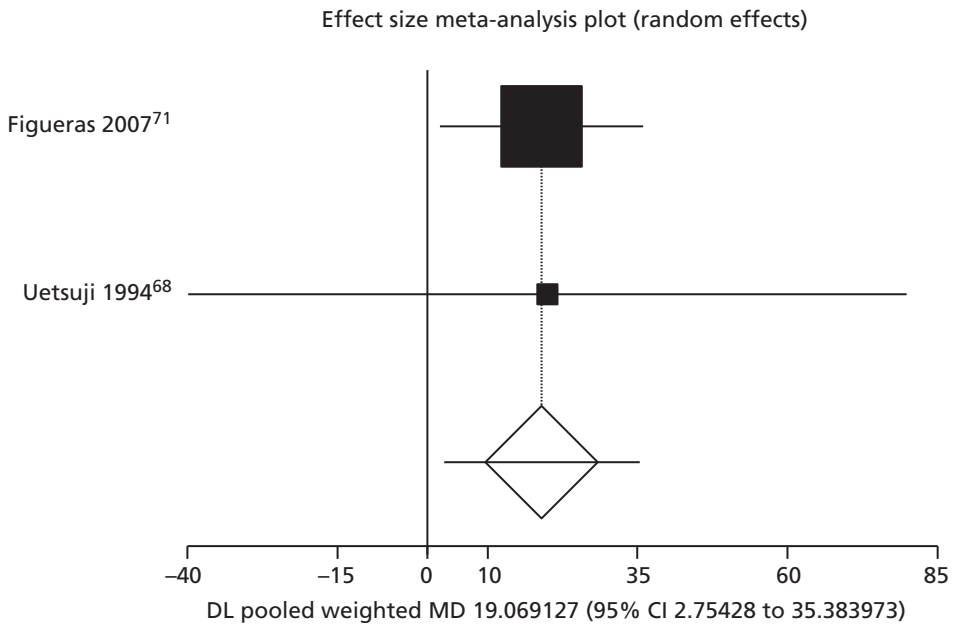

FIGURE 76 Mean duration of hepatic resection with liver mobilisation in minutes: fibrin sealant vs. standard care. Pooled MD 19.07 (95% CI 2.75 to 35.38; $p = 0.02$). DL, DerSimonian and Laird.[55]

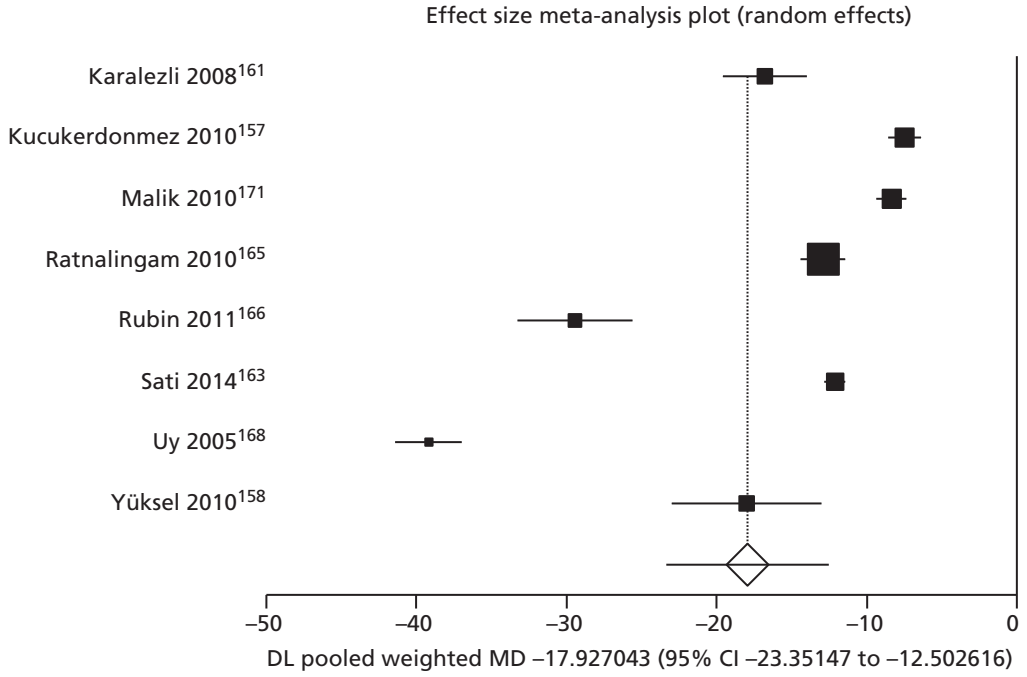

FIGURE 77 Mean duration of eye surgery in minutes: fibrin sealant vs. sutures. Pooled MD –17.93 (95% CI –23.35 to –12.50; $p < 0.01$). DL, DerSimonian and Laird.[55]

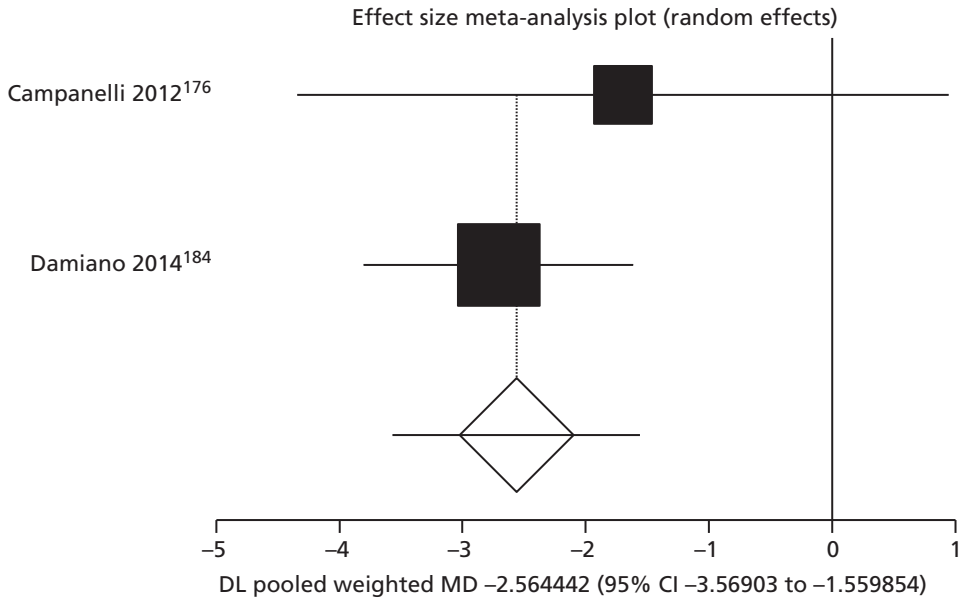

FIGURE 78 Mean duration of hernia surgery in minutes: fibrin sealant vs. sutures. Pooled MD –2.56 (95% CI –3.57 to –1.56; $p < 0.01$). DL, DerSimonian and Laird.[55]

