ROLE OF COAGULATION FACTOR CONCENTRATES IN THE OPERATING ROOM

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ABSTRACT

The use of fresh frozen plasma, cryoprecipitate, and platelets has been the mainstay of approaches to correct coagulopathies that can arise in the perioperative setting. Limitations include the time delay from obtaining results of coagulation screens to the availability of thawed fresh frozen plasma and the potential of fluid overload. With advances in both global haemostatic testing and concentrates of coagulation factors, there are increasing opportunities for innovative practice. However, there remains a paucity of studies that can provide good quality, unbiased evidence. These issues are elaborated here to form the basis for future study.

Keywords: Fibrinogen concentrate, fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), coagulation monitoring, surgery.

INTRODUCTION

Haemostasis is a natural defence against vascular injury and haemorrhage. In the context of elective surgery, the challenge of maintaining adequate haemostasis is directly proportional to the nature and duration of the operation. The initiation trigger is via tissue factor exposure from subendothelial sites to cause factor VII activation, which then leads to amplification and propagation of the coagulation process (Figure 1).[1] These pathways are well described elsewhere and the key enzymatic stages share the common template of requiring a vitamin K-dependent protein (e.g. factors VII, X, or II) and a cofactor (e.g. tissue factor, factors VIIIa or Va) assembling on phospholipid surfaces in the presence of calcium.[2] Such reactions, which are referred to as tenase or prothrombinase, respectively, accelerate coagulation activation by several 100,000-fold to ensure explosive thrombin generation.[3]

Thrombin is the cascade enzyme as it is not only essential for procoagulant consequences, through the conversion of fibrinogen into fibrin and the activation of platelets, but also in activating the protein C anti-coagulant pathway.[4] This is particularly important at the margins of injury through thrombomodulin cofactor function to contain the extent of clot formation.[4] The cross-linking of fibrin is the ultimate step in the coagulation cascade, with clot stabilisation by thrombin-activated factor XIII. The action of thrombin-activatable fibrinolysis inhibitor (TAFI) also serves to reduce the rate of clot breakdown as part of thrombin-induced tissue-type plasminogen activator (tPA) profibrinolytic actions.[5]

From a physiological perspective, this would suggest a well-regulated homeostatic process involving equal and opposite reactions resulting from thrombin generation *in vivo*. As long as the surgical or traumatic insult is not excessive, exogenous haemostatic support is unlikely to be necessary peri or postoperatively. However, in the event of unplanned surgery in the presence of infection, such as in peritonitis or for major trauma, the haemostatic capacity may be compromised. This is true even in young patients with no medical history who develop significant coagulopathy perioperatively after major trauma.[6] The resulting coagulopathy in such circumstances presents a major challenge for anaesthetists and intensivists as it is typically multifactorial and the clinical

status can deteriorate rapidly. It is thus important to address this problem with prompt and comprehensive clinical assessments of coagulopathy followed by appropriate and timely administration of haemostatic therapy. This review discusses the current issues around plasma transfusion support, current concepts in coagulation monitoring, and understanding the roles played by non-activated coagulation factor concentrates as perioperativetherapy for achieving haemostasis. Activated prothrombin complex concentrates (PCCs) are not reviewed here as they are typically considered in the acquired haemophilia setting. Anti-coagulant factor concentrates have certain indications in the operating room setting but are beyond the scope of this manuscript.

CURRENT ISSUES IN PLASMA TRANSFUSION SUPPORT

Primary haemostasis upon vascular injury is mediated by platelets and reinforced by coagulation factors. Transfusion of plasma and platelets has been the mainstay of haemostatic therapy for many decades. Therefore, delayed decision or administration of blood products after prolonged storage can exacerbate coagulopathy and potentially affect clinical outcomes,[7] primarily due to the risk of exsanguination, and secondarily because clot formation is a defence mechanism against infection. Equally, premature and overzealous use of blood products can be harmful. For example, studies in intensive care patients have shown an increased risk of arterial thrombosis and death with platelet transfusions in the presence of consumptive thrombocytopenia.[8] This underscores the importance of timeliness in decision making and action.

Commonly used laboratory haemostasis assessment includes prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level by the Clauss method, and platelet count. Typical turnaround time for these tests is in the region of 30–90 minutes which is not optimal in diagnosing coagulopathy or guiding haemostatic interventions. This is particularly problematic when multiple units of fresh frozen plasma (FFP) must be thawed according to laboratory procedure, which adds 30–60 minutes of processing time.

