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Prothrombin Complex Concentrate Such as Therapy and Prophylaxis in Factor X-Deficient Patient (Friuli Variant)

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Abstract

Background: Factor X (FX) deficiency is a serious, rare bleeding disorder, with 1 in 500 000 affected people. Hemorrhages, hematuria, epistaxis, and other bleeding complications are frequent. Case Report: Now, we report a case of a well-known 77-year-old FX-deficient patient (Friuli variant, level <1%, mutation $Pro^{343} \rightarrow Ser$, exon VIII) with hypertension, chronic obstructive pulmonary disease (COPD), and chronic gastritis, admitted many times to hospital due to surgical complications after aortic abdominal aneurysm (AAA) repair. Use of prothrombin complex concentrate (PCC) such as hemostatic therapy during surgeries and prophylaxis after discharge is shown in this article. Three consecutive surgeries were considered. First, endoleak postendoprosthesis; second, AAA breakage; and third, planned surgery, a new endovascular prosthesis positioning and femur-femoral bypass. No adverse events due to PCC were found by local physicians. Discussion: We discuss the methods commonly used in the treatment and prophylaxis of patients with FX deficiency to reduce hemorrhagic risk and to improve their quality of life. Conclusion: Waiting for specific therapeutic options for FX deficiency, currently, the best treatment is represented by PCC. Its correct use permits an improvement in life quality and a reduction in bleeding frequency in FX-deficient patients.

Keywords

factor X deficiency, factor X—Friuli variant, bleeding disorders, prothrombin complex concentrate, thromboprophylaxis

Introduction

Factor X (FX) deficiency is a bleeding disorder that may be inherited or acquired. The incidence of FX disease is estimated at 1 in 500 000 births,[1-3] this disorder is one of the most rare coagulation factor deficiencies. Males and females are equally affected, racial and ethnic predilections are unknown. Factor X deficiency has been identified in the 1950s by 2 independent groups (Stuart-Prower factor).[4] Factor X, a serine protease vitamin K dependent, produced in the liver, is the first enzyme in blood coagulation.[5] Its active form (FXa) turns prothrombin into thrombin, which produces active fibrinogen, thus allowing the clot formation. Inherited deficiency is autosomal recessive, the heterozygous often remain asymptomatic, instead the homozygous have hematoartroses,[6] soft tissue hemorrhages,[6,7] hematuria,[8] menorrhagia,[9,10] epistaxis,[6] and other bleeding complications.[5] Acquired deficiency may be caused by severe liver disease, vitamin K deficiency, or oral anticoagulants.[11] Sometimes, a variety of medical conditions are associated with FX disorder. Treatment of FX deficiency is very important to restore normal hemostasis, but currently there are no specific products. Plasma exchange,[12] infusion of fresh frozen plasma (FFP), infusion of prothrombin complex concentrate (PCC), and administration of vitamin K[13,14] are the most common treatments. The quality and duration of life in patients with FX deficiency depend on the etiology and severity of the disorder.

Case Report

A 77-year-old man, a well-known patient with serious FX deficiency, level <1% (Friuli variant, mutation $Pro^{343} \rightarrow$ Ser, exon VIII), hypertension, chronic obstructive pulmonary disease (COPD), and chronic gastritis, previously treated with endoprosthesis, was admitted several times to the General University Hospital of Udine for endoleak, breakage of AAA, abdominal and lumbar pain, renal insufficiency, and positioning of a new endovascular prosthesis. Now we report our experience in the use of PCC (Uman Complex D.I. 500 IU, Kedrion S.p.A.–Castelvecchio Pascoli (LU), Italy) before, during, and

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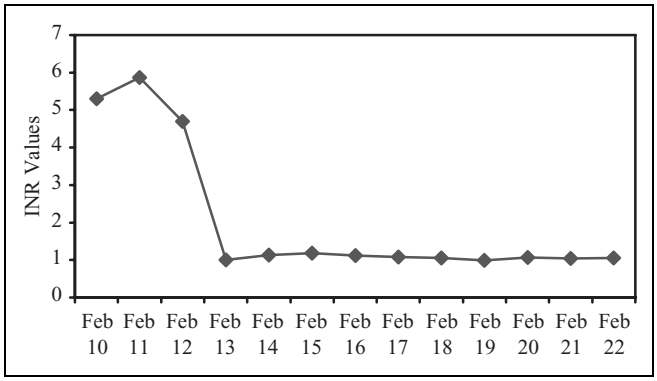

Figure 1. Reduction in international normalized ratio (INR) after PCC administration.

