Fibrinogen Replacement: A Questionable Dogma

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Hamostaseologie

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Abstract

Management of hemostasis in the perioperative setting, in trauma or in acute care, has considerably changed over the last two decades. Viscoelastic testing and single-factor replacement therapies have become cornerstones of the respective clinical approaches. Here, we illuminate the basic theories for these approaches as well as the important evidence available. Both viscoelastic assays and single-factor replacements are important improvements; their use must be based on the strongest scientific evidence available.

Keywords

- viscoelastic assays
- factor concentrates
- fibrinogen/fibrin
- factor XIII/ transglutaminases
- resuscitation

Introduction

Factor I (fibrinogen) is said to be the first coagulation factor to reach critically low levels in acute bleeding[1] and current guidelines recommend maintaining the plasma fibrinogen level above 1.5 g/L.[2] However, other coagulation components such as platelets, factor V (FV), and factor XIII (FXIII) are influenced by thrombin generation earlier during the cascade of events.[3]

Among others, fibrinogen has a critical role in the maintenance of hemostasis as it is converted to soluble fibrin to form a clot in concert with activated platelets; it is further stabilized by FXIII-mediated fibrin cross-linking.[4] Fibrinogen is an important biomarker of acute inflammation.[5] In acutely ill patients, low fibrinogen levels have been associated with poorer outcomes and increased mortality. In fact, hypofibrinogenemia is an independent risk factor for increased mortality in trauma patients, suggesting the requirement of massive transfusion[6,7]; and it is also strongly associated with shock severity.[8]

In the trauma setting, empirically based transfusion protocols used worldwide are suggesting to use early administration of plasma, platelets, and red blood cells in a 1:1:1 ratio,[9–11] while in viscoelastic assays (VEAs)-guided transfusion protocols, it seems that plasma and platelets used can be reduced, and with better results.[12–14] In addition, it seems that overtransfusion occurs more frequently when empirical massive transfusions are used as compared with VEA-driven protocols.[15,16] When analyzing these differences in detail, it becomes evident that none of the large trials evaluating massive transfusion in severe trauma[9,10] mention the type of fibrinogen replenishment in detail, fibrinogen concentrates or cryoprecipitate. Thus, the question arises whether the main difference between the two earlier-mentioned approaches (fixed ratio protocols vs. VEA-guided protocols) is, in fact, the use of specific fibrinogen supplementation.

In ongoing obstetric hemorrhage, low fibrinogen levels are associated with severe postpartum hemorrhage[17,18]; prepartum fibrinogen levels and VEAs, however, are not predictive of postpartum hemorrhage.[19,20] While low fibrinogen levels are also associated with increased bleeding in cardiac surgeries,[21,22] VEAs do not improve the ability to predict bleeding,[23,24] and preoperative fibrinogen level does not predict future transfusion needs.[25] In hip fractures,[26] only postoperative VEAs but not preoperative ones may be a predictor of transfusion requirements.

On the other hand, VEAs have been demonstrated to effectively detect hypofibrinogenemia and serve as a guide for fibrinogen replacement.[27,28] In thromboelastometry (ROTEM), the FIBTEM assay includes cytochalasin in the TF-induced assay, a cell-permeable alkaloid interacting

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with the actin filament component of cytoskeletal networks to inhibit the platelet effect on the clot. Therefore, the result reflects the nonplatelet, TF-induced clot formation supported by fibrinogen as well as FXIII activity. F XIII activity is responsible for roughly 30% of the FIBTEM amplitude.[29] In addition, FIBTEM predicts the final strength of that clot.[30]

In healthy individuals, the FIBTEM assay has an excellent correlation with fibrinogen levels as assessed by the Clauss method[31] and, accordingly, fibrinogen plasma levels are statistically very well correlated with thromboelastographic assays.[32] The Clauss fibrinogen assay is the most often used laboratory method to measure plasma fibrinogen levels. The main advantage of the FIBTEM assay over the Clauss method is that it provides useful combined information on FVIII activity, fibrinogen concentration, and, to a lesser extent, FXIII activity within 5 to 10 minutes, while the standard laboratory assays require 30 to 60 minutes before the results are available.

