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REVIEW

Usage of Fibrinogen Concentrate in Postpartum Hemorrhage: Anesthesiology and Intensive Care Perspective

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ABSTRACT

Postpartum hemorrhage is the most important cause of maternal death in the world. One of the best agents used to prevent massive bleeding is fibrinogen concentrate (FC). FC can control bleeding without causing viral complications and without volume overload as in transfusion-associated circulatory overload and transfusion-related acute lung injury. FC is easy to apply, does not require dissolution, no extra apparatus is needed. Considering blood and blood products used in large amounts, it is a cost-effective agent.

Keywords: Anesthesiology, Fibrinogen Concentrate, Postpartum Hemorrhage, Intensive Care

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INTRODUCTION

Massive postpartum hemorrhage (PPH) is constantly related with coagulopathy of impressive induction[1] and remains a leading cause of maternal mortality and morbidity and increased therapeutic intervention, mechanical ventilation, hysterectomy, and hospital stay.[2]Changes in coagulation trigger the procoagulant phase of pregnancy, which is more likely with thrombocytopenia and procoagulant factors increased and diminished fibrinolysis, though serves as physiological protection against postpartum bleeding.[3] The severity of which varies depending on the cause, with varying contributions from dilution as well as the consequences of consumption of coagulation factors. Effective replacement of blood products containing coagulation factors is crucial in the management of PPH, with the effect of volume expansion in the circulation.[4,5] The critical factor for hemostasis is fibrinogen, and the decrease in its concentration is the most important cause of blood loss in severe surgical bleeding of PPH.[6,7] Acquired hypofibrinogenemia develops early in relation to fluid resuscitation, unbalanced transfusion of blood products, and bleeding.[8] This impaired hemostasis also occurs in PPH.

Recent studies have suggested that fibrinogen concentrate (FC) replacement therapy might be effective in achieving hemostasis for PPH complicated by coagulopathy.[9,10] FC is an effective therapy for treating coagulopathy in PPH, in combination with conventional methods of management such as fresh frozen plasma (FFP) transfusion.[11]

FC is a commercially available drug produced from human plasma.[12] FC is virally inactive and does not contain blood and blood products. Classically, acquired hypofibrinogenemia is treated with FFP (2.5 g/l) and Cryo (15 g/l).[13,14] These blood products need thawing and crossmatch before infusion. Therefore, with FFP, a volume of 800 mL would be required to deputy 2 g of fibrinogen, corresponding to 133 mL of cryoprecipitate (Cryo). Nevertheless, the use of FFP is associated with several transfusion-related complications rendering it a suboptimal treatment for early prevention of fibrinogen deficiency.

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USAGE AREAS OF FC

FC has various uses in surgery and intensive care. One of them is trauma patients. Severe trauma is a major cause of mortality. Uncontrolled post-traumatic bleeding is the leading cause of death among these patients. Fibrinogen is a plasma glycoprotein synthesized by the liver which plays a critical role in hemostasis. Fibrinogen supplementation can be achieved using fresh-frozen plasma, Cryo or plasma-derived, virally-inactivated, and FC, with the available therapeutic approaches differing from country to country.[15] Current European guidelines recommend supplementation of FC in trauma patients if significant bleeding is accompanied by viscoelastic signs of a functional fibrinogen deficitor a plasma fibrinogen level of <1.5–2.0 g/L (grade 1C).[16]

Trauma hemorrhage is aggravated by a complex interplay of clotting abnormalities and may result in a trauma-induced coagulopathy. Augmentation of blood fibrinogen levels necessitates the use of a concentrated form of fibrinogen supplementation (e.g., cryopre-cipitate or FC) because FFP alone is ineffective in trauma patients too. One study suggested that, increasing interest in the timely administration of concentrated sources of fibrinogen to patients with major traumatic bleeding. They suggested that if FC is given faster, it will be more effective.[17] In a systematic review, they search for randomized and controlled trials (RCTs) and non-randomized studies investigating FC in bleeding patients and included 30 studies of 3480 identified (7 RCTs and 23 non-randomized). In the available RCTs, which all have substantial shortcomings, they found a significant reduction in bleeding and transfusions requirements.[18]

Congenital fibrinogen deficiency is an inherited disorder due to genetic mutations reduced fibrinogen levels (hypofibrinogenemia), absence of fibrinogen in circulation (afibrinogenemia), abnormal functioning (dysfibrinogenemia), or both reduced levels and abnormal functioning (hypodysfibrinogenemia) of fibrinogen. The decreased fibrinogen levels require replacement therapy with FFP, Cryo, or human FC. However, the use of FFP and Cryo is limited owing to their longer transfusion time, need of high doses, high volume, risk of viral transmission, and other safety concerns. The availability of human FC has made it the preferred replacement alternative due to its reduced risk of viral transmission, smaller infusion volume, and accurate dosing.[19]

Patients with congenital fibrinogen disorders in pregnancy, there is an increased risk of spontaneous abortion, which occurs at 6–8 weeks of gestation if no replacement therapy is given. Patients with afibrinogenemia can have successful pregnancies if treated with FC. However, pre-term delivery appears to be more frequent in these women despite replacement therapy. Replacement treatment should be organized at the first opportunity in pregnancy in order to prevent fetal loss. It should be continued throughout the pregnancy aiming at fibrinogen levels >1.0 g/L.[20] During labor, some authors recommend higher levels (>2.0 g/L) to prevent placental abruption.[21]

