Commentary

Coagulation Factor XIII - Last to think about?

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FACTOR XIII

Factor XIII (FXIII) is a transglutaminase that plays a crucial role in the final stages of the coagulation cascade. It stabilizes the fibrin clot by cross-linking fibrin molecules and increases clot strength, improving resistance to fibrinolysis. FXIII has a unique feature: it circulates in plasma as two catalytic subunits (FXIII-A_2) and two noncatalytic subunits (FXIII-B_2) arranged in a complex (FXIII-A_2B_2). The A subunit is synthesized in bone marrow-derived cells, and the B subunit is synthesized in the liver. The final formation of the FXIII- A_2B_2 complex occurs in the plasma[1]. The A subunit is the active form, but the B subunit protects the A subunit from proteolysis and effectively prolongs its circulating half-life (4-11 days)[2].

Katona *et al.*[3] demonstrated that the FXIII-A_2B_2 complex is the main circulating form of FXIII in plasma. However, in some body fluids (cerebrospinal fluid and tears), the FXIII-A_2 subunit is dominant (almost more than 80%)[3], indicating that FXIII is uniquely present in the body. The question remains how these differences are regulated and the primary function/role of FXIII in these different tissues and organs. Cellular FXIII is present in platelets, monocytes, macrophages, osteoblasts, chondrocytes, and adipocytes. Recent research revealed that FXIII-A_2 is not only involved in blood coagulation but also plays diverse roles in angiogenesis, maintaining pregnancy, inflammation, infection, and various diseases[4]. The entire biological distribution and all the roles of FXIII are still unknown.

ROLE OF FXIII IN THE BLEEDING

While various definitions exist for major, severe, or life-threatening bleeding, they tend to differ in aspects such as the timeframe, the volume of blood products used, and whether it should result in the activation of a massive transfusion protocol. The inconsistency in quantifying bleeding raises questions about useful and wasteful interventions.

Coagulation FXIII is a critical component of the coagulation cascade, stabilizing fibrin clots and enhancing clot strength and durability in the final stages of hemostasis[5]. Maintaining hemostatic integrity is crucial in managing bleeding patients, especially in massive hemorrhage cases where clot stability is essential for achieving hemostasis. Bleeding with ongoing thrombin generation leads to the consumption of coagulation factors, including FXIII[6].

Most current massive bleeding protocols involve administering standard hemostatic agents, such as fresh frozen plasma (FFP), platelets, and specific clotting factors, such as fibrinogen or prothrombin complex concentrates (PCC). The role of FXIII is recognized

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in the later stages of clot formation, and its deficiency is typically addressed if identified through specific laboratory tests rather than preemptive administration[7].

However, we currently lack the technology to detect FXIII coagulation status in real time. It is impressive that most coagulation assays are "silent" for FXIII coagulation status[7]. Still, some studies have shown a correlation between fibrinogen levels and FXIII concentration; TEG or ROTEM has proven adequate and beneficial for assessing FXIII activity due to FXIII deficiency[8]. In the work of Hetz, the authors demonstrated a significant increase in MCF in FIBTEM measurements in the trauma cohort and reduced maximum lysis in EXTEM measurements after the *in vitro* administration of FXIII[9].

Measuring FXIII activity levels is the only exact way to diagnose acquired FXIII deficiency; however, it is not always available and can be time-consuming.

Nevertheless, the most relevant guidelines suggest monitoring FXIII. Updated trauma guidelines suggest that monitoring FXIII activity should be included in coagulation support algorithms[10] because, initially, low levels of FXIII have been found in patients with major trauma and coagulopathy. In some European countries where cryoprecipitate is unavailable, and a clotting factor concentrates-based strategy is used, minimal factor XIII is administered. Consequently, trauma guidelines recommend replacing FXIII if its activity falls as part of coagulation support algorithms[10]. However, the optimal level of FXIII replacement in major trauma patients and optimal timing have not been clearly determined.

The use of FXIII concentrate (timing, dosing, monitoring) in other clinical guidelines is still debatable, with limited evidence supporting its recommendations[11,12].

The European Society of Anaesthesiology recommends using FXIII concentrate in cases of ongoing or diffuse bleeding and low clot strength, even when fibrinogen concentrations are adequate if FXIII activity is significantly reduced (however, the actual threshold is not defined). Also, in the presence of ongoing bleeding unresponsive to multimodal coagulation therapy or wound healing defects in critical illness, the same guidelines suggest monitoring FXIII. Still, the target level (>60%) was deleted after voting in the final version of the paper[11]. In contrast, The International Society of Thrombosis and Hemostasis (ISTH) advises against using FXIII concentrates for managing perioperative bleeding due to unproven benefits in acquired FXIII deficiency[12].