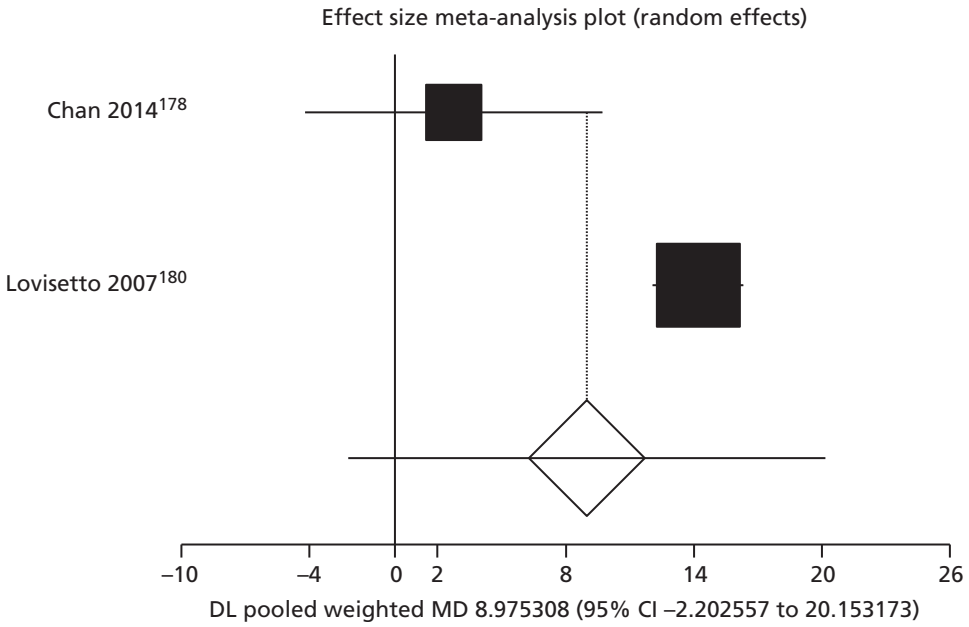

FIGURE 79 Mean duration of hernia surgery in minutes: fibrin sealant vs. staples. Pooled MD 8.98 (95% CI –2.20 to 20.15; $p = 0.12$). DL, DerSimonian and Laird.[55]

Length of hospital stay

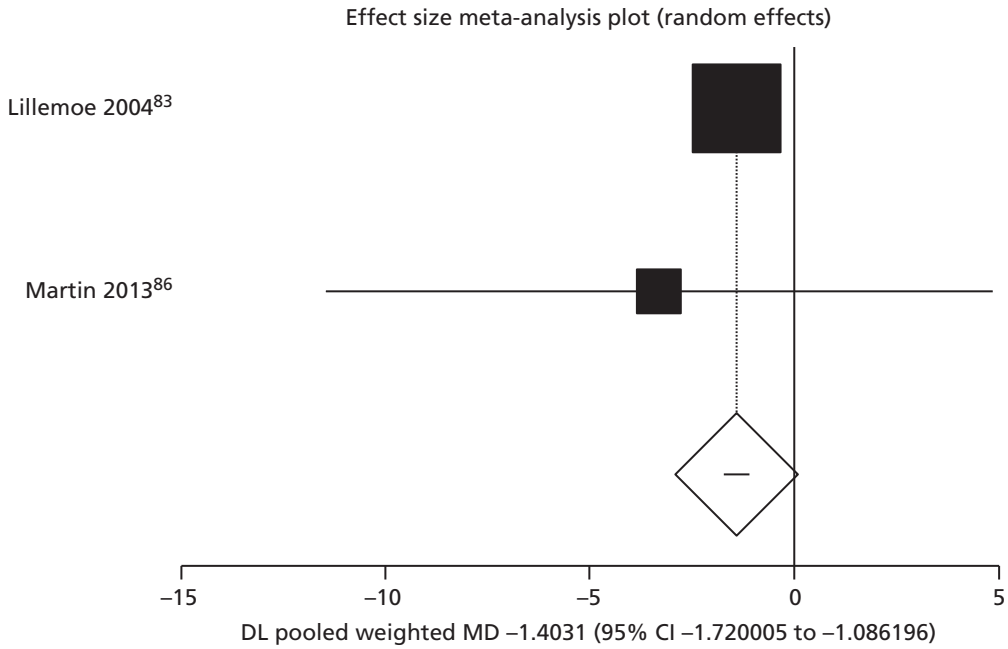

FIGURE 80 Length of hospital stay in days in pancreatic surgery: fibrin sealant vs. standard care. Pooled MD –1.40 (95% CI –1.72 to –1.09; $p < 0.01$). DL, DerSimonian and Laird.[55]

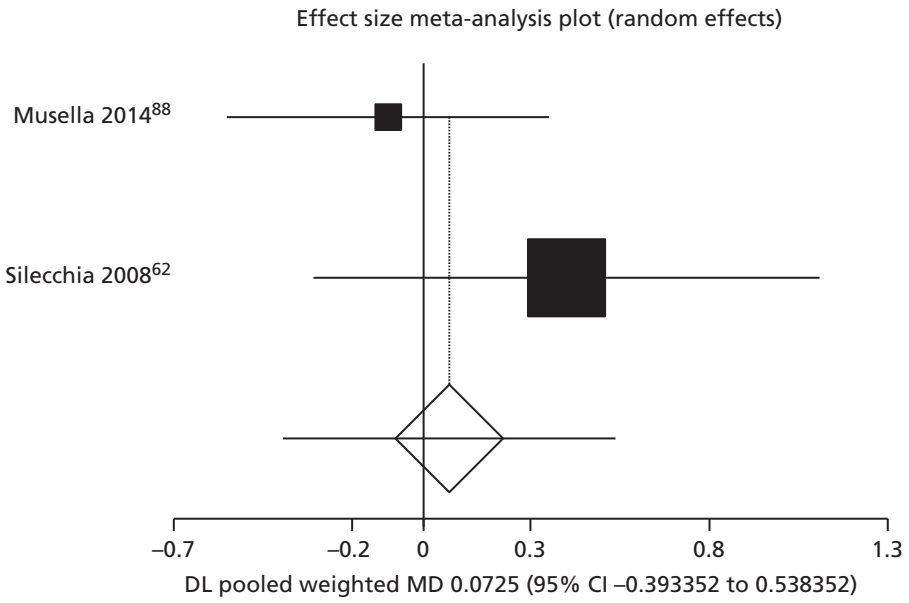

FIGURE 81 Length of hospital stay in days in gastric surgery: fibrin sealant vs. standard care. Pooled MD 0.07 (95% CI –0.39 to 0.54; $p = 0.76$). DL, DerSimonian and Laird.[55]