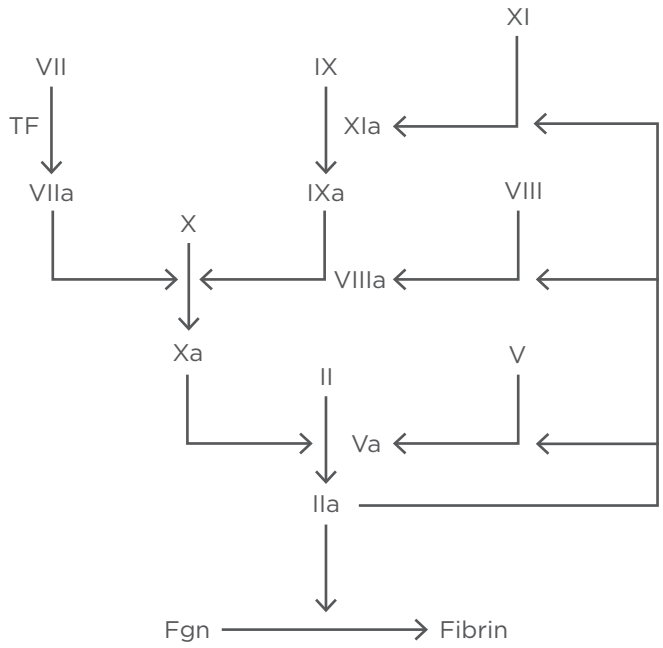

Figure 1: Schematic representation of how coagulation factor replacement promotes haemostasis.
Initiation of coagulation activation via the TF pathway leads to tenase and prothrombinase reactions to generate thrombin (IIa). This can then amplify the process through thrombin-mediated generation of factors IXa, VIIa, and Va. Thrombin conversion of Fgn to fibrin is then propagated. Fresh frozen plasma contains all of these coagulation factors in an unactivated form, whereas available coagulation factor concentrates provide those that are vitamin K-dependent; i.e. factors II, VII, IX, and X, with VII being the most variable between products.
TF: tissue factor; Fgn: fibrinogen.

FFP can contain variable but near normal levels of pro and anti-coagulant proteins and coagulation inhibitors. The relatively low concentrations of coagulation factors in therapeutic FFP (as compared to concentrates) makes it difficult to achieve a significant increase in patients' circulating levels without administering large volumes. Based on rough guidance, as much as 2.5 L of plasma transfusion may be required to improve clot times.[9,10] On the other hand, coagulation factor concentrates enable larger increases without large infusion volumes.[11] Large volumes of plasma transfusion are poorly tolerated in patients with limited cardiopulmonary reserve and can lead to intractable fluid overload. In addition, transfusion-related acute lung injury (TRALI) is a potentially lethal complication of plasma transfusion, although the preferential use of male donor plasma has significantly reduced its incidence.[10,12]

Although FFP has been available for approximately 60 years, evidence from randomised controlled trials (RCTs) proving its efficacy and safety is lacking, and recommendations in current guidelines (Table 1) are mainly based on observational studies.[13-15] In addition, studies from Europe, Canada, USA, and Australia have shown that both the use of FFP and cryoprecipitate are often inappropriate for reasons outside of clinical guidelines.[13,14] Administering FFP in patients with minimally elevated international normalised ratio values has been shown to be ineffective in producing meaningful corrections.[9,16]

RATIONALE FOR USING COAGULATION FACTOR CONCENTRATES

Prothrombin Complex Concentrates

In view of the practical problems of administering FFP, PCC could be advantageous because of the smaller volume required to replace deficient factors and the relative speed in reconstituting a lyophilised powder with 10–20 mL of sterile water. However, PCC only contains vitamin K-dependent proteins, i.e. factors II, VII, IX, and X, and acquired deficiency of factors V and VIII would not be remedied. Different formulations contain varying amounts of proteins C and S but PCCs are mainly distinguished by their factor VII content.[17] These are often referred to as three or four factor concentrates based on the levels of factor VII. PCC is licensed primarily for the management of bleeding in patients treated with vitamin K antagonists (VKA).[15,18] In Europe, there is a broad indication for PCC in the management of patients with low levels of factors II, VII, IX, and X. In the perioperative setting, PCC is often used in the management of severe bleeding in patients undergoing cardiovascular or other surgeries,[19,20] especially those with prolonged PT.[15] An advantage to their use is the reduced likelihood of TRALI due to the lack of antibodies in PCC. As to whether these products can induce further activation of coagulation and lead to adverse clinical outcomes, a meta-analysis of 27 studies for the reversal of VKA showed the overall incidence of thromboembolic complications as 1.4%.[21] The authors concluded that there was a 'low but quantifiable' risk of thromboembolic events in patients receiving PCC, but there was no direct comparison against a control (non-PCC treated group). The mortality rate was 10.6% and only a few cases could be attributed to thromboembolic events. As such, a clear link between PCC use and mortality from thromboembolic complications could not be made.[21] Data from PCC infusion in a porcine model of liver injury indicate that a dose of 50 IU/kg precipitated thromboembolism in all tested animals with disseminated intravascular coagulation observed in 44% of cases.[22] These findings raise the prospect that high PCC concentrations might cause adverse clinical outcomes. However, current guidelines by the American Society of Anesthesiologists Task Force on Perioperative Blood Management indicate that the overall risk of thromboembolic events following PCC transfusion is only 0.003% (evidence from observational studies).[15] Close monitoring of the PT and clinical response is recommended, with emphasis that the available evidence for using PCC in managing perioperative bleeding in patients not treated with VKA is weak (higher risk of thromboembolism is also suggested), compared with its primary indication in reversing VKA-associated bleeding.[15,20]