Still, no single guideline can consider the complexity of coagulation, influenced by comorbidities and injured organs. Decreased FXIII activity may occur congenitally or stem from increased turnover, consumption (trauma, bacteremia, thrombosis), or reduced synthesis levels caused by liver diseases. Also, different coagulation mechanisms can promote bleeding or thrombosis. Injured cerebral tissue may release large amounts of procoagulant phospholipids and microvesicles. In addition, cerebral endothelial von Willebrand factor (vWF) can lead to a prothrombotic state when impaired clearance by ADAMTS13 occurs[13]. Similarly, injuries to organs such as the pancreas, lung, or urogenital system can release tissue plasminogen activator (tPA), leading to fibrinolysis and promoting bleeding[14].

Consequently, major hemostatic interventions should consider the underlying causative injury state and each patient's characteristics to be fully effective.

WHY NOT?

When major bleeding occurs, the body activates its hemostatic response to prevent further blood loss. This response involves the rapid activation of the coagulation cascade to form clots at the injury site. Significant bleeding can induce a hypercoagulable state characterized by an increased tendency for clot formation due to elevated levels of procoagulant factors, reduced levels of anticoagulants, and impaired fibrinolysis. Inflammation, tissue injury, and endothelial damage contribute to this hypercoagulable state, promoting thrombus formation.

In the case of hypovolemic shock from massive bleeding, the bleeding phenotype progresses to a thrombotic one with reduced blood flow and stasis, particularly affecting the microcirculation, with an increased risk for thrombosis[15]. According to Virchow's triad (stasis, endothelial injury, and hypercoagulability), this clinical situation is a well-known risk factor for thrombotic complications. Further, proinflammatory cytokines have been shown to amplify clot formation in severe injury and extensive tissue damage by increasing thrombin generation and worsening endotheliopathy[15]. Therefore, current protocols[10-12] emphasize a balanced approach to managing coagulopathy, avoiding the indiscriminate use

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of any single hemostatic agent. Consequently, despite a good safety profile, we are unsure if there is a risk of excessive clotting and thrombotic complications from premature administration of FXIII.

WHY DO AND WHY EARLIER?

In cases of trauma or surgical-related bleeding, a reduction in FXIII activity levels below 60-70 % may increase blood loss and the need for transfusion. Administration of FXIII concentrates on major trauma patients with ongoing bleeding as part of a goal-directed transfusion protocol, reducing the proportion of patients requiring massive transfusions[16]. Factor XIII supplementation may improve hemostasis, wound healing, and overall outcome while reducing the patient's exposure to blood products in trauma[17].

It has been proven that FXIII activity is already lowered during the early phase of hemorrhagic shock because it is rapidly consumed by massive bleeding[18]. Available sources of FXIII include FFP and cryoprecipitate. FFP contains clotting factors, including FXIII, though in lower concentrations, and cryoprecipitate, derived from plasma, offers a more concentrated source of FXIII (**Figure 1**). Cryoprecipitate, though beneficial in treating severe bleeding, carries risks such as infection and allergic reactions, as it is usually pooled from multiple donors. Their role in FXIII replacement diminishes as specific FXIII concentrates become available. However, the availability of FFP and cryoprecipitate varies significantly across regions. High-income countries often have better access to FXIII concentrates due to their higher efficacy, controlled dosing, and lower risk of adverse effects. In contrast, low- and middle-income countries may rely more on cryoprecipitate (for safety reasons, pathogen-reduced or virus-inactivated) due to cost constraints and limited availability of FXIII concentrates. Neither plasma transfusions nor cryoprecipitate transfusions adequately maintained FXIII levels throughout resuscitation[18].

There are differing opinions and experiences regarding the timing and potential effects of FXIII deficiency in major trauma. Some believe that FXIII deficiency could be a late complication of major trauma, typically occurring 2-3 weeks after, due to hepatic dysfunction. On the other hand, some argue that FXIII deficiency occurs 3-7 days after trauma, especially in cases of major surgery. However, it's worth noting that one-third of trauma patients have FXIII activities of less than 60% upon admission, which is associated with the amount of blood loss, suggesting that reduction in FXIII activity decreases immediately after the initial trauma[19,20].

