Diagnostic and therapeutic medical devices for safer blood management in cardiac surgery: systematic reviews, observational studies and randomised controlled trials

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Scientific summary

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Scientific summary

Background

Organ injury and sepsis are common and severe complications of cardiac surgery. In a recent trial, clinically significant sepsis and kidney, lung and myocardial injury occurred in 23%, 34%, 16% and 11% of patients, contributing to 43%, 41%, 36% and 24% of all deaths respectively. Anaemia and coagulopathic bleeding are common in cardiac surgery patients, often require multiple blood management interventions and are associated with increased rates of organ failure, sepsis and death. As a consequence, the safe and effective management of anaemia and bleeding are considered key determinants of outcome. However, there is clinical uncertainty as to how these conditions should be managed clinically because of our limited understanding of the underlying mechanisms and the lack of clinical efficacy for most blood management interventions that have been evaluated in clinical trials. This leads to significant variability in care.

Coagulopathic haemorrhage is observed in up to 25% of patients. Large-volume blood transfusion (LVBT) or emergency re-sternotomy for life-threatening haemorrhage increased mortality two- to eightfold. Current guidelines recommend that the risks of coagulopathy may be mitigated by careful preoperative risk assessment combined with the use of near-patient or point-of-care (POC) diagnostic tests for coagulopathy, to allow targeted treatment of specific defects in coagulation or platelet function. Existing bleeding or transfusion risk scores are not widely used, however, and the value of existing POC tests are unclear.

Perioperative anaemia is common (30–90%) and is thought to contribute to morbidity by reducing tissue oxygen delivery. Reversal of severe anaemia using red cell transfusion has been shown in recent trials to reduce mortality. However, the haemoglobin threshold at which transfusion is indicated is unclear and this is likely to differ between patients, as well as for individual patients, over their perioperative course. Near-infrared spectroscopy (NIRS) devices are in common use as monitors of tissue (brain, kidney) oxygenation and it has been hypothesised that these may provide personalised indicators of the need for red cell transfusion in anaemic patients. Safer transfusion may move the balance of risks and benefits to favour the more aggressive treatment of anaemia.

Pathological changes occur in donor red cells during blood bank storage. These changes, commonly referred to as the storage lesion, have been implicated in inflammation and organ failure in transfusion recipients. The clinical importance of the storage lesion is unclear; however, it has been suggested that mechanical washing of red cells using commercially available red cell salvage devices may remove some of the harmful by-products of storage and allow safer transfusion, and this approach has been in common use in paediatric cardiac surgery until recently. The safety and efficacy of this approach in adult cardiac surgery is unknown.

Aim

The aim of this programme was to critically evaluate medical devices in common use as blood management adjuncts in cardiac surgery. The programme involved three distinct workstreams.

Workstream 1: diagnosis of coagulopathy and assessment of bleeding and transfusion risk

The objectives of workstream 1 were to evaluate the predictive accuracy of presurgical bleeding and transfusion risk assessment and the added value of the routine use of near-patient POC haemostasis tests or an expanded range of laboratory reference tests for the diagnosis and prevention of coagulopathic bleeding.

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Workstream 2: the use of near-infrared spectroscopy as a patient-specific indicator of regional tissue oxygenation and the need for red cell transfusion in cardiac surgery

The objectives of workstream 2 were to evaluate the clinical effectiveness and cost-effectiveness of NIRS-based algorithms for the personalised optimisation of tissue oxygen delivery during cardiopulmonary bypass, including a patient-specific indicator for the administration of red cells in anaemic patients.

Workstream 3: the use of mechanical red cell washing devices to remove the red cell supernatant from stored red cells, thereby reducing inflammation and organ injury attributable to the storage lesion

The primary objective of workstream 3 was to evaluate the safety and efficacy of mechanical red cell washing in a randomised trial in adult cardiac surgery patients. A secondary objective was to assess the inflammatory mechanisms underlying our clinical findings.

Methods and results

Within each workstream there were a number of components, including systematic reviews, risk model development, prospective diagnostic accuracy studies, health economic analyses, randomised controlled trials (RCTs) and mechanism substudies. In total, 11 pieces of work were undertaken. These may be summarised as follows.

