EDITORIALS

When more is less efficacious: fibrinogen concentrate in complex cardiac surgery

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In a previous issue of the British Journal of Anaesthesia an important multicentre, randomized controlled trial was published comparing fibrinogen concentrate vs placebo in patients undergoing complex cardiovascular surgery complicated by bleeding.1 This study showed a statistically significant increase in the use of blood products in those patients randomly assigned to receive fibrinogen concentrate. It provides additional important information to three recent publications that have shown no statistically significant benefit with the use of fibrinogen concentrate. This is an important study that will help to guide clinical practice and the design of future trials in bleeding patients with regard to the role of fibrinogen replacement.

The standard of care to treat bleeding patients is variable around the world. However, the general principles are to replace red cells, clotting factors, and platelets lost with haemorrhage and manage any coagulopathy that occurs as a result of the underlying condition (e.g. disseminated intravascular coagulation in post-partum haemorrhage or trauma). Treatment can follow an approach whereby results are checked and deficiencies are replaced, or if the bleeding is too rapid and ongoing, without time to wait for results of testing, a ratio-based approach can be followed. There are many guidelines outlining the optimal approach, but a recent systematic review found little evidence to support one approach over another.7 Importantly, acquired hypofibrinogenemia can arise in the bleeding patient. In the developed world, fibrinogen replacement can be provided in the form of fresh frozen plasma (FFP), cryoprecipitate, or fibrinogen concentrate. A recent review of critical fibrinogen levels in bleeding identifies that ‘historically’ a fibrinogen threshold level of 1.0 g/L has been used to guide the need for supplementation, and the vast majority of current treatment guidelines use this level to trigger replacement.2 In part, the trigger to replace fibrinogen has been guided by those unfortunate and rare patients who have congenital afibrinogenemia. In general, a target fibrinogen concentration of >1 g/L is effective in preventing bleeding in these patients while undergoing major surgery or with haemorrhage.3 The available options for supplementing fibrinogen and a comparison of the different plasma products, cryoprecipitate, and fibrinogen concentrate have also recently been outlined.7 In some countries, routine use of fibrinogen concentrate has already been adopted without robust clinical evidence, therefore this and other recent publications are welcomed in order to inform us of how best to manage patients who are bleeding with regard to fibrinogen supplementation.

The search for a magic haemostatic agent has remained elusive, and while there were high expectations that recombinant factor 7a would be beneficial in the bleeding patient, numerous clinical trials did not show improved outcomes and raised concern regarding thromboembolic complications.5,6 Thus an important lesson was learned when the randomized controlled trials (RCTs) showed the drug to be non-efficacious in this clinical setting.

In their study, Rahe-Meyer and colleagues1 report the results of an RCT where fibrinogen concentrate was compared with placebo for bleeding patients undergoing elective aortic surgery requiring cardiopulmonary bypass. Bleeding was measured as a 5-min bleeding mass of 60–250 g after separation from cardiopulmonary bypass and surgical haemostasis. A transfusion
algorithm was then followed. The primary outcome was the number of allogeneic blood products (ABPs) used. A total of 519 of the 579 patients consented were randomized; of those, 152 had a bleeding mass >60 g and received fibrinogen concentrate or placebo. Unexpectedly, there was a greater need for allogeneic blood transfusion in the group randomized to receive fibrinogen concentrate. In the fibrinogen group, the median ABP use was 5 (interquartile range (IQR) 2.0–11.0) units compared with 3 (IQR 0.0–7.0) units in the placebo group (P = 0.026). In addition, among those receiving fibrinogen, fewer patients avoided postoperative transfusion [12/78 (15.4%)] compared with those receiving placebo [21/74 (28.4%)] (P = 0.047). The main difference in ABP transfused patients appeared to be the requirement for FFP rather than red cells or platelets (P = 0.017). Return to theatre for surgical bleeding was also higher in the fibrinogen concentrate group [6/78 (8%)] compared with placebo [3/74 (3%)]. In post hoc exploratory analysis, the group assigned to receive fibrinogen required more postoperative transfusions, even when separately analysing patients where the transfusion algorithm was successfully followed. These results suggested a potentially adverse effect of fibrinogen concentrate on bleeding outcomes following complex cardiac surgery.