Another area of using FC is cardiovascular surgery. Using of FC is indicated in cases of excessive bleeding regardless of time during cardiac surgery. Bleeding is higher in patients with a longer cardiopulmonary bypass (CPB) time. There was no interaction between CPB time and FC or Cryo treatment. A post hoc analysis of the Fibrinogen Replenishment in Surgery study compared the use of FC with Cryo to treat post-CPB bleeding in adult patients undergoing heart surgery. The hemostatic efficacy of FC was not inferior to Cryo in cardiac surgery, regardless of the time.[22]

ROTATIONAL THROMBOELASTOMETRY (ROTEM®)

The use of fibrinogen as part of coagulation factor concentrate-based therapy guided by point-of care (POC) viscoelastic coagulation monitoring (ROTEM or thromboelastography) appears promising. In addition to reducing patients' exposure to allogeneic blood products, this strategy may reduce the risk of complications such as transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and thromboembolic adverse events.

The FIBTEM assay measures elasticity of the fibrin-based clot, which is dependent not only on fibrinogen but also on other proteins such as Factor XIII. Although correlations between FIBTEM MCF and fibrinogen concentration have been observed, the involvement of other proteins confounds extrapolation between these parameters.[23]

McNamara et al.[24] present their 4 years' experience since the introduction of a ROTEM-FIBTEM guided algorithm, with further evaluation of its impact in terms of blood product use and clinical outcomes and treatment of coagulopathy in obstetric haemorrhage. POC testing allows for early diagnosis and personal treatment of coagulopathy. This is supported by reported advanced results.

FC IN PPH

FC is used to treat severe PPH in obstetric settings. One study shows the effectiveness of FC in terms of plasma fibrinogen levels as the first-line treatment for coagulopathy from PPH. RBC, FFP, and PC requirement were reduced after

using FC. Adequate FC therapy prevented unnecessary RBC, FFP, and Cryo replacement and prevented blood product-related complications and volume overload.[25]

The patient group for which FC works most effectively is cases with severe hypofibrinogenemia. The essence of the transfusion algorithm in critical obstetric hemorrhage is to approach the target value for obtaining hemostasis, ensure an accurate and prompt grasp of the severity using point-of-care testing, and introduce a massive transfusion protocol.[26]

For European Society of Anaesthesiology Guideline, they recommend that PPH should be managed by a multidisciplinary team. Risk awareness and early recognition of severe PPH are essential. They suggest assessing fibrinogen levels in parturients with bleeding, as levels <2 g/L may identify those at risk of severe PPH and recommend against pre-emptive fibrinogen replacement; however, in ongoing PPH with hypofibrinogenaemia, recommend fibrinogen replacement. Fibrinogen functionality might be impaired by dilution, local, or disseminated consumption. The underlying obstetrical cause of bleeding should guide the clinical suspicion of impaired hemostasis. Trigger levels for fibrinogen substitution vary between 1 and 2 g/1 and FIBTEM A5 <12 mm, with a mean administered dose of 2–4g. FIBTEM-guided fibrinogen substitution might improve patient outcomes. No serious adverse events were reported with FC in the obstetric setting.[27]

PPH is the leading cause of maternal deaths. Pregnancy has a marked effect on sensitive equilibrium that normally exists between pro-coagulants, anticoagulant system, and fibrinolytic procedure. These changes leave the pregnant woman in a theoretical pro-thrombotic state at the end of the third trimester to help combat the hemorrhagic challenge presented by delivery. Fibrinogen deficiency is the main cause of ongoing bleeding from the early to late stages of PPH. FFP and Cryo have some plasma fibrinogen level. However, in PPH as in other settings, FC may be considered preferable due to easy administration, convenient storage, standardized fibrinogen content, and low risk of complications such as transmission of pathogens and TRALI. Adding FC therapy reduces the risk of TACO, reduces the rate of intensive care admission, and reduces the risk of hysterectomy.[28]

One of the advantages of FC is that large amounts of fibrinogen can be delivered quickly and in small volumes. Fibrinogen levels deteriorate faster than other coagulation factors in conditions such as severe trauma, surgical bleeding, and postpartum. Therefore, aggressive complementation of fibrinogen plays an important role in hemostasis. FC can be given conveniently and quickly regardless of ABO compatibility. FC may change the result of a life-saving procedure compared with an ordinary transfusion strategy consisting of an allogenic transfusion. Hence, this is an advantage in emergency settings.[29]

Disseminated intravascular coagulopathy usually occurs in association with placental abruption, amniotic fluid embolism, or very severe hemorrhage. The pro-thrombotic state during pregnancy protects against coagulopathy. Plasma fibrinogen levels <2 g/L are strongly predictive of bleeding and should be provided above this. Fibrinogen levels are important during PPH, being the only factor independently associated with ongoing severe Bleeding. For every 1 g/L decrease in fibrinogen, the risk of progression to severe PPH is almost tripled. Fibrinogen level <2 g/L carries a 100% positive predictive value for progression, while fibrinogen level >4 g/L has a negative predictive value of 79%.[30]

CONCLUSION

Massive obstetric hemorrhage patients leading to heavy hypofibrinogenemia, fibrinogen is the marker that indicates the critical violence, and early fibrinogen supplementation centering on hemostatic resuscitation is a vital treatment to stabilize a fatal situation. Massive transfusion takes time and raises volume overload for PPH, which can cause acute lung injury and pulmonary edema. FC therapy as the first- line agent can reduce the risk of massive transfusion complications.

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