Workstream 1

1. A systematic review and meta-analysis of RCTs compared POC haemostasis test-based algorithms for the prevention of post-cardiac surgery bleeding and organ injury. None of 15 trials randomising a total of 8737 participants was classified as being at low risk of bias. Pooled effect estimates demonstrated that POC testing algorithms reduced transfusion and bleeding rates but had no benefit with respect to clinically important outcomes. The GRADE (Grades of Recommendation, Assessment, Development and Evaluation) summary of the evidence for clinical outcomes was low.
2. The COagulation and Platelet laboratory Testing in Cardiac surgery (COPTIC) study was a predictive accuracy study that evaluated the benefits of commonly used pre- and postoperative POC haemostasis testing devices [rotational thromboelastometry (ROTEM) (ROTEM® Delta; TEM International GmbH, Munich, Germany), thromboelastography (TEG) (TEG® 5000 Thromboelastograph® Haemostasis Analyzer; Haemonetics Corporation, Niles, IL, USA) and Multiplate® analyzer (Roche, Rotkreuz, Switzerland)] for the prediction of bleeding and adverse outcome compared with that achieved using routinely measured baseline factors. In a prospective diagnostic accuracy study of 1833 participants we demonstrated that a multivariable predictive model for severe bleeding based only on baseline clinical characteristics had an area under the receiver operating characteristic (ROC) curve (AUC) of 0.72 [95% confidence interval (CI) 0.69 to 0.75] and correctly classified 76.8% of participants. Adding the results of the most predictive near-patient test results before surgery (platelet aggregometry) and after surgery (platelet aggregometry and viscoelastic tests) to the baseline characteristics model improved the prediction of clinical concern about bleeding after surgery (AUC 0.75, 95% CI 0.72 to 0.77) but increased the proportion of participants correctly classified by only 0.98%.
3. A prospective diagnostic accuracy study evaluated the benefits of pre- and post-surgery laboratory reference tests of platelet and coagulation pathway function for the prediction of bleeding and adverse outcomes beyond that achieved using routinely measured baseline factors. The value of adding laboratory reference tests for postoperative factor Xa activity, endogenous thrombin potential, von Willebrand factor, Clauss fibrinogen, factor XIII activity and D-dimer levels to the clinical prediction model from the COPTIC cohort was assessed. The addition of the laboratory reference test with the greatest predictive accuracy (post-surgery fibrinogen concentration) resulted in small but statistically significant increases in accuracy (AUC clinical risk score 0.711, AUC clinical risk score plus reference tests 0.744; $p < 0.0001$). This was of uncertain clinical significance.

4. A health economic analysis was carried out to assess the cost-effectiveness of introducing POC tests (TEG, ROTEM and/or Multiplate test) into routine clinical care. A cost–utility analysis demonstrated that, for each of the POC test options, the mean differences in costs and life-years compared with current practice were small and not statistically significant; the largest difference in costs was £33, approximately 0.2% of the total costs, and the largest difference in life-years was 0.0043, equivalent to 1.6 days. Based on the point estimates of the incremental cost-effectiveness ratio (ICER), TEG and TEG plus the Multiplate test were dominated by current practice as they were both more costly and less effective. ROTEM and ROTEM plus the Multiplate test were both more costly and produced more life-years and, if a decision-maker was willing to pay £8000 for an additional life-year, they would be considered cost-effective. However, there was great uncertainty around these results because of the small differences in costs and life-years gained.
5. A narrative literature review was carried out of existing risk prediction scores for bleeding (measured as LVBT) and transfusion in cardiac surgery. We identified significant limitations in existing risk prediction scores for bleeding and transfusion, including, importantly, that they had been developed in small cohorts of patients, often from single centres, and, with one exception, had not been independently validated.
6. To overcome the limitations of existing risk prediction scores we developed and validated two novel risk scores for preoperative clinical assessment of bleeding and transfusion risk using data from 29 cardiac centres and two countries. The AUC was 0.77 (95% CI 0.77 to 0.77) and 0.80 (95% CI 0.79 to 0.80) for the any transfusion and LVBT (bleeding) scores respectively. In comparison, the AUC for existing scores ranged from 0.69 to 0.71. The any transfusion and LVBT scores were published as free to use e-calculators.