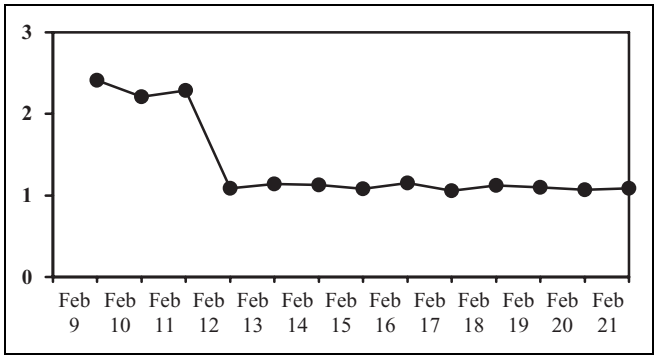

Figure 2. Reduction in activated partial thromboplastin time (aPTT) after prothrombin complex concentrate (PCC) administration.

after 3 consecutive surgeries and its use during prophylaxis as in this FX-deficient patient.

On February 10, 2006, the patient was admitted to our surgical department for endoleak postendoprosthesis, performed in 2002 at the General Hospital of Pordenone. At the time of hospitalization, international normalized ratio (INR) was 5.30, which decreased to 4.70 two days later when the intervention was planned. Hemostatic therapy before surgery is commonly recommended in patients with serious coagulation deficiencies to avoid bleeding risk and consequent hemorrhagic shock. First, 12 mL/kg FFP, 2 hours before, and then, 60 IU/kg PCC, 1 hour before surgery, were administered to the patient. After treatment, INR and activated partial thromboplastin time (aPTT) decreased to 1.00, allowing the surgical intervention on February 13. After surgery and for 3 consecutive days, 30 IU/kg PCC and 0.2 mL calcic nadroparin (Seleparina, Italfarmaco S.p.A.–Cinisello Balsamo (MI), Italy or Fraxiparina, GSK–Verona, Italy), necessary to prevent postsurgical venous thromboembolism (VTE), were administered to the patient every 12 hours; 1000 mg tranexamic acid (Tranex, Lusofarmaco S.p.A.) was administered every 8 hours, when INR and aPTT were in normal range, PCC was reduced to 10 IU/kg and administered every 6 hours.

This treatment was maintained for 7 days. On February 22, the patient was discharged; hemostasis and vital functions were

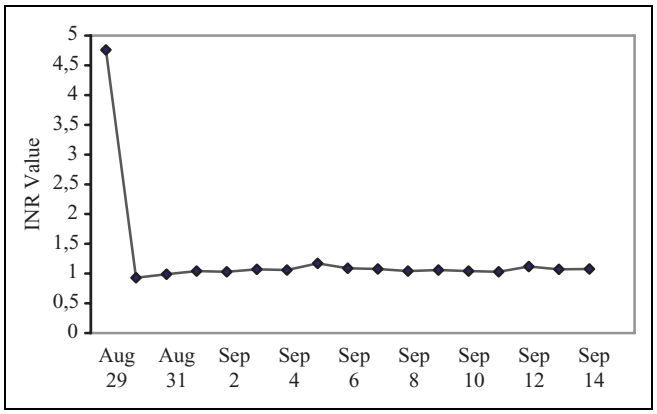

Figure 3. Rapid decrease in international normalized ratio (INR) after PCC administration.

normalized (Figures 1 and 2). No prophylactic therapy was administered at home.

On May 23, 2006, the patient was readmitted to the General University Hospital of Udine for breakage of AAA, renal insufficiency, and hemorrhagic shock. On the day of hospitalization, INR was 1.2, aPTT ratio 1.54, and aPTT time 31.9 seconds; before aorto-bifemoral bypass surgery, 50 IU/kg PCC was administered to the patient.

Postsurgery, and for 15 days, 10 IU/kg PCC and 500 mg tranexamic acid were administered to patient every 6 hours; 0.2 mL calcic nadroparin was administered every 12 hours. During the treatment with PCC, mean INR value was 1.33 (1.14-1.55), mean of aPTT ratio was 1.50 (1.32-1.65), and mean of aPTT time was 31.1 seconds (27.2-33.8).

On the fifth day after surgery, INR and aPTT ratio increased, reaching, respectively, 1.55 and 1.49; to reinstate to the normal range, another 10 IU/kg PCC was administered to the patient. Two days later, the physicians decided to transfuse 2 U of packed red blood cells (RBCs), because of a low level of hemoglobin (10.3 g/dL). The patient had complained about administering the hemostatic therapy.