Replacement therapy with coagulation factor concentrates has several advantages, such as allowing standardized doses to be rapidly administered in a small volume compared with fresh frozen plasma (FFP), which requires a larger volume to replace clotting factors that potentially lead to fluid overload. Coagulation factor replacement has a very good safety profile, as all products are being virally inactivated during the manufacturing process. The RETIC trial,[33] a single-center randomized trial, randomly allocated 48 patients to receive FFP and 52 to receive fibrinogen concentrate (FC) plus FXIII concentrate (with every second fibrinogen dose), looking for differences in transfusion requirements and development of multiorgan failure (MOF). This trial was prematurely stopped due to safety reasons in the FFP arm, as half of these patients required rescue therapy, 30% needed massive transfusion, and 66% developed MOF compared with 4, 12, and 50%, respectively, in the factor concentrates arm. The study concludes that early and effective coagulation factor supplementation, as per the study protocol, is essential when managing severe bleeding in multiple trauma.

With this whole body of evidence in the literature, there has been a change in the treatment of severe bleeding in the acute care setting in the last decade, prioritizing early and aggressive factor concentrate replacement over FFP. However, before continuing down this path, clinicians might want to answer these two questions:

1. Has fibrinogen replacement been linked to better outcomes?
2. Are VEAs fibrinogen-specific?

Regarding the first question, the CRYOSTAT-2 randomized clinical trial,[34] performed in 26 major trauma centers in the United Kingdom and the United States, has recently allocated 1,604 patients with major trauma hemorrhage to receive as early as possible cryoprecipitate ($n = 799$) versus standard care ($n = 805$). There has not been an improvement in clinical outcomes, the main target being all-cause mortality at day 28 after trauma (OR = 0.96 (95% CI = 0.75–1.23), $p = 0.74$). These patients had no fibrinogen levels measured before supplementation, but all patients in both arms received early hemostatic resuscitation and damage control surgery. This result is likely pointing out that treatment with fibrinogen as a sole factor is not as important as the whole early and coordinated damage control approach. Also, fibrinogen replacement by itself has not been shown to improve clinical outcomes in cardiac surgery, obstetrics, or liver transplant.

In relation to the second question, beyond healthy individuals, the correlation between VEAs and fibrinogen plasma levels is not uniform across the literature, suggesting that VEA results may be less specific to fibrinogen levels than frequently assumed. For example, in surgical patients, FVIII activity, and not fibrinogen, shows the highest correlation with thromboelastographic assays.[35] In the trauma setting, large interindividual variabilities have been reported, where a Fibtem A10 of 5 mm corresponds to a Clauss assay result anywhere between 0.6 and 2.0 g/L, and a Clauss result of 2 g/L to a Fibtem A10 between 5 and 15 mm.[36] Consequently, VEAs have shown a moderate correlation with fibrinogen levels in severely injured patients,[37] as well as in obstetric hemorrhage[38,39] and cardiac surgery.[40] In liver transplant, the FIBTEM assay correlates well with fibrinogen levels in the pre-reperfusion period, but not after graft reperfusion.[41] In addition, a FIBTEM assay may overestimate fibrinogen contribution to clot firmness in the presence of a high platelet count,[42] despite platelet inhibition. However, this is an unlikely scenario in a trauma setting or liver transplant, but one that may occur in cardiac surgery. Also, in this particular setting, VEAs have shown a very high negative predictive value for hypofibrinogenemia, as a FIBTEM amplitude above a defined cut-off level (usually 8 mm at 10 minutes) virtually excludes the likelihood of low plasma levels of fibrinogen. However, the positive predictive value is rather low, below 0.7.[43] To sum up, there is a varying degree of correlation between VEAs and fibrinogen levels in different clinical contexts, suggesting that VEAS believed to be relatively specific for fibrinogen indeed are probably not.