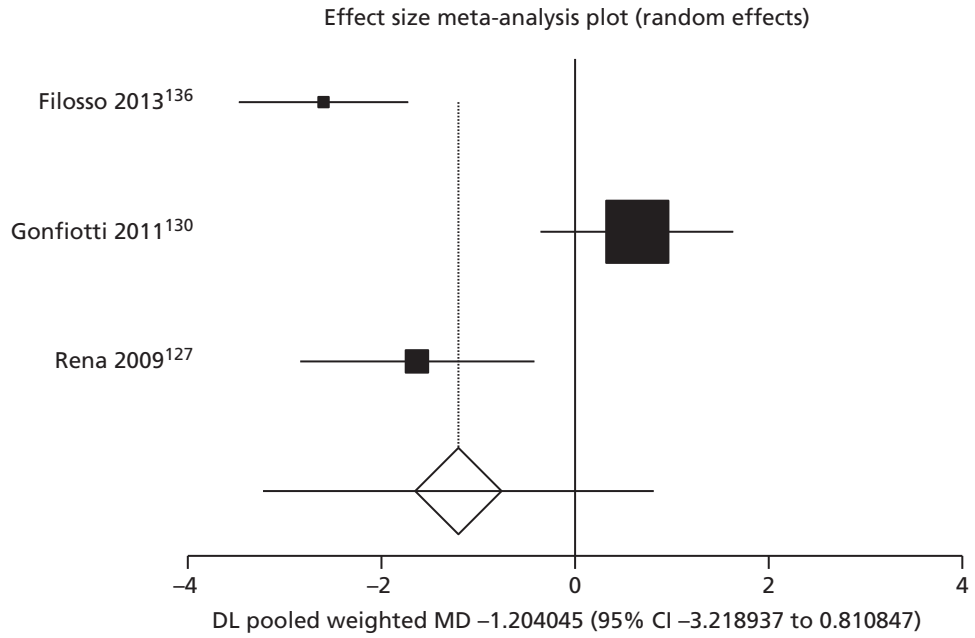

FIGURE 82 Length of hospital stay in days in cardiothoracic lung surgery: fibrin sealant vs. standard care. Pooled MD –1.20 (95% CI –3.22 to 0.81; $p = 0.24$). DL, DerSimonian and Laird.[55]

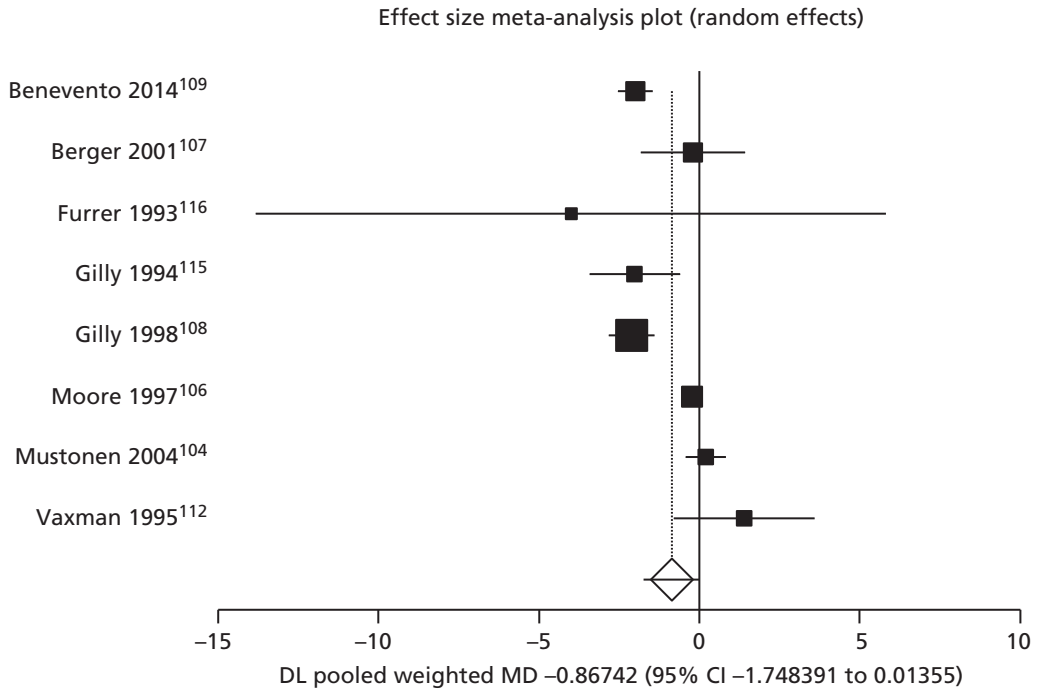

FIGURE 83 Length of hospital stay in days in breast surgery: fibrin sealant vs. standard care. Pooled MD –0.87 (95% CI –1.75 to 0.01; $p = 0.05$). DL, DerSimonian and Laird.[55]

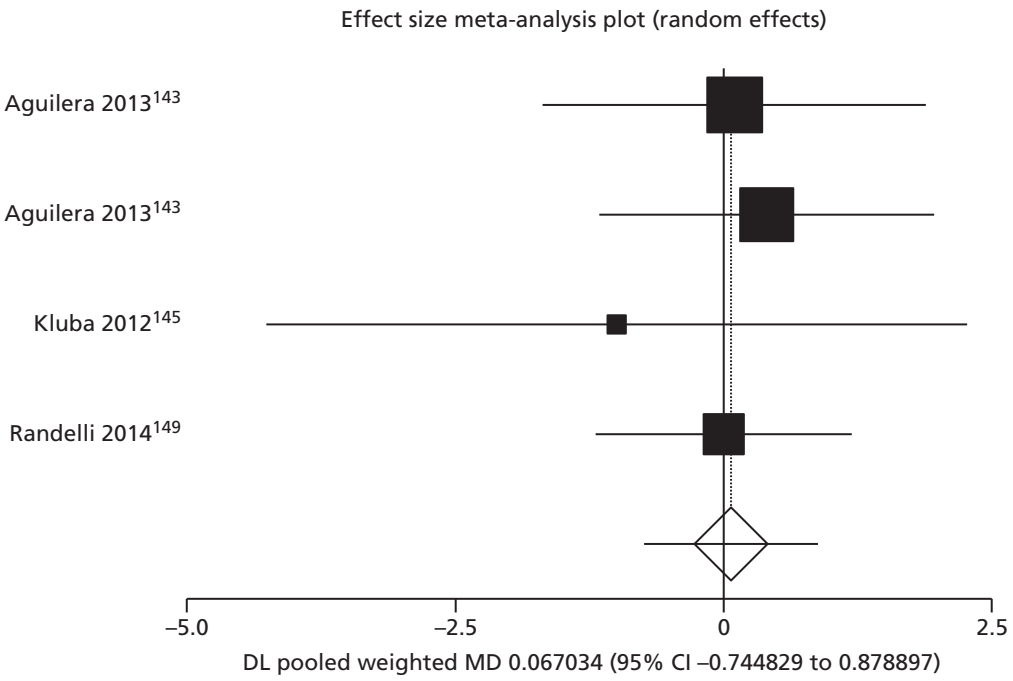

FIGURE 84 Length of hospital stay in days for knee surgery: fibrin sealant vs. standard care. Pooled MD 0.07 (95% CI –0.74 to 0.88; $p = 0.87$). DL, DerSimonian and Laird.[55]

