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Early cryoprecipitate for trauma patients is feasible, but will it improve outcome?

B. S. Sachais and B. H. Shaz*

New York Blood Center, 310 East 67th Street, New York, NY 10065, USA
*Corresponding author. E-mail: bshaz@nybloodcenter.org

In this issue of BJA, Curry and colleagues1 demonstrate the feasibility of administering cryoprecipitate as a fibrinogen source within 90 min of admission of trauma patients. This study is important because cryoprecipitate contains fibrinogen and fibronectin, which are critical to clotting; data are variable on the need for cryoprecipitate in trauma patients, and no randomized controlled trials looking at the administration of fibrinogen concentrate or cryoprecipitate in trauma patients have been performed. However, the completion of the randomized clinical trial on the early use of cryoprecipitate is needed before implementation of this practice. Trauma patients receive plasma, which also contains fibrinogen and fibronectin, but at lower amounts and not in therapeutic doses. In some countries, prothrombin complex concentrates are used, which contain some but not all of the clotting factors. Also, fibrinogen concentrates are being used in trauma patients and require less volume for administration.

Fibrinogen (factor I) is a 340 kDa protein comprised of two sets of disulfide-bridged Aα, Bβ and γ chains. Thrombin cleavage of fibrinopeptide A from the Aα chains creates fibrin, which polymerizes and forms the proteinaceous structural basis for blood clots.2 As such, maintaining adequate fibrinogen concentrations in bleeding patients seems to be a rational objective. However, our understanding of what constitutes an adequate concentration in a bleeding patient, how to determine fibrinogen concentrations rapidly and meaningfully, and what products to use for replacement is relatively poor.3 4 A 2013 review in the Cochrane Collaboration examining the use of fibrinogen concentrates in bleeding patients found only six randomized controlled trials (248 subjects), of which two had mortality data.4 While they concluded that there was a suggestion of benefit on reduction of red blood cell (RBC) transfusions, the authors were unable to draw any conclusions on mortality. Interestingly, the studies reviewed showed no effect on other outcomes, including thrombotic adverse events. A systematic review of fibrinogen concentrate in trauma revealed 12 articles, including a single prospective study.5 Again, conclusions by the authors were limited, but suggested a reduction in the use of RBC transfusions in this setting. Taken together, these studies suggest that administration of fibrinogen may result in earlier haemorrhage control.

Given that 40% of trauma-related mortality is attributable to uncontrolled bleeding, a deeper understanding and optimization of fibrinogen supplementation is of great interest. There has been a substantial focus on the early administration of plasma and platelets (plasma:platelet:RBC transfusion ratio); a ratio of 1:1:1 compared with 1:1:2 did not demonstrate improved survival, but showed that more plasma and platelets help to achieve earlier haemostasis (although there was no decrease in the use of RBC transfusions within the two groups).6 However, cryoprecipitate has not been as well studied. Indeed, fibrinogen deficiency (as defined by concentrations below 100 mg dl−1)7 develops early in trauma.8 The lower amount of fibrinogen administration via blood products, including whole blood, plasma, and cryoprecipitate, and defined as fibrinogen:RBC ratio has been associated with higher mortality in military trauma,9 a lower cryoprecipitate:RBC ratio has been associated with higher mortality in civilian trauma,10 and data from an observational cohort study relates low fibrinogen at admission to higher trauma mortality at 24 h and 28 days.11 These studies indicate that increasing fibrinogen concentrations in trauma patients may be beneficial. However, there are no randomized trials looking specifically at fibrinogen or cryoprecipitate in trauma patients. It is from this perspective that the study by Curry and colleagues,1 published in this issue of the BJA, takes on importance.

