

Case Report

Successful Major Surgical Procedures in a Severe FXI Deficient Patient Using Fresh Frozen Plasma: A Case Report

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Abstract

Replacement therapy is desirable in case of surgical procedures in patients with severe FXI deficiency or milder deficiencies with a disposition to severe bleeding. Either FXI concentrates or FFP can be used in this setting. We report here the positive outcome of a series of consecutive surgical procedures in an aged patient with severe FXI deficiency treated with FFP and monitored with aPTT. In the two most recent major surgeries, the total dose of FXI administered pre-operatively was around 29 IU/kg (=mL/kg) during the first surgical procedure and around 19 IU/kg during the second one. Surgical hemostasis was judged "adequate" during these two major surgical procedures. APTT was close to upper normal value prior surgery and maintained ≤ 60 seconds at least 72 hours post-op. In the last major surgery both a PTT and FXI levels were monitored. FXI in-vivo recovery was found to be above 2%/IU/kg. Pre-op FXI plasma value was 45%, reaching the recommended value of 45 IU/dL for major surgeries. The post-op FXI plasma level was then rapidly below this value without any associated bleeding tendency. The clinical and aPTT monitoring were indeed not indicative of any additional transfusion need during the post-op period. So, FXI substitutive therapy using FFP monitored by aPTT was a safe and efficient procedure for planned consecutive surgical procedures. Clinical and aPTT-based laboratory monitoring of the patient led to a lesser intensive post-operative transfusion protocol than the protocol followed if the patient's monitoring would have been based on the recommended FXI plasma levels.

ABBREVIATIONS

aPTT: activated Partial Prothrombin Time; cm: centimeter; dL: deciliter; FXI: coagulation factor XI; FFP: Fresh Frozen Plasma; Hgb: hemoglobin; IU: international unit; Kg: kilogram; Max: maximum; Min: minimum; mL: milliliter

INTRODUCTION

We report here the successful completion of multiple surgical procedures in a severe coagulation factor XI (FXI) deficient patient substituted with Fresh Frozen Plasma (FFP) (Octaplas® and OctaplasLG®, Octapharma) and followed-up with activated Partial Thrombin Time (aPTT) and/or FXI assays.

FXI deficiency is a rare bleeding disorder with bleeding

phenotypes unrelated to patient's FXI plasma levels [1,2]. In case of severe FXI deficiency (FXI \leq 20%) or milder deficiencies with a disposition to severe bleeding, it is generally considered indicated to correct at least partially the FXI deficiency before surgery [3]. Substitutive treatment modalities include administration of FFP or FXI concentrate. Treatment with antifibrinolytics, desmopressin and/or fibrin sealant can also help controlling the bleeding tendency. Considering the long biological half-life of FXI (around 60 hours), pre-operative administration of FFP over 48 hours allow correcting the bleeding tendency with a limited risk of volume overload. While measurement of thrombin generation by TGA (Thrombin Generation Assay) could probably be the most predictive test to perform for monitoring FXI deficient patients during the course of a surgical procedure [4,5] this test deserves

further standardization and is not feasible in routine. Follow-up of FXI levels is recommended while considered not correlated to bleeding risk and not easily available in routine. So, correction of aPTT is frequently used for the monitoring of patients' haemostatic potential.

CASE PRESENTATION

The (female) patient's FXI deficiency was diagnosed in 2006 (FXI=4%) at the age of 66 years at the occasion of the preoperative assessment of bleeding risk (isolated prolonged aPTT) prior to a mastectomy for breast adenocarcinoma. The patient was successfully operated under FFP treatment. In October 2012, a total hip replacement was performed under FFP without problem.

In March 2013, a sigmoidectomy with lateral ileostomy had to be performed because of neoplasm. aPTT was measured during the perioperative period using STA-Cephascreen 10 reagent (Stago) according to the routine validated standard operating procedure of the laboratory. At hospital entry, patient's aPTT was 101 seconds (normal laboratory range: 25-35 seconds) and hemoglobin (Hgb) 10.1 g/dL (normal laboratory range: 11-14 g/dL). She received 11 units of 200 mL FFP (Octaplas®, Octapharma) over the 48 hours (total 24 mL/kg for a weight of 92 kg) preceding the operation and one red cell concentrate. Pre-operative monitoring of aPTT indicated the efficacy of the substitutive therapy and allowed eliminating the presence of a FXI inhibitor. On the day of the operation, aPTT was 37 seconds and Hgb was 10.9g/dL, which was considered satisfactory for starting the operation. The day after surgery, her aPTT was 40 seconds and 1 additional unit of plasma was administered as well as 2 units of red blood cell concentrate because of low hemoglobin (8.3g/dL). Post-transfusion aPTT was 38 seconds; post-transfusion Hgb was 9.5 g/dL. Six days after the operation her aPTT was 63 seconds. Efficacy of the transfusion protocol on peri-operative bleeding and hemostasis has been judged "adequate" with no excessive blood losses observed. (Figure 1) summarizes the biological follow-up and the transfusion protocol used for this surgical procedure.