Duration of drainage

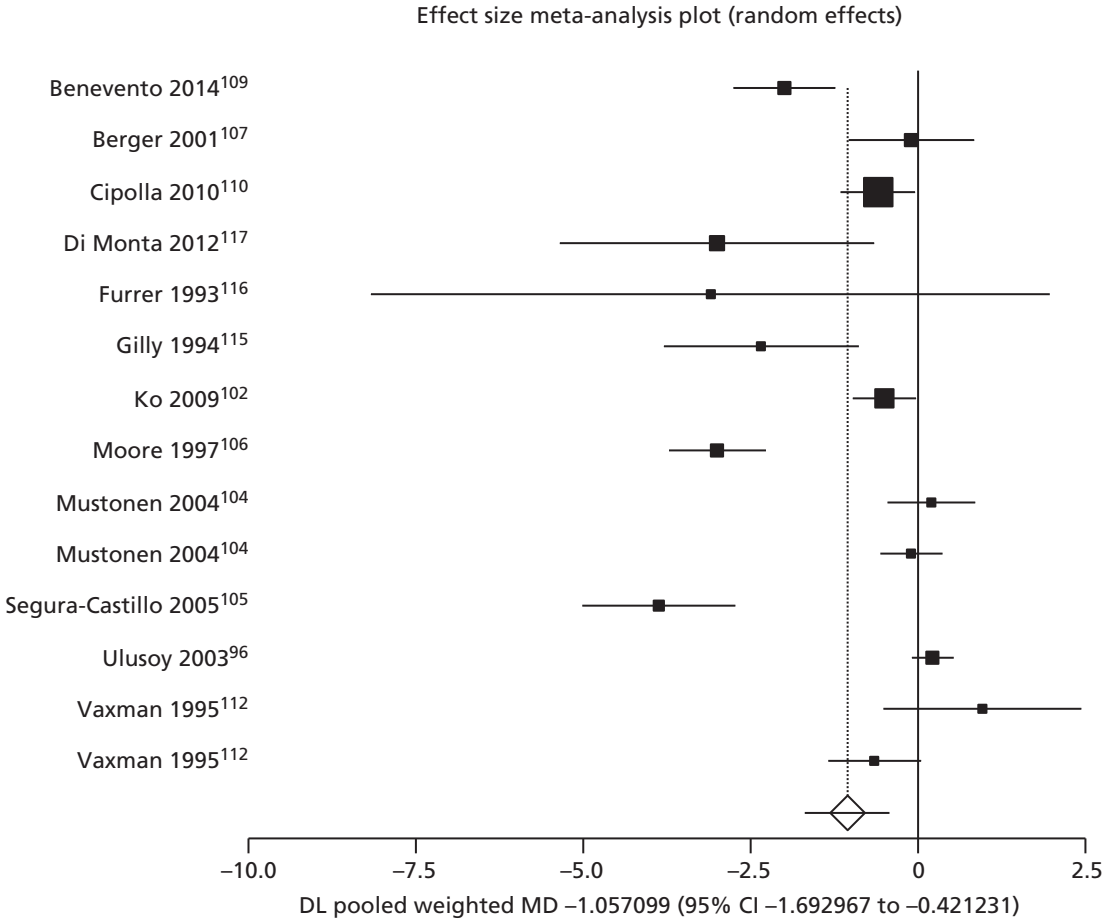

FIGURE 85 Duration of drainage in days in breast and axillary lymph nodes surgery: fibrin sealant vs. standard care. Pooled MD –1.06 (95% CI –1.69 to –0.42; $p = 0.00$). DL, DerSimonian and Laird.[55]

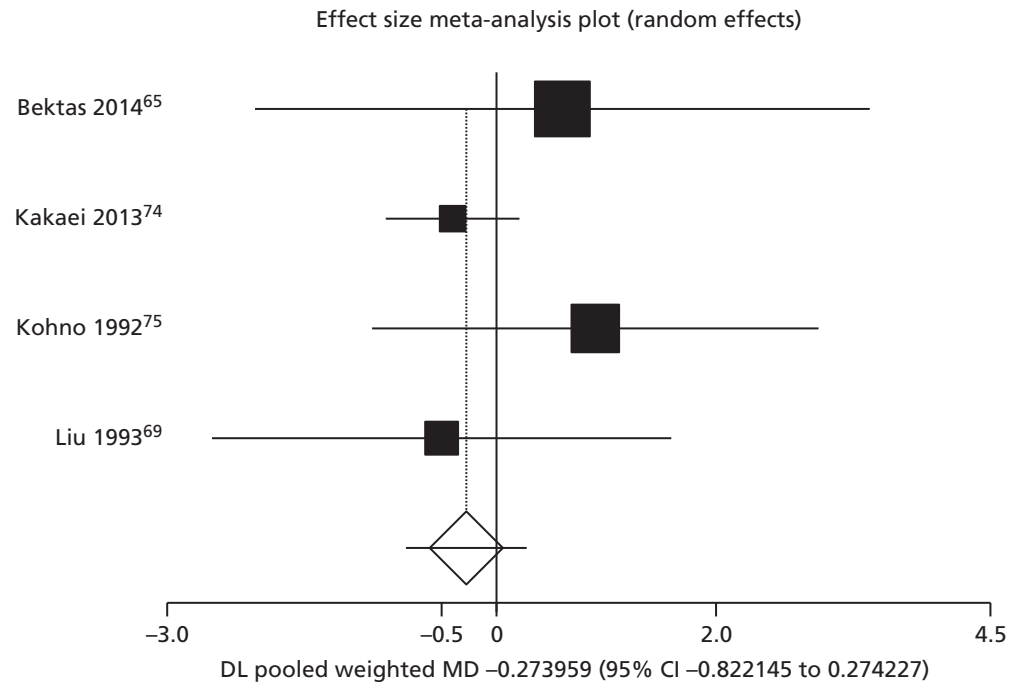

FIGURE 86 Duration of drainage in days for liver surgery: fibrin sealant vs. standard care. Pooled MD –0.27 (95% CI –0.82 to 0.27; $p = 0.33$). DL, DerSimonian and Laird.[55]