In their study, Curry and colleagues1 performed a feasibility study to determine whether it is possible to administer cryoprecipitate as a fibrinogen source within 90 min of admission of trauma patients. This is operationally complex because cryoprecipitate must be thawed and then delivered and cannot be stored for more than 6 h. Secondary objectives included laboratory...
measurement of fibrinogen and a variety of predetermined clinical outcomes. Forty-three subjects were randomized between standard therapy (STANDARD) or two early pools of cryoprecipitate (∼4 g of fibrinogen) in addition to standard therapy (CRYO).

The primary objective of administration of cryoprecipitate within 90 min was achieved in 85% of patients in the CRYO group. Patients in the CRYO group received cryoprecipitate significantly earlier than those in the STANDARD group, with a median time of 60 vs 108 min. The STANDARD group received cryoprecipitate as part of the second package of the major haemorrhage protocol. During the period of active bleeding, fibrinogen concentrations were increased in the CRYO group compared with the STANDARD therapy patients. Although the authors report no significant difference in mortality between the groups, this pilot study was not powered to measure mortality. Low numbers of patients in this pilot study and a trend towards older and more severely injured patients in the STANDARD arm make interpretation of other outcomes difficult.

Given the many logistical difficulties that can arise in transfusion studies of trauma patients, this study is significant in that it demonstrates that cryoprecipitate can be delivered and transfused to trauma patients early in their resuscitation and that transfusion of cryoprecipitate in this setting leads to a short-term elevation of fibrinogen, which should predict earlier cessation of haemorrhage. As such, it paves the way for the design and implementation of randomized clinical trials in this area.

One of the unanswered questions that should be addressed in future trials is the dose, both the amount and the frequency, of fibrinogen administration. In the study by Curry and colleagues,1 standard dosing of two pools of five units of cryoprecipitate (∼4 g of fibrinogen) was given to all CRYO patients. This dose was determined empirically via ex vivo ROTEM (Tem International GmbH, Munich, Germany) assays, specifically using the EXTTEM CA5 value (which measures clot formation via tissue factor activation) and the FIBTEM CA5 value (which inhibits platelet activation and is strongly influenced by fibrinogen function). While this approach to determining dose is reasonable given the paucity of data available, it is not clear whether lower doses would suffice or if higher doses would improve efficacy. Therefore, the use of additional doses, including lower and higher doses, should be explored, particularly as there is some evidence that transfusion of fibrinogen to high normal concentrations in cardiac surgery may decrease bleeding.12 13

ROTEM has the potential for assisting in the management of traumatic bleeding, although data are sparse, but slowly coming. One study showed that the CA5 value using ROTEM was a good predictor of acute traumatic coagulopathy (with a CA5 <35 mm predicting 77% of instances).14 As the use of thromboelastography, including ROTEM, has been gaining popularity in the management of trauma patients, any future clinical trials examining fibrinogen replacement in trauma should explore the utility of thromboelastography for determining the need for fibrinogen administration, monitoring therapeutic interventions, or both. Predictive values (positive and negative) should be calculated for one or more clinically meaningful end points.

Another question is whether the source of fibrinogen matters in the control of bleeding trauma patients. In theory, if fibrinogen is the sole important protein in cryoprecipitate for control of bleeding in the trauma setting, then the efficacy of cryoprecipitate and purified fibrinogen concentrate should be equivalent. However, cryoprecipitate contains other haemostatic proteins, including fibrinectin, factor XIII, factor VIII, and von Willebrand factor, any or all of which may contribute to the control of bleeding. Additionally, the fibrinogen concentrate could be administered in lower volumes than the cryoprecipitate, which may result in improved outcomes.15 Therefore, studies that examine cryoprecipitate transfusion may not be generalizable to all fibrinogen sources.

Although the trauma community has made significant improvements in reducing mortality from haemorrhage, there continues to be room for further improvements. We now have the means to administer fibrinogen rapidly and not have cryoprecipitate wastage, both through fibrinogen concentrate, and we have a way of measuring fibrinogen concentrations rapidly. Given the association of increased fibrinogen, cryoprecipitate, or both to RBC transfusions and decrease RBC use and improved mortality, the follow-up randomized controlled study will provide us with critical information.