The 15th day after surgery, hemostatic therapy was stopped, but the patient was not discharged due to a renal, cardiovascular, and respiratory insufficiency. Three days later, a breakage in aorto-bifemoral bypass prosthesis obliged the patient to a new intervention. Before suture surgery, to prevent bleeding, 10 IU/kg PCC and 500 mg tranexamic acid were administered every 6 hours; 0.2 mL calcic nadroparin was administered every 12 hours. The same treatment was maintained for the following 7 days. When the patient was discharged, hemostatic therapy was stopped, INR and aPTT were in normal range. During hospitalization, the concentration of FX (%) was monitored; mean 44 (26-68).

Two months later, the patient was hospitalized again for hemorrhagic shock in endoprosthesis site, INR value was 4.76; therefore, 60 IU/kg PCC was administered to stop hemorrhage and to bring INR and aPTT in normal range (Figures 3 and 4). To maintain normal hemostasis by reducing bleeding risk, 15 IU/kg PCC and 1000 mg tranexamic acid were

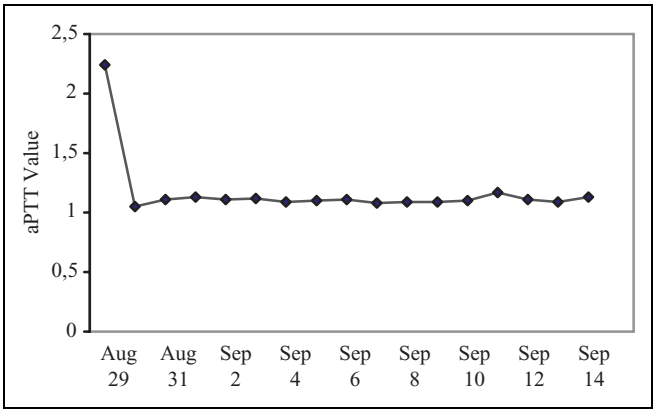

Figure 4. Rapid decrease in activated partial thromboplastin time (aPTT) after prothrombin complex concentrate (PCC) administration.

administered to the patient, every 8 hours. After a fortnight, the therapy was discontinued and the patient came back home. The fifth day after hemorrhage and subsequent hospitalization, a single administration of AT, 1500 IU, was infused to the patient because AT was decreased below the normal range (70%-140%).

Once discharged, prophylactic therapy was established in 60 IU/kg PCC, a single administration, weekly, and 1000 mg tranexamic acid, every 8 hours. After discharge, daily, and subsequently every 20 days, INR, aPTT, and plasmatic FX were monitored; mean INR 1.10 (1.02-3.17), mean aPTT 1.16 (1.07-1.74), and mean FX 3.25% (2-8).

Five months later, on January 29, 2007, the patient was admitted again to our surgical department for a planned surgery: endovascular prosthesis positioning and femur-femoral bypass. During hospitalization (from January 29 to February 9), blood values, INR, and aPTT were in normal range: mean INR 1.16 (1.04-1.27) and mean of aPTT 1.17 (1.07-1.33). To maintain normal hemostasis, 500 IU PCC every 6 hours, 1000 mg tranexamic acid every 8 hours, and a single daily administration of 0.2 mL calcic nadroparin were administered to the patient. Once discharged, prophylactic therapy was established in 60 IU/kg PCC, a single weekly administration, and 1000 mg tranexamic acid, every 12 hours. After this last intervention, the patient returned to hospital only for normal follow-up controls, then no more surgeries or hospitalizations were necessary.

