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

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Scientific summary

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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 Ongoing and unpublished randomised controlled trials (RCTs) were identified from clinicaltrials.gov, controlledtrials.com and clinicaltrialsregister.eu.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

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