Published in final edited form as:

Haemophilia. 2019 November ; 25(6): e377–e378. doi:10.1111/hae.13855.

Mechanistic Rationale for Factor XIII Cotreatment in Hemophilia

Joan D. Beckman^{*}, Alisa S. Wolberg[†]

^{*}Department of Medicine, Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, Minnesota, United States

[†]Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, Chapel Hill, United States

Refractory bleeding in patients with hemophilia A (HA) due to the absence, deficiency, or inhibition of factor VIII (FVIII) remains a prominent clinical challenge.^{1–3} Use of factor concentrates reduces bleeding through the ability to promote thrombin generation, however complete resolution of major bleeding typically requires several days of therapy.² Furthermore, the presence of inhibitors to FVIII in patients with congenital HA (CHA) or acquired HA (AHA) reduces or eliminates the benefit of factor concentrates. Bypassing therapies, which include activated prothrombin complex concentrate [APCC], recombinant activated factor VII [rFVIIa], or recombinant porcine FVIII [rpFVIII], are approved for inhibitor patients, but also may not completely resolve bleeding, leading to prolonged hospitalization, pain, and other serious complications.^{3,4} When bleeding is refractory despite therapy, many clinicians use multiple overlapping hemostatic therapies that may increase risk of thrombotic complications.^{3,4} Therefore, strategies to safely and effectively treat refractory bleeding in patients with AHA or CHA with inhibitors are desirable.

In a recent case series of patients with AHA or CHA¹, Abdulrehman *et al* identified co-existing factor XIII (FXIII) deficiency in 4 of 5 AHA patients and 3 of 15 CHA patients that was most likely attributable to consumption of plasma FXIII. Administration of plasma-derived FXIII was associated with improved clinical outcome in 3 of the AHA patients whom demonstrated cessation of bleeding after concurrent administration of plasma-derived FXIII with hemostatic therapies (APCC, rFVIIa, or rpFVIII). These observations echo previous findings by Ng *et al* whom observed reduced bleeding and clinical improvement following sequential administration of rFVIIa and plasma-derived FXIII to a severe CHA patient with inhibitor.³

We note these observations with interest, as they provide a translational bridge to *in vitro* data from our group and others suggesting co-administration of FXIII with replacement or bypassing therapies enhances hemostatic capacity in HA.^{5–8} Briefly, based on the observation that FXIII activation is delayed in hemophilic whole blood⁹, several *in vitro*

Address correspondence to: Alisa S. Wolberg, PhD, 8018A Mary Ellen Jones Building, CB#7035, Chapel Hill, NC 27599-7035, alisa_wolberg@med.unc.edu, Phone: (919) 962-8943.

Authorship Contributions

JDB and ASW wrote the manuscript.

Disclosures of Conflicts of Interest

The authors have no other conflicts of interest.

studies subsequently showed hemostatic effects from cotreatment of hemophilia plasma or whole blood with FXIII and rFVIIa or FVIII, compared to rFVIIa or FVIII, alone.^{5–8} Effects included accelerated FXIII activation, increased clot density, decreased clot permeability, and improved clot stability^{5–8}, each of which are associated with enhanced hemostatic capacity.¹⁰ More recently, using platelet-poor plasma and whole blood from CHA patients with inhibitors and AHA patients, we showed that although FXIII cotreatment with hemostatic agents does not alter thrombin generation, it accelerates and increases α -chain crosslinking, including increased α_2 -antiplasmin crosslinking to fibrin and formation of high molecular weight crosslinked fibrin species.⁵ Consistent with the observation that α -chain crosslinking promotes RBC retention in contracted whole blood clots¹¹, we also showed that cotreatment of HA whole blood with FXIII plus FEIBA, rFVIIa, or rpFVIII increases red blood cell retention in clots and consequently, enhances contracted whole blood clot weight⁵, restoring clot weight to that of healthy subjects without HA.

Abdulrehman *et al* detected a high incidence of FXIII deficiency (80%) in patients with AHA¹, providing rationale for FXIII cotreatment to reduce refractory bleeding in these patients. However, the incidence of FXIII deficiency was lower in patients with CHA¹, raising questions about the potential value of FXIII treatment in patients with normal FXIII. In general, thromboelastography (TEG) is not used to diagnose or manage FXIII deficiency; however, published literature and our own unpublished data demonstrate that when FXIII levels are low (~50% or lower), TEG exhibits decreased maximum amplitude and increased lysis, reflecting decreased fibrin crosslinking.^{12,13} Although we did not explicitly measure plasma FXIII concentrations in our twelve patient samples, we did not observe TEG measurements suggestive of low FXIII levels.⁵ Nonetheless, co-administration of 2 U/mL FXIII with conventional hemostatic therapies still demonstrated enhanced hemostatic effects. This ability of increased FXIII to enhance FXIII activation is consistent with the premise that the K_m of thrombin-dependent FXIII activation is higher than the plasma FXIII concentration. Thus, increasing plasma FXIII accelerates the thrombin-dependent activation and activity of FXIII(a) even when plasma FXIII is normal. As our group and Abdulrehman *et al* have noted, the technical challenges and relatively limited availability of quantitative tests for FXIII may limit ability to quickly establish baseline FXIII levels in patients with refractory bleeding.^{1,14} However, our preliminary data suggest one could consider FXIII cotreatment without knowledge of baseline FXIII during emergencies in at-risk patients.