A principal strength of this study is its multisite randomized design, which lends strong generalizability to the conclusions. The study is the largest randomized trial of fibrinogen concentrate in cardiac surgery. Cardiac surgical patients are a group who typically can utilize a large number of blood products and transfusion has been associated with worse outcomes, therefore cardiac surgery patients seem to have been a good choice of patients to study.

Three limitations in this study may have influenced the observed outcome. First, the inclusion criteria were designed to identify the subset of complex cardiac patients with early post-bypass haemorrhage by using a bleeding mass of 60–250 g during the first 5 min. This criterion, while immediate and practical, may not have identified patients most likely to benefit from supplemental fibrinogen and fails to consider the circulating fibrinogen level of the patient at the time of fibrinogen administration. Second, while a transfusion algorithm was followed, such algorithms are difficult to validate for effectiveness. The algorithm was followed in 68% of patients, and while there is some variability across study centres, the study was randomized and therefore the effect of this should be balanced across the two groups. Finally, data were not provided regarding the use of cell salvage or the number of patients receiving tranexamic acid, which may reduce bleeding in this patient group.

In contrast to the use of fibrinogen concentrate as a treatment for bleeding, two previously published single-site RCTs examined the role of prophylactic fibrinogen concentrate in cardiac surgery. These studies have conflicting results. The single-centre Italian study by Ranucci and colleagues found that when prophylactic fibrinogen concentrate, at a median dose of 4 g, was given to patients after complex cardiac surgery, they used fewer blood products: 39/58 (67.2%) patients in the fibrinogen concentrate group received no ABPs vs 26/58 (44.8%) in the placebo group (P = 0.012). A Swedish study by Jeppson and colleagues randomized patients undergoing cardiopulmonary artery bypass grafting to receive 2 g of fibrinogen concentrate prophylactically or placebo. The primary outcome was the mediastinal drain volume in the first 12 h postoperatively. Twenty-six patients were randomized to each arm. There was no statistical difference in the amount drained at 12 h in either group (median of 650 ml fibrinogen concentrate vs 730 ml placebo; P = 0.29). There are several reasons why these studies may have varying results, including the slightly different patient groups, the larger dose in the more complex surgical group, and the different primary outcomes. As a result of these two studies, the question of optimal study design with relation to these factors is highlighted.

Another patient group in whom bleeding can be a major problem is women with post-partum haemorrhage (PPH). In Denmark, Wikkelso and colleagues performed a multicentre RCT in 249 subjects with severe PPH. In this study they randomized patients to a single dose of 2 g of fibrinogen concentrate (in 100 ml sterile water) vs placebo (100 ml saline). They hypothesized that the fibrinogen concentrate would reduce the need for red blood cell (RBC) transfusion in patients with PPH. The primary outcome was RBC transfusion up to 6 weeks post-partum. The mean blood loss was 1459 ml. Post-partum blood transfusion occurred in 25 (20%) of the fibrinogen group and 26 (22%) of the placebo group, which was not statistically significant. There was also no difference in the predefined secondary outcomes. Importantly, no thromboembolic events were noted, although the study was not powered to detect a difference in thromboembolic events. The baseline mean fibrinogen concentration was 4.5 g/l in both groups with only one patient in the fibrinogen concentrate group and four patients in the placebo group having a fibrinogen concentration < 2 g/l.

The study by Wikkelso and colleagues and that by Rahe-Meyer and colleagues would suggest that there is a threshold at which fibrinogen becomes crucial to haemostasis. Previous evidence, as outlined above, would suggest that this threshold is < 1.0 g/l. This informs us that future studies assessing the role of fibrinogen concentrate should carefully consider inclusion criteria and that those patients without a low level of fibrinogen are unlikely to benefit from this therapy and indeed there may be unexpected adverse effects as demonstrated in this study.