In addition, functional fibrinogen polymerization assays are not equally efficient in eliminating platelet contribution to clot strength. Therefore, they seem not uniformly accurate to evaluate the fibrinogen part of the result, with cytochalasin-D-based assays such as FIBTEM seemingly being more accurate than glycoprotein-IIb/IIIa inhibition-based assays, such as functional fibrinogen-TEG.[44]

The most relevant point, however, is assuming the (misleading) concept that clot strength is determined only by fibrinogen and platelets; misleading because activated factor XIII (FXIII), hematocrit, and FVIII all have a relevant impact on the amplitude and clot strength.[32,45,46] As said, FXIII activity is responsible for around 30% of the FIBTEM amplitude.[29] In fact, in the above-mentioned RETIC trial,[33] FXIII concentration measurements were obtained on admission, and FXIII concentrate was administered with each second fibrinogen dose and in patients with bleeding scores 2 to 3, exhibiting FXIII concentrations below 60%. By the end of the study, more than 40% of the recruited patients received FXIII concentrate (27 in the CFC group and 11 in the FFP group). In obstetric hemorrhage, the largest prospective observational study ($n = 1,309$) in which postpartum blood loss was objectively measured, FXIII was found to be the only prepartum coagulation factor associated

with postpartum blood loss, as compared with fibrinogen and prothrombin.[20] FXIII stabilizes the fibrin mesh and increases clot resistance,[47] which is why it is important that acquired FXIII deficit is common in the acute care setting and might explain the associated poorer outcomes.[48]

What is more, in the RETIC trial,[33] fibrinogen plasma levels at 48 hours after trauma increase while FXIII levels decrease at the same time point, indicating continued consumption. In the authors' clinical experience, in patients with an ongoing inflammatory response or in the prepartum setting, VEAs and fibrinogen measured by Clauss assay are usually high, and fibrinogen replacement is not required. On the other hand, FXIII has the longest half-life of clotting factors, and the transcription of the gene that regulates its synthesis is slow, inducing only a slower increase of plasma levels as compared with other coagulation factors. This seems to explain the continued evolution of FXIII deficiency over a longer period; besides the RETIC trial, more data on a correlation between time after trauma and the reduction of FXIII activity beyond 7 days after trauma have been reported.[49]

With all the available data, including some solid evidence that reduction of F XIII is associated with a poorer outcome, we want to stress that FXIII levels need to be assessed early in potential deficiency settings to avoid delays in diagnosing the deficiency and initiating replacement if necessary.[50] Indeed, in surgical patients at high risk for bleeding, the early intraoperative use of FXIII has been beneficial in reducing blood loss.[51]

To sum up, VEAs are important to detect coagulation factor deficiencies early on; unfortunately, they do not provide factor-specific measurements yet. If low fibrinogen levels (as evidenced by factor-specific assays) occur, they are associated with impaired clinical outcomes and linked to increased morbidity and mortality. However, there is so far no proof of causality between these observations, as fibrinogen levels are not predictors of bleeding or transfusion requirements, and replacing fibrinogen does not improve outcome. Thus, data available to date do not suggest that fibrinogen replacement by itself will improve outcomes. Over the last years, evidence has been accumulating that strongly suggests that acquired FXIII deficiency is very prevalent in the perioperative, perinatal, and trauma setting and that FXIII replacement can improve clinical outcome. However, early FXIII administration and FXIII threshold levels for administration are still under investigation in different clinical contexts. In the acute care setting, it is suggested to be supplemented for a trigger of 60 to 70% as levels below 40% are associated with increased morbidity and major bleeding.[50] In postpartum hemorrhage (PPH), the SWIss Factor XIII Trial in PPH (SWIFT) trial is an ongoing phase 4 study; its goal is to determine if postpartum blood loss can be reduced by replenishing coagulation factor XIII (FXIII) at an early stage of PPH.

Considering that VEA use has been associated with both reduction in blood product use and increased fibrinogen use, clinicians should be aware of the potential bias when VEAs are used to guide coagulation factor replacement therapy. A general hemostatic resuscitation approach should include early control damage and escalating hemostatic replacement, primarily based on using factor concentrates (FXIII, fibrinogen) along with optimization of predisposing factors (anemia, hypocalcemia, and hypothermia) as the first step.

Other Financial or Nonfinancial Interests

Director, HICC—Haemostasis in Critical Care GmbH.

Conflict of Interest

Potential conflicts of interests for this manuscript in the last two years exist with Takeda, Sobi and Sysmex.

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