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EDITORIAL

How to replace fibrinogen in postpartum haemorrhage situations? (Hint: Don't use FFP!)

Postpartum haemorrhage (PPH) remains a leading cause of maternal morbidity and mortality worldwide, causing up to 75% of severe maternal morbidity.[1] Despite a dramatic reduction in maternal deaths from PPH, the incidence has been increasing in many countries for reasons that are not entirely explained by obvious risk factors.[2–4] In many cases several causes may co-exist and haemostatic impairment is common.

Fibrinogen is the most abundant coagulation factor in the human body and its concentration has increased 150–200% by the third trimester of pregnancy.[5] As the precursor molecule for fibrin, adequate concentrations are necessary for haemostasis.[6,7] During a PPH, fibrinogen is the first coagulation factor to fall precipitously,[8] and although the mechanism has not been elucidated, it is likely to be secondary to loss of fibrinogen through bleeding, increased fibrinolytic activity, and haemodilution from fluids given as part of resuscitation management. The contribution of each to the fall in plasma fibrinogen may be affected by the pathophysiology of PPH; for example in some situations excessive blood loss may be the primary cause whereas in other situations excessive fibrinolysis may predominate.[9]

It is now clear that fibrinogen is an early biomarker for the progression of PPH, when the risk of progression to severe PPH increased 2.63 fold for each 1 g/L decrease in fibrinogen concentration.[10] There was a positive predictive value of 100% for progression to severe PPH when the fibrinogen concentration was ≤2 g/L, and a negative predictive value for progression of 79% for values >4 g/L.[10] A plasma fibrinogen concentration <2 g/L has 99.3% specificity for prediction of severe PPH.[11] Even higher concentrations are associated with progression to severe PPH (odds ratio [OR] 1.90 (95% CI 1.2 to 3.1) when plasma fibrinogen is 2 to 3 g/L, compared with OR 11.99 (95% CI 2.6 to 56.1) when the plasma fibrinogen concentration is <2 g/L.[11] More recently, the utility of visco-elastic testing using rotational thromboelastometry (ROTEM®, TEM International, Munich) for earlier prediction of progression to severe PPH has been demonstrated.[12] The key advantages of visco-elastic testing are the rapid assessment of coagulation status during bleeding; and information about aspects of haemostasis that is difficult to obtain with traditional laboratory coagulation testing, for example about clot strength and fibrinolysis.

In this issue of the journal, Seto et al.[13] present a single-centre cohort study examining the impact of an algorithm-driven approach to the management of coagulopathy in women experiencing massive PPH (defined by the investigators as blood loss >1000 mL). Overall blood loss, the amount of blood products required and the complications of therapy were reported. In this study hypofibrinogenaemia was treated with fibrinogen concentrate, rather than with fresh frozen plasma (FFP), as had been used in a historical control group. Blood loss fell from a mean of 1110 mL (SD 1399 mL) to 229 mL (SD 187 mL) after implementing the new algorithm, which was both a statistically and clinically significant change. There was also a greater than 50% reduction in the volume of FFP given, in association with the increased use of fibrinogen concentrate.

This study highlights the importance of selecting the correct blood product for the replacement of fibrinogen in acquired bleeding situations. The dramatic decrease in blood loss is likely to be due to the change from FFP as the primary source of fibrinogen to fibrinogen concentrate, in addition to the benefits seen with the implementation of algorithm-based care.[14] When fibrinogen replacement is required there are generally three options available: FFP, cryoprecipitate and fibrinogen concentrate, although some blood products may not be available in all regions.

Fresh frozen plasma continues to be used extensively in perioperative settings, despite evidence of increased morbidity associated with its use.[15,16] The fibrinogen concentration of units of FFP varies between 1 and 3 g/L.[17] Correction of hypofibrinogenaemia during active bleeding requires large volumes of FFP, which may contribute to haemodilution or transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI). A dose of 12.2 mL/kg (approximately 2 units) has been shown to increase plasma fibrinogen concentration by only 0.4 g/L, whereas even in larger doses (33.5 mL/kg, approximately 5 units), the plasma fibrinogen increased by only 1 g/L.[18] Computer modelling has highlighted that, in bleeding situations, there is an exponential increase in the amount of

fibrinogen required as the target fibrinogen concentration approaches the concentration of the fibrinogen source.[19] The clinical implication is that concentrated forms of fibrinogen are required to reach even modest target levels in acquired bleeding. Due to safety concerns and the low concentration of fibrinogen in FFP, several authors recommend that FFP not be used for fibrinogen supplementation.[20,21]

Cryoprecipitate is prepared by thawing FFP to between 1 and 6°C, centrifugation and resuspension of the precipitated proteins. Although presented in a comparatively small volume, cryoprecipitate contains fibrinogen in a much higher concentration then FFP, although the concentration may vary widely (3–30 g/L).[22] Readers with access to cryoprecipitate are encouraged to learn the expected concentration that their transfusion service provides. Generally, each unit contains approximately 200–250 mg of fibrinogen, and a standard recommended dose in adults is 8–10 units,[20] but because the units may have been sourced from multiple donors, cryoprecipitate carries a greater risk of viral transmission per dose than FFP.[23] Safety concerns about viral activity mean that it is not available in all countries, and some authors have suggested that it would not now gain regulatory approval.[24] However, in many centres it remains the primary source of fibrinogen, and is an appropriate therapeutic option if access to specific factor concentrate is not available.