One month later, the patient received 8 units of FFP for the implantation of a Port Chamber (port-a-cath) with no bleeding problem. In November 2013, reimplantation of the lateral ileostomy was performed successfully with transfusion of 8 units of FFP.

In June 2014, a new major surgical procedure (total hip replacement) was planned for August. FXI inhibitor was checked and was found negative at that moment besides the past repeated administrations of FFP. At this occasion, transfusion efficacy has been monitored during the perioperative period by both aPTT and FXI plasma levels. 8 units (1,600 mL) of plasma (OctaplasLG®, Octapharma) have been administered to the patient over 48 hours prior to surgery. aPTT was measured using STA-Cephascreen 10 reagent (Stago) according to the routine validated standard operating procedure of the laboratory. FXI plasma levels were measured using STA-deficient XI and STA-CK PREST reagents (Stago) according to the validated standard operating procedure in place in the laboratory. The procedure implies duplicate testing and specific dilutions to measure

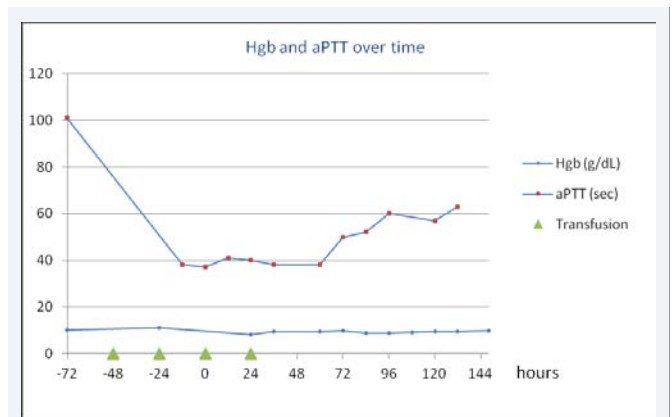


Figure 1 Evolution of Hgb and aPTT over time and transfusion of blood components. Green arrows indicate transfusion: pre-op (2FFP+1PRC; 5FFP; 4FPP) and post-op (1FFP+1PRC) FFP = Octaplas.

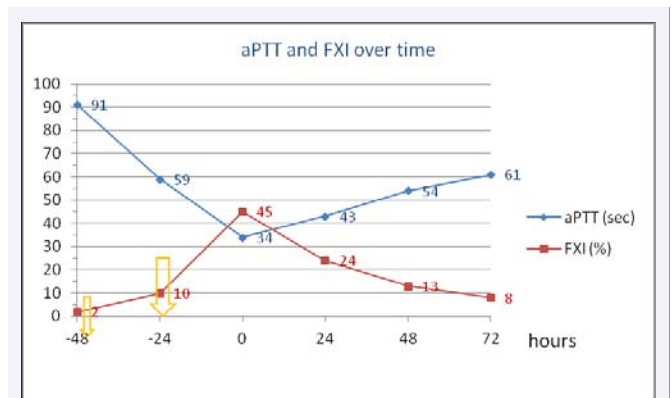


Figure 2 aPTT and FXI over time and transfusion of blood components. Yellow arrows indicates OctaplasLG® transfusion (2 units and then 6 units) pre-op.

FXI values below 5%. aPTT was 91 sec (Normal values: 25-37 sec) and FXI plasma level was 2% prior to plasma transfusion. After OctaplasLG® administration, aPTT was within normal values (34 sec) and FXI plasma level reached 45%. Considering the total dose of FXI administered (1,600 IU) and the patient's body weight (85kg), and the observed increased of FXI plasma level (45%-2%=43%), the overall observed in-vivo recovery in our patient is 2.28%/IU/kg. The surgical procedure has been conducted without any abnormal bleeding. No additional plasma transfusion and no other blood products were transfused peri-operatively. Surgical hemostasis was judged "adequate" by the surgical team. Peri-operative aPTT and FXI values are presented in the figure 2 below.

DISCUSSION

Replacement therapy is desirable in case of surgical procedures in patients with severe FXI deficiency or milder deficiencies with a disposition to severe bleeding. Because of, among others, the risk of inhibitor appearance, the surgical procedure should be absolutely indicated and planned meticulously in severe FXI deficient patients. Testing for the presence of FXI inhibitor is recommended especially in case of

severe deficiency and history of transfusion. FXI concentrates, if available, are a possible mean for substituting deficient patients but should be used, as recommended in their Summary of Product Characteristics, with caution in patients at risk of thrombosis (pre-existing cardiovascular disease, elderly patients, malignant disorders, pregnancy, etc.). Replacement therapy can make use of FFP. In this case, considering the long half-life of FXI but the need for administering large volume, this substitutive therapy should be made pre-operatively within a period of 24 to 48 hours depending of the patient's cardiovascular status so as to minimize the risk of volume overload. Preventive measures of volume overload such as administration of diuretics and fluid restriction are to be considered.