A fundamental question to resolve is whether one source of fibrinogen supplementation is better than another. Is fibrinogen concentrate more efficacious than cryoprecipitate? While it could be argued that there is limited evidence for the use of cryoprecipitate, this is considered standard practice in the setting of low fibrinogen and it would seem unethical to compare cryoprecipitate to placebo in an RCT of the bleeding patient with low fibrinogen. No prospective trials have compared the efficacy of these two products in the bleeding setting. While the later product requires thawing and no viral inactivation has occurred, both products are plasma derived and carry a theoretical risk of infectious disease transmission, even though this risk is extremely low. There is a misconception that cryoprecipitate exposes patients to a large number of donors, but each unit of cryoprecipitate is made from a single donor and therefore a treatment dose of 5–10 units exposes the patient to 5–10 donors. In comparison, fibrinogen concentrate is made from thousands of donors, and while the viral inactivation step (pasteurization) in production of this product adds additional safety compared with cryoprecipitate, the product is derived from many more donors. There is also the possibility of using virally inactivated plasma products, but the availability of these products depends on in which part of the world the patient resides. Both products are derived from plasma and therefore the possible risk of variant Creutzfeldt–Jakob disease transmission from either product exists. Unlike fibrinogen concentrate, cryoprecipitate contains several other clotting factors that may be beneficial in the haemorrhaging patient, such as von Willebrand factor, factor VIII, fibronectin, and factor XIII. In most countries, the production cost of cryoprecipitate is also likely to be less than that of fibrinogen concentrate. A randomized clinical trial comparing the efficacy of cryoprecipitate vs fibrinogen concentrate for patients.
with bleeding would help identify which of these products is superior in efficacy. If there is a logistical advantage in terms of time to deliver one product into the bleeding patient, then this will become apparent in a properly conducted RCT and we should not assume that one product is superior. A recent feasibility study has shown that it is possible to deliver cryoprecipitate within 90 min in 85% of study participants in the setting of haemorrhage in trauma. 12 Authorship of the study by Rahe-Meyer and colleagues 1 also includes employees of CSL Behring and it was funded by CSL Behring. Designers of future studies will hopefully be able to convince the suppliers of these two different products that a clinical trial comparing the efficacies of these two products is important for patient care.

Perhaps counterintuitively, this study informs us that the use of fibrinogen concentrate increased the use of blood products in the bleeding patient undergoing elective aortic surgery. A puzzling question is the mechanism by which fibrinogen concentrate led to increased blood product use. The study raises several other remaining questions, including the most appropriate clinical scenario in which fibrinogen replacement may be efficacious, whether cryoprecipitate may be a superior source of fibrinogen, and what the threshold for treatment and the proper dose should be. The study’s results should not only caution those clinicians who have adopted off-label use of fibrinogen concentrate, but also invite a re-examination of the evidence in those countries where it is already approved.

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References

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Oxygen supplementation during prolonged tracheal intubation should be the standard of care

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In a previous issue of the BJAn, Steiner and colleagues compared deep insufflation of oxygen during laryngoscopy to standard practice direct laryngoscopy without oxygen insufflation during nasotracheal intubation in children. They demonstrated the superiority of two different oxygen insufflation methods. One method consisted of laryngoscopy with the Truview PCD video-laryngoscope and the other provided deep insufflation of oxygen via a tracheal tube attached to the side of a standard laryngoscope. These deep insufflation methods enabled the delivery of supplemental oxygen in close proximity to the glottic opening. The administration of supplemental oxygen was able to preserve normoxemia, for a longer period of time than standard laryngoscopy without oxygen supplementation in these paralyzed patients. This was effectively illustrated by the authors’ use of classic Kaplan-Meier survival curves, to demonstrate times to achieve a 1% oxygen desaturation in the three different