As an alternative to cryoprecipitate, fibrinogen concentrate has been used in the management of acquired bleeding states, although only recently have clinical trials been conducted in obstetric haemorrhage. It is produced from pooled human plasma and undergoes processing to reduce the risk of viral transmission and remove the need for blood-group matching.[25] At least four fibrinogen concentrates are available commercially, although Haemocomplettan/RiaSTAP (CSL Behring) appears the most widely used.[20] Fibrinogen concentrate is recommended in some international guidelines for the management of acquired bleeding,[26] but licensed indications vary considerably from country to country and do not always match local guidelines.[24] The other advantages of fibrinogen concentrate are that it contains a standardised concentration of fibrinogen and is stored as a powder at room temperature. This powder can be rapidly reconstituted and administered in a low infusion volume, thus avoiding delays associated with cross-matching or thawing.[27]

Studies comparing the efficacy of cryoprecipitate and fibrinogen concentrate are limited, particularly in obstetrics.[28] This is almost certainly due to both products not being available in many centres. In one retrospective review of major obstetric haemorrhage in a single institution over a two and a half year period, only 34 women received either product and their efficacy appeared similar.[29] The mean dose of cryoprecipitate was 2.2 pooled units (equivalent to approximately 3.2 g of fibrinogen) and the mean dose of fibrinogen concentrate was 4 g, resulting in an increase in the plasma fibrinogen concentration of 2.01 (SD 0.19) g/L and 2.11 (SD 0.26) g/L respectively. Of the other comparative studies performed to date, fibrinogen concentrate and cryoprecipitate appear equally efficacious in increasing the plasma fibrinogen concentration when dosed appropriately.[28] However, clot activation (measured using the clotting time with ROTEM analysis) is faster with cryoprecipitate than with fibrinogen concentrate, an effect most likely explained by the additional coagulation factors (Factors VIII, XIII and von Willebrand factor) present in cryoprecipitate.[30]

What is the future for coagulation management in PPH? The importance of fibrinogen as a biomarker of severity is now accepted. Although there is considerable interest in the utility of visco-elastic testing to enable rapid assessment of fibrinogen concentrations, what remains unclear is what fibrinogen concentration should trigger supplementation when using visco-elastic testing and what is an appropriate post-treatment target concentration. Whether the pre-emptive supplementation of fibrinogen early in PPH may improve outcomes has been the focus of recent attention. Wikkelso et al.[31] randomised 249 women with severe PPH to receive either 2 g of fibrinogen concentrate or placebo. Despite the mean blood loss at study entry being 1459 mL, the measured fibrinogen concentration at that time was 4.5 g/L (SD 1.2), and only 2.2% of women had a concentration below 2 g/L. Despite significant haemorrhage, the high starting fibrinogen concentration in most of their participants probably explains the lack of benefit seen in that trial. More recently, Collins et al.[32] randomised 55 women with an ongoing major PPH to receive early fibrinogen concentrate if their ROTEM Fibtem A5 value was $\leq$15 mm. They found no benefit from the early administration of fibrinogen concentrate in relation to overall blood loss or allogeneic units transfused. However, subgroup analysis suggested a potential benefit in women with a Fibtem A5 of $\leq$12 mm. These studies have two important implications. Firstly, despite significant blood loss many obstetric patients will not have haemostatic impairment and may not require correction with blood products. Secondly, the decision to transfuse blood products should be made in response to measured abnormalities of coagulation; and only based on clinical grounds if there is a high suspicion or likelihood of coagulopathy in an actively bleeding patient.

Finally, the study by Seto et al.[13] highlights the benefits of implementing protocol- or algorithm-based care in complex situations such as PPH. Consensus algorithms for PPH management have been published,[33] as have other PPH care bundles.[34] Widespread implementation of protocols to manage obstetric haemorrhage has been shown to reduce blood product usage and improve

patient safety.[14] Use of specific transfusion management algorithms with ROTEM guidance in PPH is associated with fewer blood product transfusions, fewer complications associated with those transfusions, and lower cost.[35,36]

Nevertheless, the question remains: what is the optimal source of fibrinogen in PPH? It is now clear that FFP is an inappropriate source of fibrinogen in acquired bleeding, with cryoprecipitate and fibrinogen concentrate both having clear advantages. Currently many centres only have access to either cryoprecipitate or fibrinogen concentrate. Whether one product is clearly superior to the other is unproven in randomised trials to date. We would recommend that, given the crucial role of fibrinogen in obstetric haemorrhage, centres that manage obstetric patients should ensure that they have ready access to either cryoprecipitate or fibrinogen concentrate. For centres without a permanent on-site transfusion service or with limited availability of cryoprecipitate, carrying a supply of fibrinogen concentrate is desirable. The dose of either agent required to correct critical hypofibrinogenaemia is often high and frequently underestimated, so to ensure patient safety, centres must provide rapid access to adequate product.

Conflict of interest statement

Nolan McDonnell sits on the National Advisory Board for RiaSTAP (CSL Behring) in Australia and has received speaker support from Tem International. Roger Browning has no conflicts of interest to declare.

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