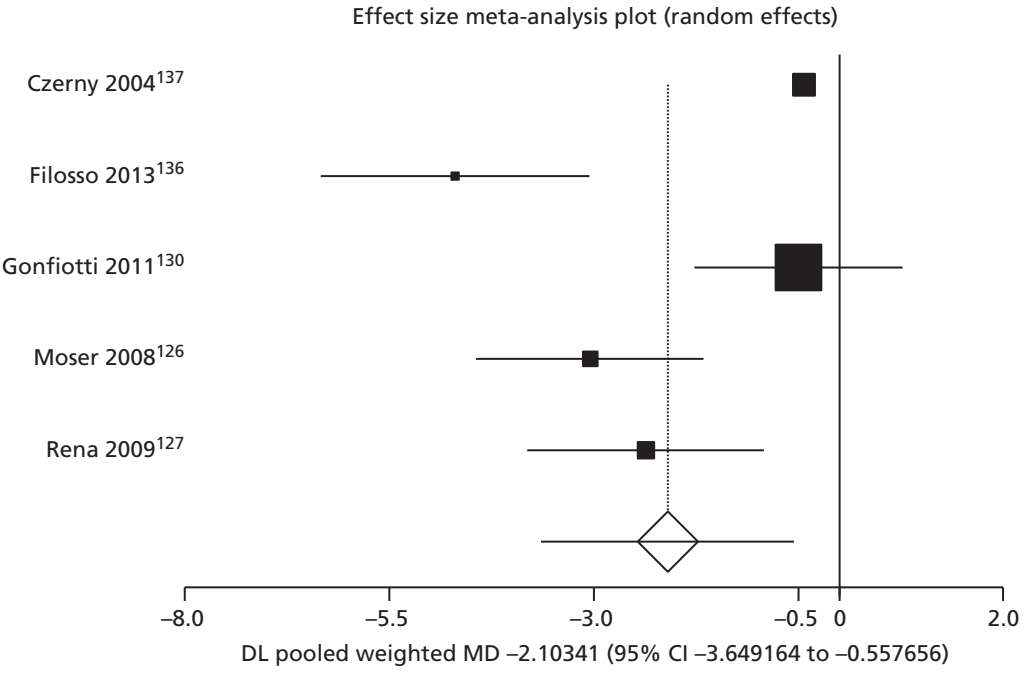

FIGURE 87 Duration of drainage in days for lung surgery: fibrin sealant vs. standard care. Pooled MD –2.10 (95% CI –3.65 to –0.56; $p = 0.01$). DL, DerSimonian and Laird.[55]

Appendix 9 Data tables for randomised controlled trials

TABLE 40 Seroma development data: all RCTs

Study (author, year)	Group (*n*/*N*)		Total population size across all studies
	Fibrin sealant	Standard care	
Altinli *et al.*, 2007[206]	0/16	1/16	–
Benevento *et al.*, 2014[109]	1/30	6/30	–
Berger *et al.*, 2001[107]	11/29	13/31	–
Boldo, 2008[173]	9/22	8/22	–
Bracale *et al.*, 2014[174]	3/50	0/50	–
Carlson *et al.*, 2008[94]	9/70	11/67	–
Chan *et al.*, 2014[178]	9/64	7/65	–
Damiano *et al.*, 2014[184]	5/216	10/252	–
Dinsmore *et al.*, 2000[97]	6/14	3/13	–
Gilly *et al.*, 1994[115]	2/19	1/21	–
Gilly *et al.*, 1998[108]	1/50	1/58	–
Hester *et al.*, 2013[231]	4/75	4/75	–
Jain *et al.*, 2004[99]	10/29	12/29	–
Johnson *et al.*, 2005[100]	14/38	20/44	–
Ko *et al.*, 2009[102]	10/47	12/48	–
Lau, 2005[172]	16/46	5/47	–
Llewellyn-Bennett *et al.*, 2012[101]	1/48	0/53	–
Mabrouk *et al.*, 2013[214]	1/30	11/30	–
Maharaj *et al.*, 2006[230]	1/28	5/22	–
Miri Bonjar *et al.*, 2012[103]	5/31	7/29	–
Moench *et al.*, 2014[76]	4/65	3/61	–
Moore *et al.*, 2001[111]	3/19	2/7	–
Moore *et al.*, 2001[111]	4/19	2/7	–
Moore *et al.*, 2001[111]	6/21	2/7	–
Mortenson *et al.*, 2008[120]	3/16	3/14	–
Mustonen *et al.*, 2004[104]	7/19	10/21	–
Neuss *et al.*, 2009[118]	12/29	10/29	–
Olmi *et al.*, 2007[259]	1.7/50	12/150	–
Olmi *et al.*, 2007[259]	1.7/50	15/150	–
Olmi *et al.*, 2007[259]	1.7/50	13/150	–
Segura-Castillo *et al.*, 2005[105]	2/22	8/23	–
Sözen *et al.*, 2011[212]	6/25	2/25	–

continued

TABLE 40 Seroma development data: all RCTs (*continued*)

Study (author, year)	Group (*n*/*N*)		Total population size across all studies
	Fibrin sealant	Standard care	
Swan *et al.*, 2011[113]	17/36	19/38	–
Tolver *et al.*, 2013[181]	3/50	5/50	–
Udén *et al.*, 1993[98]	23/36	17/32	–
Ulusoy *et al.*, 2003[96]	5/27	3/27	–
Wong *et al.*, 2011[182]	1/30	1/26	–
Total	228/1586	275/1886	3472

TABLE 41 Haematoma development data: all RCTs

Study (author, year)	Group (*n*/*N*)		Total population size across all studies
	Fibrin sealant	Standard care	
Aguilera *et al.*, 2013[143]	0/42	2/42	–
Aguilera *et al.*, 2013[143]	3/41	1/41	–
Bektas *et al.*, 2014[65]	5/35	4/35	–
Boldo, 2008[173]	0/22	2/22	–
Canonico *et al.*, 1999[177]	0/25	2/25	–
Cipolla *et al.*, 2010[110]	1/80	1/79	–
Cormio *et al.*, 2012[222]	0/49	3/47	–
Hester *et al.*, 2013[231]	1/75	4/75	–
Johnson *et al.*, 2005[100]	2/38	2/44	–
Lassen *et al.*, 2006[141]	2/22	4/36	–
Lee *et al.*, 2009[227]	0/9	2/9	–
Llewellyn-Bennett *et al.*, 2012[101]	5/48	8/53	–
Miri Bonjar *et al.*, 2012[103]	2/31	2/29	–
Moore *et al.*, 2001[111]	1/19	0/7	–
Moore *et al.*, 2001[111]	3/21	0/7	–
Neuss *et al.*, 2009[118]	1/29	2/29	–
Noun *et al.*, 1996[70]	6/35	9/42	–
Oliver *et al.*, 2001[228]	1/20	0/20	–
Olmi *et al.*, 2007[259]	0/50	3/150	–
Olmi *et al.*, 2007[259]	0/50	3/150	–
Olmi *et al.*, 2007[259]	0/50	4/150	–
Sabatini *et al.*, 2012[148]	2/35	6/35	–
Siemer *et al.*, 2007[221]	40/92	22/93	–
Sroka *et al.*, 2015[90]	1/49	2/47	–
Swan *et al.*, 2011[113]	1/36	1/38	–

TABLE 41 Haematoma development data: all RCTs (*continued*)

Study (author, year)	Group (*n*/*N*)		Total population size across all studies
	Fibrin sealant	Standard care	
Tolver *et al.*, 2013[181]	0/50	5/50	–
Vaiman *et al.*, 2002[188]	0/68	0.5/34	–
Vaiman *et al.*, 2002[188]	0/68	0.5/34	–
Wang *et al.*, 2001[144]	1/25	4/28	–
Total	58/1214	99/1451	2665