Discussion

Factor X deficiency is a serious, rare bleeding disorder, with 1 in 500 000 people affected.[1-3] Severe FX deficiency is inherited as an autosomal recessive disorder (homozygous), its prevalence is greater among populations in which consanguineous marriages are common. The heterozygous affected by FX deficiency are usually clinically asymptomatic, but they often have a significant bleeding tendency due to inhibition of one of the reactions in the coagulation cascade by a mutant protein or due to insufficient enzymatic activity by wild-type FX.[15] Friuli variant is a particular form of FX deficiency, determined by a mutation Pro^{343}→Ser in exon VIII, isolated in Friuli-Venezia Giulia, a Northeast region of Italy, by Fair et al,[16] and characterized by an unusual longevity of the patients, normally related to the fact that the FX activity in these patients is not very low.[17] Diagnosis of FX disorder is made through a bleeding time test, prothrombin time (PT) test, and partial thromboplastin time (PTT) test. Diagnosis can be confirmed by FX assay or ruffle viper venom time assay. Currently, there are no specific products for the treatment of patients with FX deficiency, the therapy is based on plasma exchange or the use of FFP, PCC, and other hemostatic agents.[12,18,19] United Kingdom Haemophilia Centre Doctor's Organisation (UKHCDO)[15] published in 2004 the Guidelines for management of FX deficiency and other coagulation disorders based on literature and clinical experience. These guidelines established that the viral inactivated FFP should be used 20 mL/kg followed by 3 to 6 mL/kg twice daily to maintain the plasma factor level concentration above 10 to 20 IU/dL, amount generally sufficient for normal hemostasis.[15] The same recommendations are given by Menegatti and Peyvandi,[18] who, however, also highlighted the fact that in children and in elderly individuals, fluid overload stemming from the use of large amounts of FFP may represent a serious problem. Other hemostatic methods are commonly used to avoid this complication. Particularly useful for mucosal bleeding, but often used for a wide range of hemorrhagic conditions, the tranaxemic acid, a synthetic antifibrinolytic agent, intravenously administered (10 mg/kg followed by infusion of 1 mg/kg per hour), causes reductions of 29% to 54% relative to placebo in postoperative blood losses in patients undergoing cardiac surgery with cardiopulmonary bypass.[20] In our hospital, the local guidelines recommend the use of tranexamic acid for all patients with serious hemorrhagic risk with 1 or more coagulation disorders, still in association with PCC, when the physicians consider it necessary, evaluating the clinical situation of each patient.

Currently, the best method of treatment available to physicians for bleeding in patients with FX deficiency is the use of PCC, considered by UKHCDO guidelines[21] "the treatment of choice (Level IV, Grade C)." In case of bleeding, required dosage of PCC is based on the empirical finding that 1 IU FX/kg bodyweight raises the FX level by 1.5% compared to the normal one. In this case, our elderly patient usually had a very low level of FX (<1%) and during his life was admitted several times to hospital for hemorrhagic complications, but despite these problems, he has had a normal life, got married, had children, and was working for years in a local firm. Serious coagulation disorder,[5,6] associated with advanced age and diseases such as hypertension, COPD, and chronic gastritis, caused a more difficult resolution of surgical complications. According to published studies, the patient was managed with PCC.[22,23] First surgery: the patient was admitted to the hospital for endoleak treatment postendoprosthesis of AAA, blood parameters were impaired and the risk of haemorrhagic shock was high. Use

of PCC after FFP infusion, when the hemostatic parameters were still not in normal range, allowed the surgery to be done without bleeding and with normalized INR and aPTT. No adverse reactions due to PCC were found; neither VTE nor cardiovascular or cerebral events were found. The second surgery: a breakage in AAA, associated with renal insufficiency and hemorrhagic shock, reported the patient back into the operating room. Still, in this second surgery, no PCC-related complications were found. The third surgery was a "planned surgery." Prothrombin complex concentrate was administered during and after surgery. No related complications were found and soon the patient was discharged. Usually, after surgery, to avoid thromboembolic risk, a prophylaxis with heparins is recommended, but in this patient, with a serious FX deficiency, a high hemorrhagic risk was still present; thus, the normal dose of low-molecular-weight heparin (LMWH) was reduced to 0.2 mL/d. Prothrombin complex concentrate is used increasingly as regular prophylaxis in FX-deficient patients. McMahon et al[24] reported 4 cases of FX deficiency in children, treated using small volume infusion of lyophilized PCC. Kouides and Kulzer[25] reported the prophylactic treatment with PCC (30 IU/kg twice weekly) in a FX-deficient young man, who presented frequent epixtasis and bleeding; the follow-up showed that use of PCC in prophylaxis decreases the frequency of bleeding, allowing the patient's quality of life to improve. The same result was obtained in 1992 by Sandler and Goss,[26] when a child with 3 episodes of ICH was managed with PCC (40 IU/kg) for prophylactic treatment; during the follow-up of 8 months, no hemorrhages or thrombotic events were found. In our case, once discharged, the patient was treated with a single weekly administration of PCC (60 IU/kg). Weekly prophylaxis with PCC has allowed us to bring the patient from a state of severe deficiency (FX < 1%) to a state of a moderate one, in which the plasmatic FX concentration, constantly about 3%, ensures a significant reduction in even mild bleeding events. In the following months, the patient was subjected to periodic checkups, which showed all the vital signs; INR and aPTT were in normal range. Prophylaxis with PCC has normalized the patient. During treatment, the patient lived at home with his wife; his life was fairly good and there were no serious related complications caused by FX deficiency or any thromboembolic events.

Conclusion

Waiting for specific therapeutic options for FX deficiency, currently, the best treatment is represented by PCC, because it permits a reduction in bleeding frequency, with an improvement in the quality of life.

Authors' Note

All the authors contributed equally to this study.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

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