Given these findings, FXIII cotreatment may offer several therapeutic advantages for patients, irrespective of plasma FXIII concentrations. First, as highlighted by Abdulrehman *et al*¹, plasma FXIII is often reduced, wherein replacement would be important for clot stability and normal hemostatic function. Second, FXIII does not increase thrombin generation^{5,6}, and in the absence of sufficient thrombin generation, even supraphysiologic FXIII does not increase fibrin formation or FXIII activation.⁵ Accordingly, FXIII administration has not been associated with thromboembolic events¹⁵, mitigating concerns about thrombotic risk if used with hemostatic agents (FVIII, APCC, rFVIIa, or rpFVIII). Third, except in cases of FXIII consumption, FXIII has a relatively long half-life (9–19 days), potentially simplifying dosing to reduce bleeding events. Fourth, FXIII does not require renal or hepatic metabolism, which would be advantageous in older patients with

comorbidities, a group most commonly afflicted with AHA. Consequently, FXIII cotreatment with hemostatic therapies is a potentially attractive treatment strategy for reducing refractory bleeding in hemophilia.

In conclusion, together with findings from *in vitro* and *ex vivo* studies^{5–8}, the case series^{1,3} provide strong support for the use of FXIII cotreatment with conventional hemostatic agents in hemophilia. Regardless of baseline FXIII levels, co-administration of FXIII may accelerate FXIII activation and consequently, enhance fibrin and α_2 -antiplasmin crosslinking and promote hemostasis. Continued discussion regarding the merits, safety, and feasibility of FXIII cotreatment for hemophilic patients with refractory bleeding is warranted.

Acknowledgements

Work discussed in this letter was supported by research funding from the National Institutes of Health (R01HL126974 to ASW and T32HL007149 to the University of North Carolina and JDB) and a 2016 Mentored Research Award from the Hemostasis and Thrombosis Research Society (HTRS) to JDB which was sponsored by an educational grant to HTRS from CSL Behring.

Work discussed in this correspondence was supported by research funding from a 2016 Mentored Research Award from the Hemostasis and Thrombosis Research Society (HTRS) to JDB which was sponsored by an educational grant to HTRS from CSL Behring. CSL Behring provided funds to HTRS for the Mentored Research Award program but had no input into selection of awardees. CSL Behring had no direct interaction with the authors regarding the design or results of the study. ASW has research funding from Novo Nordisk outside the submitted work.

References

1. Abdulrehman J, Houston BL, Chaudhry H, Rivard G-E, Teitel JM, Sholzberg M. Acquired haemophilia A and concomitant factor XIII consumption. *Haemophilia*. 2019;25(3):e180–e183. [PubMed: 30843631]
2. Dargaud Y, Lienhart A, Negrier C. Prospective assessment of thrombin generation test for dose monitoring of bypassing therapy in hemophilia patients with inhibitors undergoing elective surgery. *Blood*. 2010;116(25):5734–5737. [PubMed: 20810929]
3. Ng C, Silliman CC, Pearl G, Smith W, Manco-Johnson M, Wang M. Treatment of refractory hemorrhage with Factor XIII in a patient with hemophilia A with inhibitor. *Pediatr Blood Cancer*. 2013;60(7):E23–25. [PubMed: 23382082]
4. Gringeri A, Fischer K, Karafoulidou A, Klamroth R, Lopez-Fernandez MF, Mancuso E. Sequential combined bypassing therapy is safe and effective in the treatment of unresponsive bleeding in adults and children with haemophilia and inhibitors. *Haemophilia*. 2011;17(4):630–635. [PubMed: 21323801]
5. Beckman JD, Holle LA, Wolberg AS. Factor XIII cotreatment with hemostatic agents in hemophilia A increases fibrin alpha-chain crosslinking. *J Thromb Haemost* 2018;16(1):131–141. [PubMed: 29080382]
6. Rea CJ, Foley JH, Sorensen B. Factor XIII in the treatment of hemophilia A. *N Engl J Med* 2012;366(3):281–283. [PubMed: 22256823]
7. Rea CJ, Foley JH, Ingerslev J, Sorensen B. Factor XIII combined with recombinant factor VIIa: a new means of treating severe hemophilia A. *J Thromb Haemost* 2011;9(3):510–516. [PubMed: 21155966]
8. Rea CJ, Foley JH, Okaisabor O, Sorensen B. FXIII: mechanisms of action in the treatment of hemophilia A. *J Thromb Haemost* 2014;12(2):159–168. [PubMed: 24354581]
9. Brummel-Ziedins KE, Branda RF, Butenas S, Mann KG. Discordant fibrin formation in hemophilia. *J Thromb Haemost* 2009;7(5):825–832. [PubMed: 19192107]

10. Wolberg AS. Plasma and cellular contributions to fibrin network formation, structure and stability. *Haemophilia*. 2010;16 Suppl 3:7–12.
11. Byrnes JR, Duval C, Wang Y, et al. Factor XIIIa-dependent retention of red blood cells in clots is mediated by fibrin alpha-chain crosslinking. *Blood*. 2015;126 (16):1940–1948. [PubMed: 26324704]
12. Theusinger OM. The inhibiting effect of factor XIII on hyperfibrinolysis. *Anesth Analg*. 2012;114(6):1149–1150. [PubMed: 22615440]
13. Theusinger OM, Baulig W, Asmis LM, Seifert B, Spahn DR. In vitro factor XIII supplementation increases clot firmness in Rotation Thromboelastometry (ROTEM). *Thromb Haemost*. 2010;104(2):385–391. [PubMed: 20431856]
14. Beckman JD, Kasthuri RS, Wolberg AS, Ma AD. Challenges in diagnosis and management of acquired factor XIII (FXIII) inhibitors. *Haemophilia*. 2018;24(6):e417–e420. [PubMed: 30144219]
15. Ashley C, Chang E, Davis J, Mangione A, Frame V, Nugent DJ. Efficacy and safety of prophylactic treatment with plasma-derived factor XIII concentrate (human) in patients with congenital factor XIII deficiency. *Haemophilia*. 2015;21(1):102–108. [PubMed: 25377187]