TABLE 42 Seroma and haematoma development combined data: all RCTs

Study (author, year)	Group (*n*/*N*)		Total population size across all studies
	Fibrin sealant	Standard care	
Aguilera *et al.*, 2013[143]	0/42	2/42	–
Aguilera *et al.*, 2013[143]	3/41	1/41	–
Altinli *et al.*, 2007[206]	0/16	1/16	–
Bektas *et al.*, 2014[65]	5/35	4/35	–
Benevento *et al.*, 2014[109]	1/30	6/30	–
Berger *et al.*, 2001[107]	11/29	13/31	–
Boldo, 2008[173]	9/22	10/22	–
Bracale *et al.*, 2014[174]	3/50	0/52	–
Canonico *et al.*, 1999[177]	0/25	2/25	–
Carlson *et al.*, 2008[94]	9/70	11/67	–
Chan *et al.*, 2014[178]	9/64	7/65	–
Cipolla *et al.*, 2010[110]	1/80	1/79	–
Cormio *et al.*, 2012[222]	0/49	3/47	–
Damiano *et al.*, 2014[184]	5/216	10/252	–
Dinsmore *et al.*, 2000[97]	6/14	3/13	–
Gilly *et al.*, 1994[115]	2/19	1/21	–
Gilly *et al.*, 1998[108]	1/50	1/58	–
Hester *et al.*, 2013[231]	5/75	8/75	–
Jain *et al.*, 2004[99]	10/29	12/29	–
Johnson *et al.*, 2005[100]	16/38	22/44	–
Ko *et al.*, 2009[102]	10/47	12/48	–
Lassen *et al.*, 2006[141]	2/22	4/36	–
Lau, 2005[172]	16/46	5/47	–
Lee *et al.*, 2009[227]	0/9	2/9	–
Llewellyn-Bennett *et al.*, 2012[101]	6/48	8/53	–
Lovisetto *et al.*, 2007[180]	5/99	3/98	–

continued

TABLE 42 Seroma and haematoma development combined data: all RCTs (*continued*)

Study (author, year)	Group (*n*/*N*)		Total population size across all studies
	Fibrin sealant	Standard care	
Mabrouk *et al.*, 2013[214]	1/30	11/30	–
Maharaj *et al.*, 2006[230]	1/28	5/22	–
Miri Bonjar *et al.*, 2012[103]	7/31	9/29	–
Moench *et al.*, 2010[250]	4/65	3/61	–
Moore *et al.*, 2001[111]	4/19	2/7	–
Moore *et al.*, 2001[111]	4/19	2/7	–
Moore *et al.*, 2001[111]	9/21	2/7	–
Mortenson *et al.*, 2008[120]	3/16	3/14	–
Mustonen *et al.*, 2004[104]	7/19	10/21	–
Neuss *et al.*, 2009[118]	13/29	12/29	–
Noun *et al.*, 1996[70]	6/35	9/42	–
Oliver *et al.*, 2001[228]	1/20	0/20	–
Olmi *et al.*, 2007[259]	1.67/50	15/150	–
Olmi *et al.*, 2007[259]	1.67/50	18/150	–
Olmi *et al.*, 2007[259]	1.67/50	17/150	–
Sabatini *et al.*, 2012[148]	2/35	6/35	–
Segura-Castillo *et al.*, 2005[105]	2/22	8/23	–
Siemer *et al.*, 2007[221]	20/92	22/93	–
Sözen *et al.*, 2011[212]	6/25	2/25	–
Sroka *et al.*, 2015[90]	1/49	2/47	–
Swan *et al.*, 2011[113]	18/36	20/38	–
Tolver *et al.*, 2013[181]	3/50	10/50	–
Udén *et al.*, 1993[98]	23/36	17/32	–
Ulusoy *et al.*, 2003[96]	5/27	3/27	–
Vaiman *et al.*, 2002[188]	0/68	0.5/34	–
Vaiman *et al.*, 2002[188]	0/68	0.5/34	–
Wang *et al.*, 2001[144]	1/25	4/28	–
Wong *et al.*, 2011[182]	1/30	1/26	–
Total	282/2310	366/2566	4876

TABLE 43 Haemorrhage (bleeding) data: all RCTs

Study (author, year)	Group (*n*/*N*)		Total population size across all studies
	Fibrin sealant	Standard care	
Canonico *et al.*, 1999[177]	1/25	6/25	–
Czerny *et al.*, 2000[205]	2/9	1/7	–
Jain *et al.*, 2004[99]	1/29	0/29	–
Kakaei *et al.*, 2013[74]	0/15	5/15	–
Ko *et al.*, 2009[102]	3/47	2/48	–
Kohno *et al.*, 1992[75]	2/31	2/31	–
Lang *et al.*, 2004[134]	1/95	0/91	–
Marta *et al.*, 2010[135]	2/148	4/151	–
Moench *et al.*, 2010[250]	1/65	1/61	–
Montorsi *et al.*, 2012[84]	1/145	3/130	–
Nativ *et al.*, 2012[59]	1/4	0/3	–
Saha *et al.*, 2012[197]	1/70	1/70	–
Silecchia *et al.*, 2008[62]	0/160	2/160	–
Suc *et al.*, 2003[85]	7/102	11/80	–
Taylor *et al.*, 2003[199]	4/100	4/99	–
Uy *et al.*, 2005[168]	1/11	0/11	–
Yüksel *et al.*, 2010[158]	1/29	0/29	–
Total	29/1085	42/1040	2125

TABLE 44 Reoperation data: all RCTs

Study (author, year)	Group (*n*/*N*)		Total population size across all studies
	Fibrin sealant	Standard care	
Aguilera, 2013[143]	1/42	1/42	–
Aguilera, 2013[143]	1/41	1/41	–
Anegg *et al.*, 2007[125]	2/75	1/77	–
Berger *et al.*, 2001[107]	0/29	1/31	–
Bochicchio *et al.*, 2015[239]	0/480	1/239	–
Furrer *et al.*, 1993[116]	2/15	2/15	–
Hutter *et al.*, 2014[237]	6/113	10/116	–
Huang and Qian, 2014[93]	0/48	12/47	–
Kjaergard and Trumbull, 1998[138]	0/11	1/12	–
Llewellyn-Bennett *et al.*, 2012[101]	10/48	8/53	–
Maisano *et al.*, 2009[140]	3/59	8/60	–
Marta *et al.*, 2010[135]	6/148	5/151	–
Martin and Au, 2013[86]	5/25	8/32	–
Schwartz *et al.*, 2004[77]	10/58	23/63	–
Suc *et al.*, 2003[85]	15/102	15/80	–
Tavilla *et al.*, 2015[60]	23/722	27/714	–
Total	84/2016	124/1773	3789

TABLE 45 Infections data: all RCTs

Study (author, year)	Group (*n*/*N*)		Total population size across all studies
	Fibrin sealant	Standard care	
Aguilera *et al.*, 2013[143]	0/42	1/42	–
Aguilera *et al.*, 2013[143]	1/41	1/41	–
Chalmers *et al.*, 2010[198]	4/75	5/72	–
Chan *et al.*, 2014[178]	5/64	2/65	–
Fischer *et al.*, 2011[72]	1/60	2/59	–
Frilling *et al.*, 2005[73]	4/53	2/59	–
Gonfiotti *et al.*, 2011[130]	0/91	3/94	–
Huang *et al.*, 2015[64]	0/21	1/21	–
Jain *et al.*, 2004[99]	1/29	1/29	–
Ko *et al.*, 2009[102]	3/47	2/48	–
Kohno *et al.*, 1992[75]	1/31	2/31	–
Levy *et al.*, 1999[14]	2/29	1/29	–
Lillemoe *et al.*, 2004[83]	3/58	3/66	–
Maharaj *et al.*, 2006[230]	1/28	0/22	–
Marta *et al.*, 2010[135]	1/148	1/151	–
Martin and Au 2013[86]	5/25	3/32	–
Mellin and Kondler 1989[170]	4/51	16/39	–
Moench *et al.*, 2010[250]	3/65	1/61	–
Montorsi *et al.*, 2012[84]	0/145	2/130	–
Moore *et al.*, 2001[111]	1/19	0/7	–
Moore *et al.*, 2001[111]	2/19	0/7	–
Moore *et al.*, 2001[111]	1/21	0/7	–
Mortenson *et al.*, 2008[120]	7/16	7/14	–
Nativ *et al.*, 2012[59]	0/4	1/3	–
Neuss *et al.*, 2009[118]	10/29	11/29	–
Tachibana *et al.*, 2003[122]	1/21	2/22	–
Tavilla *et al.*, 2015[60]	5/722	9/714	–
Ulusoy *et al.*, 2003[96]	1/27	1/27	–
Total	67/1981	80/1921	3902