Cryoprecipitate

The use of cryoprecipitate (primarily to replenish fibrinogen) has been largely withdrawn by several European countries amid safety concerns, especially with regards to transmission of pathogens.[23,24] Current guidelines indicate that literature evidence is insufficient to evaluate the intra or postoperative transfusion of cryoprecipitate in the management of bleeding.[15] As a replacement, fibrinogen concentrates are increasingly used to replenish depleted fibrinogen levels.[25] FFP may also be used to supplement fibrinogen in the absence of cryoprecipitate.

Fibrinogen Concentrates

With regard to fibrinogen concentrates, there are distinct advantages over cryoprecipitate. Firstly, there is no requirement for ABO group matching.[26,27] Secondly, its administration does not involve the time delay from thawing. Thirdly, higher amounts of fibrinogen are dissolvable in small volume infusions to enable administration within a short time period and also avoid the potential of fluid overload.[27,28] The target fibrinogen level is usually set at 1 g/L, based on the literature on congenital fibrinogen deficiency,[29] but there has been a trend for earlier and higher targets of fibrinogen replacement in severe trauma.[30-33] Another advantage is in terms of viral safety because of the ability to pasteurise and filter these concentrates in the manufacturing process.[34] In a recent analysis of almost three decades of pharmacovigilance data related to fibrinogen concentrate transfusion, a small number of suspected viral transmission cases have been identified.[35] However, it was concluded that a direct causal link to fibrinogen concentrates was unlikely as polymerase chain reaction results were negative and/or alternative explanations were found.[35] As for contraindications to fibrinogen concentrate use, these include a history of anaphylactic reactions to the concentrate[36] and ongoing thrombosis or a high prothrombotic risk.[28]

In regards to approvals for the administration of fibrinogen concentrates in Europe, these are granted nationally and an approval by the European Medicines Agency (EMA) does not exist. This reflects differing strategies both to the transfusion of blood products and the approval of blood products from across European countries.

CURRENT CONCEPTS IN MONITORING COAGULATION

While most guidelines on the use of FFP and cryoprecipitate are in reference to the degree of abnormality in PT, aPTT, or fibrinogen, the availability of point-of-care testing using rotational thromboelastometry (ROTEM®) or thromboelastography (TEG®) in providing information would be important to examine for clinical value in the perioperative setting.[37] The viscoelastic properties of whole blood clot formation, as assessed by ROTEM and TEG, are dependent on thrombin-mediated fibrin formation and its polymerisation. Indeed, the extent of fibrin polymerisation as an endpoint would appear to offer an advantage because fibrin clot firmness cannot be assessed by PT, aPTT, or fibrinogen level. Different stages of ROTEM/TEG can give insights into: a decrease or inhibition of the different coagulation factors that are required for thrombin formation (early phase); the kinetic interaction of platelets and fibrin that are required for enhancing clot strength (intermediate phase); and maximum clot strength (final phase). As such, ROTEM/TEG can monitor evolving changes in the coagulation profile and identify hypofibrinogenemic, hyperfibrinolytic, and hypercoagulable states as well as the presence of low platelet/factor levels (or their inhibition).[38] This enables prompt transfusion decisions to be made, sometimes based on specific institutional algorithms, with fibrinogen concentrates, cryoprecipitate, FFP, platelets, or tranexamic acid.[38] The effect of the treatment is assessed soon after transfusion and depending on the ROTEM/TEG results, further transfusions can be tailored to the patient's specific needs. It must be emphasised that although ROTEM and TEG are based on similar principles, the results obtained with the two tests may not be interchangeable[39] because of differences in the activating reagents and operating characteristics. This may therefore result in different blood products being transfused based on which test was used.[40] It has been suggested that in the surgical setting, ROTEM may be the most appropriate test because of its faster turnaround time.[40] The new generation of viscoelastic coagulation monitoring devices with cartilage-based systems (TEG 6S, ROTEM sigma) might widen the use of these assays in the perioperative setting. The full-automation in these new devices will reduce variations in results related to pipetting, handling of blood, and prior manipulation of reagents. Finally, it must be stated that the recent European guideline for managing major bleeding and coagulopathy following trauma highlighted that the usefulness of viscoelastic tests has been questioned, and a number of significant limitations have been recently reported by several studies.[41] Therefore, the guidelines indicate that more thorough studies are required in this area and emphasise that clinicians should use judgement when designing and implementing local policies.[41]

