Case Study

Successful Use of Four Factor-Prothrombin Complex Concentrate for Congenital Factor X Deficiency in the Setting of Neurosurgery

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ABSTRACT

Congenital factor X deficiency is an extremely rare coagulation disorder that can place patients at risk for spontaneous hemorrhage or excessive bleeding in the setting of trauma or invasive procedures. Given the rarity of this disorder, there is little published guidance on how best to prevent or treat bleeding. Herein, we report a case of a 56-year-old white man with congenital factor X deficiency who was scheduled for major neurosurgery and who was treated perioperatively with 4-factor prothrombin complex concentrate (4F-PCC). Doses of 4F-PCC at 15 U per kg, administered immediately preoperatively and once at 24 hours

postoperatively, allowed for successful completion of an anterior cervical discectomy and fusion without excessive bleeding. Moreover, no thromboembolic complications were observed. As such, given the wide availability of 4F-PCC, it may be considered as a first-line therapy and an alternative to fresh frozen plasma for factor X deficiencies, particularly in high-risk operative cases.

Keywords: Congenital factor X deficiency, prothrombin complex concentrate, neurosurgery, transfusion medicine, blood banking, coagulation

Congenital factor X (FX) deficiency is an exceedingly rare coagulation disorder that has been associated with moderate to severe bleeding that occurs spontaneously, with trauma or pregnancy, or during surgical interventions.¹ Historically, fresh frozen plasma (FFP) had been a mainstay of therapy in the United States for treatment or prevention of bleeding associated with FX deficiency.¹ With the United States Food and Drug Administration (FDA) approval of a 4-factor prothrombin complex concentrate (4F-PCC; containing therapeutic levels of factors II, VII, IX, and X)² in 2013, as well as a purified FX concentrate approved in late 2015,³ there are now several more specific therapeutic options available. However, there have been few published

reports of use of factor concentrates in managing the health of adults with congenital FX deficiency, particularly in the surgical setting.^{2,4,5} Moreover, there is virtually no guidance available in the literature on how best to proceed in bleeding prophylaxis in the neurosurgical setting for such patients. Herein, we report our experiences with the use of 4F-PCC to correct coagulation abnormalities before a neurosurgical procedure in the setting of congenital FX deficiency.

Case Report

The patient is a 56 year old white man with multiple neurological problems (including upper extremity numbness and poor dexterity) attributable to cervical-spine disc herniation at the C3/C4 level. His medical team recommended that he undergo anterior cervical discectomy and fusion (ACDF), to improve his neurological function. During routine preoperative screening, the patient was found to have prolongations of prothrombin time (PT, 17.7 seconds; range, 10.4-12.7 seconds) and partial thromboplastin time (PTT; 39.6 seconds; range, 23.6-37.6 seconds). The results of his remaining laboratory studies, including a complete blood count, a basic metabolic profile, and a platelet function analysis, revealed no other abnormalities. After subsequent,

Abbreviations

FX, congenital factor X; FFP, fresh frozen plasma; FDA, United States Food and Drug Administration; 4F-PCC, 4-factor prothrombin complex concentrate; ACDF, anterior cervical discectomy and fusion; PT, prothrombin time; PTT, partial thromboplastin time; 3F-PCC, 3-factor prothrombin complex concentrate

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Table 1. Preoperative Laboratory Coagulation Results Obtained During the Initial Evaluation of Our Patient, a 56-Year-Old White Man

Coagulation Test	Result	Reference Range
PT	17.7 s	10.4-12.7 s
PTT	39.6 s	23.6-37.6 s
PT mixing study (immediate)	11.9 s	10.4-12.7 s
PTT mixing study (immediate)	33.6 s	23.6-37.6 s
Fibrinogen	311 mg/dL	150-400 mg/dL
Factor II activity	98%	70%-150%
Factor V activity	106%	65%-150%
Factor X activity	25%	70%-150%
Thrombin time	19 s	12-19 s
Lupus anticoagulant screen	Negative	Negative

PT, prothrombin time; PTT, partial thromboplastin time

Table 2. Coagulation Studies in Our Patient, a 56-Year-Old White Man, Before and 90 Minutes after Dosing 10 U/kg 4-Factor Prothrombin Complex Concentrate^a

Coagulation Test	Patient's Results Before 4F-PCC Administration	Results 90 Minutes After 4F-PCC Administration
PT	17.5 s	12.0 s
PTT	38.1 s	29.5 s
Factor X activity	25.0%	51.4%

4F-PCC, 4-factor-prothrombin complex concentrate; PT, prothrombin time; PTT, partial thromboplastin time

^aThe patient was administered a limited amount of 4F-PCC during a preoperative trial run to confirm the safety and efficacy of the substance in this case.

extensive laboratory coagulation evaluation was performed (the results of which are detailed in **Table 1**), the only significant abnormality noted was decreased FX levels. On further questioning, the patient revealed no history of spontaneous bleeding but indicated that he required multiple blood products after a past surgical procedure occurring outside our facility; he was never formally told at that time that he had a discrete bleeding disorder.