Declaration of interest
None declared.

References
Selective serotonin reuptake inhibitors: depressing perioperative outcomes?

S. J. Shepherd1, C. Fiandeiro2 and R. D. Sanders3*

1 Barts and the London School of Anaesthesia, London, UK,
2 Imperial School of Anaesthesia, London, UK, and
3 Department of Anesthesiology, University of Wisconsin, Madison, USA

*E-mail: rsanders4@wisc.edu

In recent years, prescriptions for antidepressant agents have increased substantially. Selective serotonin reuptake inhibitors (SSRIs) have gradually supplanted tricyclic agents as drugs of choice because of their lower toxicity and generally better tolerability. They cause less sedation with fewer anticholinergic effects and are now widely used for the treatment of many conditions including depression and obsessive-compulsive disorder. Recent evidence suggests that they are amongst the most commonly prescribed medications in the United States.

Why should SSRIs depress perioperative outcomes?

Beyond effects upon the QT interval, drugs with serotonergic activity have been previously associated with an increase in bleeding risk particularly when administered in combination with warfarin. Serotonin promotes platelet activation; it is released from platelets in response to vascular injury, promoting both vasoconstriction and a conformational change in shape that enhances aggregation through secondary mediators. Platelets lack the ability to synthesise further serotonin, therefore inhibition of the reuptake transport by SSRIs can thus deplete intracellular concentrations with the development of impaired haemostasis. The relative frequency of bleeding complications appears proportionate to the degree of serotonin reuptake inhibition. An association between the risk of bleeding and increasing affinity for the serotonin transporter has been noted by a number of authors. Drugs such as clomipramine, fluoxetine, sertraline, and paroxetine produce more potent blockade of the serotonin transporter and further increase bleeding potential.

Clinical evidence for the effects on haemostasis

Observational studies have demonstrated an increased risk of blood loss in various settings. SSRIs have been independently associated with a gastrointestinal blood loss. Estimates of risk are variable but significant; a retrospective analysis of database studies demonstrated an odds ratio in SSRI-treated patients of increased bleeding from 1.38 to 3.6 although the confidence intervals in this setting remained wide. This association holds true after adjustment for age, gender, and the effects of other drugs such as aspirin and non-steroidal anti-inflammatories (NSAIDS) suggesting an additional if not synergistic effect. This risk decreases to pre-existing levels upon cessation. Similar large case series have demonstrated an increase risk of bleeding in patients undergoing hip fracture surgery, although without effect upon postoperative morbidity or mortality.

Both selective and non-selective serotonin antagonists have been implicated in the development of postpartum haemorrhage. A large cohort study of women from the United States demonstrated 12% of women were exposed to SSRIs at the time of delivery: the risk of postpartum haemorrhage was 2.8% among women with mood disorders without exposure to antidepressants and 4.0% in current users of SSRIs. This study was conducted among women enrolled in the US Medicaid program who were more likely to be younger, low income and non-Caucasian compared with national figures for pregnant women that may have resulted in significant confounding. This finding has not been borne out in other cohorts, although increase in bleeding during early pregnancy was seen in some groups albeit without effects upon outcome. A slight increase in intracerebral haemorrhage and bleeding after ischaemic stroke have also been reported, although given the rarity of these events absolute risk remains small. Case reports have also implicated SSRIs in spontaneous epidural haematoma, airway bleeding and retrobulbar haemorrhage.

The perioperative period

Recent data suggests associations of SSRIs and an increased risk of perioperative bleeding and other adverse outcomes however it is important to note patients receiving SSRIs are also more likely to have conditions such as obesity and cardiovascular disease which also impact upon surgical risk. However, an increased requirement for red-cell transfusion has been demonstrated in patients taking SSRIs who undergo coronary artery bypass and...