CURRENT PERIOPERATIVE ROLE FOR COAGULATION FACTOR CONCENTRATES

Studies reviewed by Bolliger and Tanaka[42] included retrospective studies, case-control studies, and RCTs and reported that administration of fibrinogen concentrate in patients undergoing cardiac surgery

improved clot firmness, as measured by ROTEM, significantly decreased the need for other blood products such as red blood cells and FFP. Clinically, there were also significant reductions in postoperative bleeding drainage volumes. However, several important issues relevant to clinical practice were unclear; for example, FFP was often used in conjunction to make it difficult to assess the efficacy of fibrinogen concentrate alone in securing haemostasis in the bleeding patient.[29,43-45] Also, minimum core outcome sets were not defined, such as the length of follow-up for adverse clinical events and for assessing the safety of such interventions.[43-45]

More recently, two randomised double-blinded placebo-controlled trials examined the efficacy of fibrinogen concentrates in the setting of complex cardiovascular surgery.[46,47] The study by Ranucci et al.[47] found that in 116 patients, the infusion of fibrinogen concentrates (dose calculated according to fibrin–based thromboelastometry test [FIBTEM] readings) can significantly reduce subsequent allogenic blood product transfusions as compared to placebo. However, the more recent study by Rahe-Meyer et al.[46] reported an opposite result, whereby fibrinogen concentrate infusion (after a 5-minute bleeding mass of 60–250 g) resulted in increased requirement for further allogenic blood products. This discrepancy suggested that differences in the timing of transfusion, baseline fibrinogen level before transfusion, as well as variability in algorithms used to guide doses, and requirements for further transfusion[48] can have a major impact on outcomes. Although further robust RCTs are required to resolve the conflict, it must be emphasised that doses of fibrinogen concentrates as well as the requirement for other blood products are best adjusted according to the individual patient's needs. Coagulation factor concentrate therapy when coupled with point-of-care perioperative testing algorithms in a manner that is tailored to the patient's needs was found to reduce the requirement for FFP and other blood products.[49,50]

Other systematic reviews have been published in the last few years.[27,51] These have adopted a standardised analytical approach using preferred reporting items for systematic reviews and meta-analysis. The Population Intervention Comparison Outcome and Study Design (PICOS) approach was used to define inclusion. Few studies comparing FFP to fibrinogen in a perioperative or massive trauma setting[51] involved prospective high-quality methodologies. In general, fibrinogen was found to be superior to FFP for half of the outcomes that were investigated including reducing blood loss, need for allogeneic transfusions, length of intensive care unit and hospital stay, and increasing plasma fibrinogen levels.[51] However, FFP showed positive and negative effects for 28% and 22% of outcomes, respectively, with limited evidence that FFP reduced mortality.[51] In a prospective cohort study of 144 trauma patients, the use of factor concentrates (fibrinogen or PCC) alone was found to be associated with corrected coagulopathy, reduction in the need for further allogenic blood product transfusions, and reduction in the development of multiple organ failure, whereas additional FFP transfusions did not confer further haemostatic correction and were associated with higher requirement for platelets and red blood cell transfusions.[52] Collectively, this suggested that there was no strong evidence to support the clinical merit of FFP for surgical and/or massive trauma patients. Perioperatively, there was a trend towards improved outcome measures with fibrinogen concentrate treatment but solid conclusions remain difficult to draw without further robust prospective studies.[51]