Given the new laboratory coagulation results presented in **Table 1** and the additional history of significant bleeding requiring transfusion after a previous surgical procedure, a diagnosis of congenital factor X deficiency was firmly established. Before the scheduling of the ACDF, the medical team consulted the blood bank for recommendations on FX replacement. Although FFP was initially discussed, the blood bank staff and the medical team ultimately decided that administration of 4F-PCC (Kcentra, CSL Behring) would be the optimal approach in this case. Because of the limited

literature regarding 4F-PCC for surgical interventions in FX deficiency,² we planned a presurgical 4F-PCC, to ensure its safety and efficacy. Based on the patient's weight (100 kg) and the typical content of FX in 4F-PCC (25-51 U/mL),² a 10 U/kg dose (1000 U) was administered 30 days before the operation, with the expectation of achieving approximately 50% FX activity with such dosing. The patient showed significant improvement in the results of his abnormal coagulation studies in this 4F-PCC trial run (detailed in **Table 2**), with no clinical adverse effects or thromboembolic issues noted.

Once the presurgical trial run was completed, the actual strategy for the day of the operation was slightly modified to include a modestly higher 15 U per kg (1500 U) dose of 4F-PCC, with a planned, second 1500U dose the morning after the operation. This mildly increased dosage was administered to ensure FX activity far in excess of 50% during the operation, while the administration of an additional 4F-PCC dose on postoperative day 1 was intended to help promote hemostasis for 36 to 48 hours after surgery. Ultimately, with this approach, the patient tolerated the ACDF well, and less than 30 mL of blood loss was reported during the operation. The patient required no red blood cell or FFP transfusions and maintained a stable neck circumference. He was discharged to his home 3 days after the completion of the operation without any reports of complications at the surgical site and without evidence of any thrombotic complications from 4F-PCC administration. Although repeat FX levels were not ordered postoperatively, serial standard coagulation tests were performed over the course of the patient's stay in the hospital. During this time, the PT/PTT of the patient stayed within normal range for more than 48 hours after the operation, consistent with the reported 20- to 40-hour half-life of FX.¹

Discussion

This report highlights the successful use of 4F-PCC in managing a neurosurgical procedure in a patient with congenital FX deficiency. Nevertheless, after the diagnosis of FX deficiency was established in our patient, we did not immediately or easily reach the decision to administer 4F-PCC. In fact, the best approach to achieve durable hemostasis during and after the patient's procedure was unclear to many members of the treatment team. To best evaluate all the options available, the blood bank and clinical teams held a conference to discuss all potential options.

Initially, the clinical team assumed that FFP would be the best mode of therapy. However, given a goal of attaining greater than 50% FX activity in this case, FFP would be associated with many limitations, including variable levels of FX from donor unit to donor unit, the volume of product needed to sustain such levels during and after the operation, and the potential for transfusion-associated adverse events associated with plasma infusion (particularly, the large-volume plasma infusion anticipated in this case).

Given these limitations of FFP, we discussed factor concentrates as treatment options. Because our blood bank does not carry 3-factor prothrombin complex concentrate (3F-PCC; containing therapeutic levels of factors II, IX, and X), we did not further consider administering it to our patient, although theoretically, it could have been used.² We had performed the ACDF procedure before a purified FX concentrate was commercially available in the United States,³ so using such a concentrate also was never considered. Instead, our focus was on 4F-PCC.

Many members of the clinical service had not conceived of 4F-PCC as a therapeutic choice for our patient, possibly because of its strong association with warfarin reversal. Once we discussed use of this product, it became clear that this was the ideal option for our patient. First, there is a relatively known quantity of FX in each dose/vial of 4F-PCC, with much less variation in factor levels than would be the case with randomly selected plasma units. Moreover, our calculations showed that achieving FX levels of greater than 50% for the operation would require a relatively small dose of 4F-PCC, versus the large volumes of FFP that would be required. Finally, the fact that this product is virally inactivated was also reassuring regarding the risk for transfusion-transmitted diseases in our patient.

Although 4F-PCC was successfully used in this case, it conveys certain risks. As noted earlier herein, FX deficiency is not a specific on-label indication for 4F-PCC administration, and its safety and efficacy in this setting are not well established.² Despite the presence of vitamin K-dependent anticoagulants in the formulation (ie, protein C and protein S), 4F-PCC has been associated with thromboembolic complications.^{6,7} This fact was our most significant concern in the use of 4F-PCC for our patient; we weighed carefully the many benefits of this treatment against this risk. As such, the preoperative trial run that we performed not only served as a test to ensure that we achieved the

expected increment in FX, but we also used it as a means to assess the safety profile of 4F-PCC in our patient. If the patient had had other risk factors for thrombosis, or if he had undergone a less-invasive or less-risky surgical procedure, we likely would have used FFP instead.

In general, the determination to use 4F-PCC for FX deficiency should be made on a case-by-case basis. Medical teams should carefully consider the risk of bleeding for the procedure, the urgency with which the case is to be performed, and whether some other alternative(s) may be available.

In summary, this case study highlights the potentially important role that 4F-PCC can play in hospital blood banks and transfusion services. Given the extreme rarity of FX deficiency, it is unlikely that many hospitals will routinely stock a purified FX concentrate, even at dedicated hemophilia centers. Moreover, the stocking of products such as 3F-PCC is diminishing nationwide because of the general limited utility of those products.² However, 4F-PCC (which is widely employed for warfarin reversal)² can be considered as a reasonable alternative to FFP for FX-deficient patients, particularly in cases in which there is an urgent need for intervention or very large volumes of plasma would be required. **LM**

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