Workstream 2

7. The PAtient-SPecific Oxygen monitoring to Reduce blood Transfusion during heart surgery (PASPORT) trial was a multicentre randomised controlled efficacy trial comparing a NIRS device (INVOS™ 5100, Medtronic Inc., MN, USA)-based algorithm for the personalised optimisation of tissue oxygenation and red cell transfusion with standard care. The analysis population included 203 participants from three UK centres. The trial demonstrated that the use of a NIRS-based algorithm did not result in reductions in organ injury (brain, kidney, heart) or red cell transfusion.
8. A health economic analysis was carried out of the cost-effectiveness of introducing a NIRS-based algorithm into routine clinical care. Neither the differences in costs nor the differences in quality-adjusted life-years (QALYs) were statistically significant between the groups; mean [standard error (SE)] total costs were £16,591 (£799) and £16,992 (£656) in the intervention and control arms respectively and mean (SE) QALYs to 3 months were 0.1857 (0.005) and 0.1901 (0.005) in the intervention and control arms respectively. The ICER for adopting a patient-specific algorithm rather than a generic algorithm was £51,616. If a decision-maker was willing to accept compensation of £20,000 for the loss of 1 QALY, a patient-specific algorithm would be considered cost-effective; however, there was much uncertainty around the estimates because of the small differences between the groups.
9. A systematic review was carried out of RCTs assessing the effectiveness of NIRS-based algorithms for the reduction of red cell transfusion and organ injury in cardiac surgery. In 10 trials enrolling 1466 participants we found no difference between the NIRS groups and the control groups for death, myocardial infarction, stroke, renal replacement therapy, resource use or red cell transfusion. GRADE assessments were very low for all of these outcomes.

Workstream 3

10. A multicentre RCT was carried out to assess the efficacy of allogenic red cell washing compared with standard care for the prevention of past cardiac surgery inflammation and organ injury (REDWASH trial). The trial was stopped by the funder after enrolling 60 participants because of slow recruitment. Analysis of outcome data in these participants did not support our primary hypothesis that washing would reduce inflammation and organ injury.

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11. A substudy to explore the mechanisms underlying the results of our clinical trial was completed as specified in the study protocol. We observed that washing of stored allogenic red cells removed microparticles that have direct inflammatory and activating effects on platelets, leucocytes and endothelial cells. However, washed red cells release free haem at an accelerated rate post washing, which also have inflammatory effects. These observations may explain the apparent lack of benefit observed in the clinical trial.

Summary of main findings

Workstream 1

Risk assessment using baseline clinical factors predicts with a high degree of accuracy which patients are likely to develop severe bleeding post surgery. We developed two new risk scores that have greater predictive accuracy than existing scores. These are freely available to any clinician or researcher. We did not demonstrate any added benefit from routine POC haemostasis testing or from the use of an expanded range of laboratory reference tests for the prediction of bleeding. The use of POC tests was not cost-effective. Existing trial data do not suggest that POC-based algorithms improve clinically important outcomes.

Workstream 2

We did not demonstrate clinical effectiveness or cost-effectiveness of NIRS-based algorithms for the optimisation of tissue oxygenation or to guide red cell transfusion.

Workstream 3

We demonstrated that mechanical washing of stored red cells did not reduce inflammation or organ injury in adult cardiac surgery patients receiving LVBTs.

Implications for practice

The absence of high-quality evidence to guide blood management decisions leads to variation in care. A systematic assessment of medical devices in common clinical use as blood management adjuncts did not demonstrate clinical effectiveness or cost-effectiveness. These results question the quality of current systems for approving the introduction of medical devices into clinical practice and underpin the value to patients and the NHS of careful clinical evaluation of novel technologies prior to routine clinical use.

Study registration

This study is registered as ISRCTN20778544 (COPTIC study) and PROSPERO CRD42016033831 (systematic review) (workstream 1); ISRCTN23557269 (PASPORT trial) and PROSPERO CRD4201502769 (systematic review) (workstream 2); and ISRCTN27076315 (REDWASH trial) (workstream 3).

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