Another review by Warmuth et al.[27] focussed on fibrinogen concentrate substitution in adults in the perioperative setting and with massive haemorrhage. It utilised a broader search of several databases beyond Medline, yielding 772 results between 1985 and 2010. In two RCTs and two non-RCT studies encompassing 74 patients in total, it was indicated that the administration of fibrinogen concentrate was associated with improved outcomes such as reduction in the substitution of red blood cells, FFP, and platelet concentrates as well as significantly reduced postoperative bleeding.[27] More recent systematic reviews agree that fibrinogen concentrates reduce the need for allogenic blood products transfusion in trauma and bleeding patients,[53-55] but the consensus is that the current studies are of low quality and the need for further well-designed RCTs to address the gaps in knowledge is emphasised.[53-55]

An important point to be highlighted is that some studies used maximum clot firmness as an endpoint[30] which is not a clinical outcome, but a laboratory outcome. Furthermore, Clauss fibrinogen method measurements are less sensitive to crystalloid-induced coagulation defects, whereas ROTEM is more reliable at detecting this disturbance.[56] In one study,[57] when specimens drawn from patients during major surgery were

tested in parallel using both methods, transfusion decisions based on Clauss results would result in no fibrinogen concentrate treatment in the 36 patients. Conversely, 36% of patients would have received fibrinogen concentrate if transfusion decisions were based on ROTEM guidance.[57] This stresses the critical influence of methodology on transfusion practice.

Another systematic review looked at both fibrinogen concentrates and PCC in the perioperative setting.[17] All studies included small sample sizes with highly selective inclusion criteria. However, focussing on the cardiac surgery group, prospective studies indicated that fibrinogen concentrate and/or PCC administration was associated with less allogeneic blood transfusion and reduced chest tube drainage.[17] As far as safety outcomes are concerned, it was clear that reporting was not uniform across different studies. Therefore, more robust trials with sound methodology and sufficient power are required to assess the efficacy of PCC and fibrinogen concentrates for the management of perioperative coagulopathy in bleeding patients. Finally, Table 1 provides a concise summary of the main indications for different factor-based blood products (allogenic and factor concentrates) transfusion in the perioperative setting, as adapted from current guidelines.[15]

Table 1: *Strategy for transfusion of coagulation factor concentrates in the perioperative setting.

Product	Indication for transfusion	General notes
Fresh frozen plasma	• Management of patients with severe bleeding • Reversal of VKA-associated bleeding (when PCC is not available) • Correction of specific factor deficiency (when appropriate factor concentrates are not available)	• Consider measuring PT, aPTT, and INR before FFP transfusion; viscoelastic tests may be performed
Cryoprecipitate	• Hypofibrinogenaemia • Management of patients with excessive bleeding • Management of patients with certain types of vWF and VIII deficiency (when desmopressin and/or appropriate factor concentrates are not available)	• In patients with excessive bleeding, consider measuring fibrinogen levels before cryoprecipitate transfusion. Viscoelastic tests may be performed • Desmopressin is indicated for initial management of vWF and VIII deficiency, followed by factor concentrates
Prothrombin complex concentrate	• Urgent reversal of warfarin and other VKA-associated bleeding • Patients with excessive bleeding and raised INR levels	• Little evidence is available for PCC use outside reversal of VKA-associated bleeding. Higher risk of thromboembolism is also suggested in this scenario • Optimal point-of-care testing to guide PCC administration is not available • Vitamin K may be administered in cases of non-urgent reversal of VKA-associated bleeding, except in cases where VKA is expected to commence shortly after surgery
Fibrinogen concentrate	• Hypofibrinogenaemia • Management of patients with excessive bleeding	• In patients with excessive bleeding, consider measuring fibrinogen levels before fibrinogen concentrate transfusion. Viscoelastic tests may be performed
Recombinant activated factor VII	• Management of patients with excessive bleeding when other measures (FFP, cryoprecipitate, PCC) have failed • Patients with factor VII deficiency	• Has been used in the setting of intracerebral bleeding, cerebral injury-induced coagulopathy, and in severe trauma • rFVIIa has proven value in the treatment of haemophilia patients with inhibitors

*These are general guidelines and the final decision on what and when to transfuse should always be based on careful assessment of the clinical scenario and in-line with local policies.
PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalised ratio; FFP: fresh frozen plasma; VKA: vitamin K antagonists; PCC: prothrombin complex concentrate; vWF: von Willebrand factor; rFVIIa: recombinant activated factor VII.

CONCLUSION

In summary, there is a need to better evidence the role of coagulation factor concentrates in the operating room to achieve optimal haemostasis and improve clinical outcome. The requirements include point-of-care tests that are simple to perform, rapid in result generation, and robust in providing an accurate status of *in vivo* coagulation. These could then lead to improved evidence and stronger transfusion guidelines that can be better standardised across Europe with wider applicability.

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