Considering the described thrombogenic potential of FXI concentrates, their unavailability in Belgium and the long circulating half-life of FXI, Fresh Frozen Plasma including Octaplas® and OctaplasLG®, Octapharma, was used for managing a series of planned major surgeries in an elderly patient. Six surgical procedures were conducted in this patient between 2006 and 2014. Two major surgical procedures have been followed-up with special attention. Considering the uncertainty about the haemostatic level of FXI to be reached in FXI deficient patient, patients' monitoring with aPTT was systematically used for monitoring the bleeding risk in these patients. Only at the occasion of the second surgical procedure, both FXI levels and aPTT were measured. Perioperatively in order to avoid volume overload, FFP was administered over a period of 48 hours and preventive measures of volume overload were taken including administration of diuretics (Furosemide 250 mg) the day before the surgical procedure and fluid restriction in the post-operative period.

The total dose of FXI administered pre-operatively was around 24 UI/kg (FXI level in the OctaplasLG is 1 IU/ml) in the first surgical procedure and around 19 IU/kg in the second one. FXI in-vivo recovery was above 2%/IU/kg in our patient. Mean in-vivo recovery of FXI after Octaplas administration has been previously assessed by Santagostino et al [6] to be 1.3 %/ IU/kg (min: 0.8; max: 1.8). Patient's overweight (85 kg for 169 cm) can explain the high in-vivo recovery observed in our patient. Surgical procedure is not an appropriate situation for evaluating FXI elimination half-life. The FXI time-decline curve obtained at the occasion of the last surgery shows that the terminal half-life is not as long as previously published. It is however well-known that terminal half-life varies greatly from patient to patient and that pharmacokinetics should be evaluated in non bleeding situations. During surgical procedures, FXI is indeed consumed for controlling surgical bleeding.

Risk of developing FXI inhibitors after substitutive therapy is high in particular in patients with severe deficiency homozygous for the type II null allele [3,7]. This is the reason why FXI inhibitor has been tested for before the last surgery. While suffering from a severe FXI deficiency and heavily previously transfused at various occasions with FXI-containing products, the patient has not developed a FXI inhibitor.

For major surgery, a target FXI level of 45 IU/dL for approximately 10 days is generally recommended [3,7]. For minor surgery, a trough level of 30 IU/dL during approximately

5 days is considered to be usually sufficient [3,7]. In our case, the aPTT-based laboratory and clinical monitoring performed does not indicate the need for maintaining this level of FXI so long. Surgical hemostasis was judged "adequate" during the two documented surgical procedures. aPTT was close to upper normal value prior surgery and maintained ≤ 60 sec at least 72 hours post-op. Pre-op FXI value was 45%, reaching the recommended value of 45 IU/dL for major surgery [7]. This recommended level was however not maintained during 10 days in our patient and this seems not to be needed. The post-op FXI plasma level was rapidly below this value in our patient without any associated bleeding tendency. In our case, the clinical and aPTT monitoring was indeed not indicative of any additional transfusion need during the post-op period besides FXI plasma level significantly below 45%. Securing hemostasis without increasing too much FXI plasma levels could be of interest considering the role of FXI in thrombosis. [2]

Considering the reported in-vivo recovery of FXI in OctaplasLG® [6], the recommended target plasma FXI levels (45 % for major surgery and 30 % for minor surgery) [7] and the concentration of FXI in the product (1 UI/mL), the pre-operative dose for a severe FXI deficient patient should be around 25-35 mL/kg in major surgery and around 15-25 mL/kg in minor surgery. Considering the large inter-individual variability of FXI pharmacokinetics, a close clinical and laboratory monitoring is however needed.

Monitoring of FXI concentration is recommended, however FXI level is not always correlated to haemostatic potential and aPTT is a simpler test to perform and could be, to our experience, as predictive for the measurement of the treatment efficacy on the bleeding risk. This strategy has not caused any problem in our case and avoided administering additional FFP units post-operatively that would certainly have been transfused if a FXI level of 45 IU/dL during 10 days post-operation would have been used to define the transfusion target. So, in our patient, FXI substitutive therapy using FFP monitored by aPTT and the clinics was a safe and efficient procedure in a previously-transfused severe FXI deficient patient undergoing a series of planned consecutive surgical procedures including major ones. Clinical and aPTT-based laboratory monitoring of the patient led to a lesser intensive post-operative transfusion protocol than the protocol followed if the patient's monitoring would have been based on the recommended FXI plasma levels.

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