TABLE 46 Duration of operation data: all RCTs

Study (author, year)	Group							
	Fibrin sealant			Standard care				
	n	Mean	SD	*n*	Mean	SD	Note	Surgery area
Bulbuller *et al.*, 2013[92]	6	138.2	21.57	15	138.1	19.77	C	Upper GI tract: bowel
Bulbuller *et al.*, 2013[92]	6	138.2	21.57	16	196	19.77	C	Upper GI tract: bowel
Bulbuller *et al.*, 2013[92]	6	138.2	21.57	16	166.4	19.77	C	Upper GI tract: bowel
Musella *et al.*, 2014[88]	50	82.8	5.2	50	84.3	6.2		Upper GI tract: bowel

TABLE 46 Duration of operation data: all RCTs (*continued*)

Study (author, year)	Group						Note	Surgery area
	Fibrin sealant			Standard care				
	n	Mean	SD	*n*	Mean	SD		
Pilone *et al.*, 2012[89]	15	108	21.57	15	102	19.77	C	Upper GI tract: bowel
Silecchia *et al.*, 2008[62]	160	149.4	36.5	160	142.7	34.1		Upper GI tract: bowel
Sroka *et al.*, 2015[90]	49	64	23	47	54	19		Upper GI tract: bowel
Sroka *et al.*, 2015[90]	49	64	23	49	74	21		Upper GI tract: bowel
Uetsuji, 1994[68]	25	362	131	39	280	85		Upper GI tract: liver
Liu and Lui, 1993[69]	20	294.5	65.3	20	343	184		Upper GI tract: liver without mobilisation
Noun *et al.*, 1996[70]	35	252	90	42	258	108		Upper GI tract: liver without mobilisation
Uetsuji *et al.*, 1994[68]	25	362	131	39	342	111		Upper GI tract: liver with mobilisation
Figueras *et al.*, 2007[71]	150	282	76.3	150	263	73.1		Upper GI tract: liver with mobilisation
Mortenson *et al.*, 2008[120]	16	227	16.2	14	261	16.8		Breast/lymph
Moore *et al.*, 1997[106]	32	135	16.2	31	132	16.8		Breast/lymph
Cambal *et al.*, 2012[175]	50	48.5	11.11	50	44	11.77		Hernia
Campanelli *et al.*, 2012[176]	158	39.8	12.1	158	41.5	11.9		Hernia
Damiano *et al.*, 2014[184]	216	48.89	5.71	252	51.6	6.27		Hernia
Lovisetto *et al.*, 2007[180]	99	53.8	7.61	98	39.6	7.61		Hernia
Chan *et al.*, 2014[178]	64	75.84	19.01	65	73.09	21.31		Hernia
Bahar *et al.*, 2007[169]	42	16	3.94	39	28	4	C	Eye
Bahar *et al.*, 2006[159]	39	16	3.94	26	20	4	C	Eye
Hall *et al.*, 2009[160]	25	12.04	3.94	25	26.04	4	C	Eye
Karalezli *et al.*, 2008[161]	25	15.7	2.4	25	32.5	6.7		Eye
Kucukerdonmez *et al.*, 2010[157]	32	11.22	2.4	38	18.7	2.2		Eye
Malik and Kumar, 2010[171]	50	18.24	2.2	25	26.6	1.93		Eye
Ratnalingam *et al.*, 2010[165]	68	16.93	2.85	69	29.84	5.65		Eye
Rubin *et al.*, 2011[166]	21	19.05	6.12	26	48.5	7.13		Eye
Sati *et al.*, 2014[163]	30	15.5	1.2	30	27.63	1.63		Eye
Uy *et al.*, 2005[168]	11	27.8	1	11	67	3.6		Eye
Yüksel *et al.*, 2010[158]	29	23.42	13.34	29	41.45	3.2		Eye
Filosso *et al.*, 2013[136]	13	216	24	11	240	30		Cardiothoracic: lung
Lopez *et al.*, 2013[129]	179	165.6	82.6	167	155.5	81.6		Cardiothoracic: lung
Maisano *et al.*, 2009[140]	59	249	77	60	235	59		Cardiothoracic: heart
Fischer *et al.*, 2013[241]	60	247.8	140.4	30	253.4	141.8		Mixed
Maggiore *et al.*, 2011[233]	35	98.4	7.8	35	98	9.5		Gynaecological
Takeuchi *et al.*, 2005[234]	29	112	45.8	16	103	30.6		Gynaecological
Takeuchi *et al.*, 2005[234]	30	108	41.7	16	103	30.6		Gynaecological

C, computed.

TABLE 47 Length of hospital stay data: all RCTs

Study (author, year)	Group						Note	Surgery area
	Fibrin sealant			Standard care				
	n	Mean	SD	*n*	Mean	SD		
Noun *et al.*, 1996[70]	35	10.8	4	42	11.3	5		Upper GI tract: liver
Carter *et al.*, 2013[81]	50	6.4		51	7.3	6.75	Check values	Upper GI tract: pancreas
Lillemoe *et al.*, 2004[83]	58	12.2	0.8	66	13.6	1		Upper GI tract: pancreas
Martin and Au, 2013[86]	25	14.1	12.7	32	17.4	17.5		Upper GI tract: pancreas
Musella *et al.*, 2014[88]	50	5.1	1.1	50	5.2	1.2		Upper GI tract: bowel
Pilone *et al.*, 2012[89]	15	6.5	2.65	15	7	1.5	C	Upper GI tract: bowel
Schwartz *et al.*, 2004[77]	58	9	4	63	10.5	5	Values taken from Noun *et al.*[70] (reporting on SD for liver surgery)	Upper GI tract: bowel
Silecchia *et al.*, 2008[62]	160	7.1	4.2	160	6.7	1.8		Upper GI tract: bowel
Aguilera *et al.*, 2013[143]	42	7.6	5.3	42	7.5	2.6		Joints: knee
Aguilera *et al.*, 2013[143]	41	7.2	4.5	41	6.8	2.4		Joints: knee
Kluba *et al.*, 2012[145]	12	12.67	5.1	12	13.67	2.7		Joints: knee
Molloy *et al.*, 2006[147]	50	4.82	4.3	50	5.86	2.55	C	Joints: knee
Randelli *et al.*, 2014[149]	31	9	2.3	31	9	2.5		Joints: knee
Lassen *et al.*, 2006[141]	22	7		36	7			Joints: hip
Wang *et al.*, 2003[153]	38	4.9		43	5.3			Joints: hip
Benevento *et al.*, 2014[109]	30	2.08	1.06	30	4.08	1.05		Breast/lymph
Berger *et al.*, 2001[107]	29	9.1	2.7	31	9.3	3.6		Breast/lymph
Furrer *et al.*, 1993[116]	15	18	11	15	22	16		Breast/lymph
Mustonen *et al.*, 2004[104]	19	3.9	1	21	3.7	1		Breast/lymph
Vaxman *et al.*, 1995[251]	20	10.8	3.5	19	9.4	3.5		Breast/lymph
Gilly *et al.*, 1994[115]	19	6.46	1.85	21	8.47	2.62		Breast/lymph: inguinal or axillary lymph nodes
Udén *et al.*, 1993[98]	36	5.7		32	4.3			Breast/lymph: inguinal or axillary lymph nodes
Gilly *et al.*, 1998[108]	50	8	1.6	58	10.1	2.1		Breast/lymph: axillary lymph nodes
Moore *et al.*, 1997[106]	32	1.18	0.6	31	1.41	0.69		Breast/lymph: breast and axillary lymph nodes