In the RETIC trial[19], 27 out of 50 patients (54%) in the interventional group had plasma FXIII levels below 60% and experienced either diffuse microvascular bleeding or massive bleeding requiring transfusion of more than three units of red blood cells (RBC) per hour. In a Swiss

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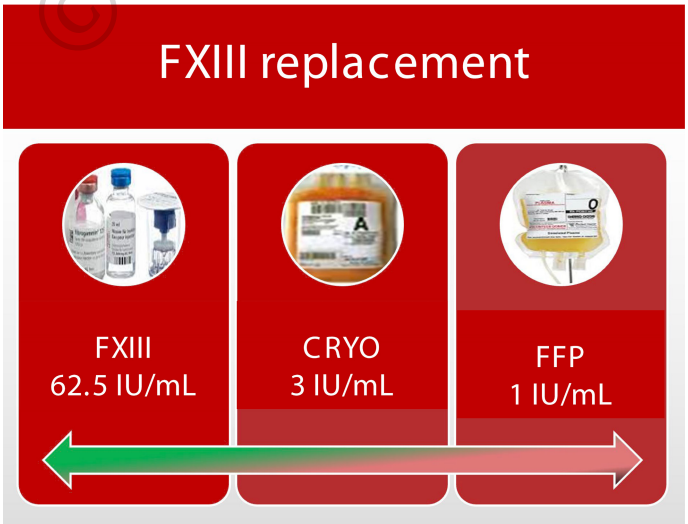


Figure 1 - FXIII replacement

observational study, using a target hematocrit range led to increased use of FXIII (15 out of 172 patients [9%] compared to 6 out of 172 [3.5%], p=0.004). This approach also decreased the proportion of patients needing RBC transfusions (11.6% *vs* 29.7% of patients, p<0.001) and the total number of transfusions[20]. However, in both studies, FXIII was part of a combined approach, and the specific impact of individual components could not be determined. In an observational study, a multivariate analysis revealed that reduced FXIII activity (59-71%) was independently associated with surgical re-exploration and increased 30-day mortality[21]. FXIII deficiency was linked to higher transfusion requirements in ECMO patients and identified as an independent risk factor for major bleeding events[22]. The association between major bleeding and FXIII has been reported in many studies.

A high degree of injury, as well as the increased need for a blood transfusion, made the patients susceptible to a low FXIII level. In addition to following major hemorrhage protocols for early resuscitation, administering hemostatic therapies promptly based on the severity and nature of coagulation deficits may allow for a targeted and personalized approach to correcting coagulopathy[9].

If there is extensive tissue damage, FXIII can help as a "molecular surgeon", with its additional beneficial effects on wound healing[4,11].

CONCLUSION

What is the rationale for current FXIII recommendations?

Limited high-quality clinical evidence demonstrates the benefits of early FXIII administration in massive bleeding. While massive bleeding can trigger thrombosis due to the body's hemostatic response, the early administration of FXIII is still not standard practice due to the lack of robust clinical evidence, the complexity of hemostatic management, and the potential risks associated with its use. Further research may elucidate specific scenarios where early FXIII administration could be beneficial, but its use remains targeted and based on specific clinical indications.

Considering FXIII's pivotal role in ensuring robust clot formation and stability, healthcare providers are encouraged to weigh the benefits of early FXIII administration in bleeding patients, particularly those at high risk of persistent bleeding or clot disruption. In this sense, authors recommend including FXIII assessment and replacement in an escalating scheme of hemostatic therapies in the acute care setting. However, the target population and the level of FXIII required to achieve hemostasis in each individual situation remain to be elucidated.

Additional clinical studies are required to determine the appropriate population, timing, dosing interval, and outcomes when using FXIII for uncontrollable bleeding (**Figure 2**). Methodological considerations related to study

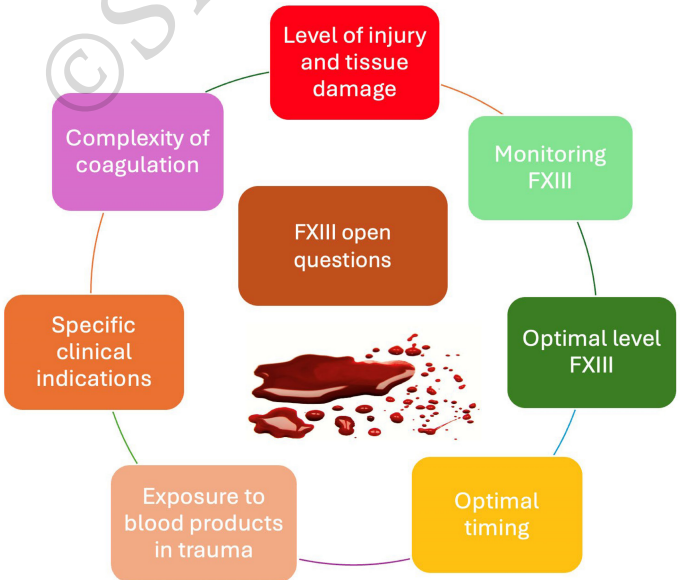


Figure 2 - FXIII open questions

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designs for assessing the timing of FXIII administration need to be addressed. These study protocols should be validated, refined in suitable multicenter trials, and monitored using large registry databases. Until then, we will depend on our decisions based on clinical situations and experience.

AUTHORS' CONTRIBUTION

All Authors contributed equally to the preparation of the paper.

The Authors declare no conflicts of interest.

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