TABLE 47 Length of hospital stay data: all RCTs (*continued*)

Study (author, year)	Group						Note	Surgery area
	Fibrin sealant			Standard care				
	n	Mean	SD	*n*	Mean	SD		
Lovisetto *et al.*, 2007[180]	99	1		98	1			Hernia
Olmi *et al.*, 2007[259]	50	1		150	1.1			Hernia
Olmi *et al.*, 2007[259]	50	1		150	1.1			Hernia
Olmi *et al.*, 2007[259]	50	1		150	1.2			Hernia
Cormio *et al.*, 2012[222]	49	2.75	1.68	47	5.15	1.74		Urology
Czerny *et al.*, 2000[205]	9	10		7	10.5			Vascular
Anegg *et al.*, 2007[125]	75	6.2	2	77	7.7	2.2	C	Cardiothoracic: lung
Droghetti *et al.*, 2008[124]	20	11	2	20	14.3	2.2	C	Cardiothoracic: lung
Fabian *et al.*, 2003[128]	50	4.6	2	50	4.9	2.2	C	Cardiothoracic: lung
Filosso *et al.*, 2013[136]	13	6.9	1.4	11	9.5	0.5		Cardiothoracic: lung
Gonfiotti *et al.*, 2011[130]	91	7.64	3.56	94	7	3.33		Cardiothoracic: lung
Rena *et al.*, 2009[127]	30	5.87	1.07	30	7.5	3.2		Cardiothoracic: lung
Tavilla *et al.*, 2015[60]	722	5.99	3.95	714	6.07	4.21		Cardiothoracic: heart

C, computed.

TABLE 48 Duration of drainage data: all RCTs

Study (author, year)	Group						Note	Surgery area
	Fibrin sealant			Standard care				
	n	Mean	SD	*n*	Mean	SD		
Maisano *et al.*, 2009[140]	59	3.9	7.4	60	2.8	4.4		Cardiothoracic: heart
Berger *et al.*, 2001[107]	29	3.8	1.9	31	3.9	1.8		Breast/lymph
Benevento *et al.*, 2014[109]	30	2	1.4	30	4	1.6		Breast/lymph
Cipolla *et al.*, 2010[110]	80	4.5	1.7	79	5.1	1.9		Breast/lymph
Di Monta *et al.*, 2012[117]	37	20	5	33	23	5		Breast/lymph
Dinsmore *et al.*, 2000[97]	14	16.5	1.9	13	12.3	2.3	C	Breast/lymph
Furrer *et al.*, 1993[116]	15	8.6	4.2	15	11.7	9.1		Breast/lymph
Gilly *et al.*, 1994[115]	19	4.85	2.06	21	7.19	2.59		Breast/lymph
Ko *et al.*, 2009[102]	47	3.3	0.9	48	3.8	1.4		Breast/lymph
Moore *et al.*, 1997[106]	32	3.9	1.7	31	6.9	1.19		Breast/lymph
Mustonen *et al.*, 2004[104]	19	3.3	1.2	21	3.1	0.9		Breast/lymph
Mustonen *et al.*, 2004[104]	19	2.2	0.8	21	2.3	0.7		Breast/lymph
Nielsen *et al.*, 1985[123]	10	4.4	1.9	20	4.4	2.3	C	Breast/lymph
Nielsen *et al.*, 1985[123]	8	6.5	1.9	20	4.4	2.3	C	Breast/lymph
Segura-Castillo *et al.*, 2005[105]	22	5.09	1.48	23	8.96	2.33		Breast/lymph
Ulusoy *et al.*, 2003[96]	27	9.88	0.59	27	9.66	0.58		Breast/lymph
Vaxman *et al.*, 1995[112]	20	5.85	2.7	19	4.89	1.9		Breast/lymph
Vaxman *et al.*, 1995[112]	20	2.3	1	19	2.95	1.2		Breast/lymph
Erba *et al.*, 2010[210]	5	4	1	5	6	1		Plastic
Oliver *et al.*, 2002[215]	5	8.2		5	6.3			Plastic
Oliver *et al.*, 2002[215]	4	9.5		4	9.3			Plastic
Oliver *et al.*, 2002[215]	5	4.6		5	9.6			Plastic
Oliver *et al.*, 2002[215]	8	4.1		8	4.9			Plastic
Czerny *et al.*, 2000[205]	9	2		7	2			Vascular
Randelli *et al.*, 2014[149]	31	0.81	0.16	31	0.8	0.11		Joints
Bektas *et al.*, 2014[65]	35	8.7	7.4	35	8.1	4.1		Upper GI tract: liver
Fischer *et al.*, 2011[72]	60	6.6	4.33	59	7.6	2.58	C	Upper GI tract: liver
Frilling *et al.*, 2005[73]	53	8.2	4.33	59	5.7	2.58	C	Upper GI tract: liver
Kakaei *et al.*, 2013[74]	15	3.66	0.97	15	4.06	0.7		Upper GI tract: liver
Kohno *et al.*, 1992[75]	31	7.2	5.1	31	6.3	2.7		Upper GI tract: liver
Liu and Lui, 1993[69]	20	7.85	3.85	20	8.35	2.81		Upper GI tract: liver
Czerny *et al.*, 2004[137]	40	2.53	0.17	40	2.97	0.14		Cardiothoracic: lung
Filosso *et al.*, 2013[136]	13	6.1	1.7	11	10.8	2.4		Cardiothoracic: lung
Gonfiotti *et al.*, 2011[130]	91	6	3.1	94	6.5	5.4		Cardiothoracic: lung
Moser *et al.*, 2008[126]	25	2.83	1.96	25	5.88	2.96		Cardiothoracic: lung
Rena *et al.*, 2009[127]	30	3.53	1.59	30	5.9	3.72		Cardiothoracic: lung

C, computed.

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