Elmer Press

Original Article J Hematol. 2016;5(3):94-98

Management of Arthropathy in Moderately Deficient Factor VII Patients: Results From Hospital Developed Treatment Protocol

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Abstract

Background: Factor VII deficiency (FVIId) is a rare inherited bleeding disorder whose prevalence is estimated to be 1 in 300,000 - 500,000 in general population. In India, the epidemiological data on factor VII (FVII) disorder are scarce. Serious arthropathy is observed in cases which are severely affected with spontaneous bleeding and hemarthrosis. In such cases, orthopedic surgery is required. Fresh frozen plasma, prothrombin complex concentrates, factor VII concentrates - plasma derived and recombinant factor VII (rFVII) are different types of preparations which are available as therapeutic options in treatment for bleeding occurring during or after surgery in FVIId patients. The main objective of our study was to give a result of the treatment protocol for FVIId patients undergoing orthopedic surgery in our hospital and compare its results with other studies conducted around the world.

Methods: A retrospective study on patients admitted during 2008 - 2014 was carried out with 10 patients diagnosed with FVIID, of whom six undergone surgery at Kasturba Hospital, Manipal, west coastal region of southern India.

Results: FVII baseline plasma levels were less than 10 IU/dL in our patients. Three patients underwent complete hip replacement, while rest of the three patients underwent various other arthroscopic procedures. rFVII was administered every 8 hours on the surgery day, followed by ever 12 - 24 hours for subsequent days in hospital depending on the type of surgery that the patient underwent. FVII levels in plasma were determined once before and once after the surgery, but the dosing of rFVII was not dependent on it. Dosing of rFVII on the day of surgery was 10 - 25 µg/kg and on following days, it was 15 - 30 µg/kg. The number of dosing on patients ranged from 16 to 31. None of our patients developed serious bleeding episode, thus no blood transfusion was required.

Conclusion: Our study results show that when rFVII is administered according to our treatment regimen, it is effective for patients with arthropathy. It also proves that rFVII is the best hemostatic agent for FVII patients.

Keywords: Factor VII; Bleeding; Arthropathy; Recombinant factor VII; Orthopedic; Arthroscopy; Thromboprophylaxis; Hemostasis

Manuscript accepted for publication September 02, 2016

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doi: http://dx.doi.org/10.14740/jh296e

Introduction

Factor VII deficiency (FVIId) is a rare inherited bleeding disorder whose prevalence is estimated to be 1 in 300,000 - 500,000 in general population [1, 2]. In India, the epidemiological data on factor VII (FVII) disorder are scarce. FVII activity levels are poorly correlated with hemorrhagic manifestation in individuals [3, 4]. Serious arthropathy is observed in cases which are severely affected with spontaneous bleeding and hemarthrosis. In such cases, orthopedic surgery is required.

Fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), factor VII concentrates - plasma derived and recombinant factor VII (rFVII) are different types of preparations which are available as therapeutic options in treatment for bleeding occurring during or after surgery in FVIId patients [5]. FFP causes fluid overload and high risk of transfusion infection, due to which it is not recommended for prolonged transfusion which is required for FVIId patients requiring surgical intervention. PCCs consist of other coagulation factors like II, IX, X and VIII, with which continuous infusion can have severe thrombogenic effects on patients who require continuous infusions. Effective management of FVIId patients has been proved by using virus inactivated FVII concentrates derived from plasma, even though theoretically it has a risk of infections transmitted due to transfusion [6, 7].

The treatment of choice for FVIId patients is rFVII as the deficient protein in plasma is substituted at a very low volume of preparations and it does not consist of any other animal or human protein in it [8]. Even though rFVII is widely used in FVIId patients, there is scarce of literature for treatment patterns in FVIId patients with surgical intervention [5, 9]. The main objective of our study was to give a result of the treatment protocol for FVIId patients undergoing orthopedic surgery in our hospital (Table 1) and compare its results with other studies conducted around the world.

Table 1. Treatment Regimen for Patients Diagnosed With Moderate Deficiency of Factor VII

Period of rFVII administration	rFVII dose for patients with moderate factor VII deficiency (> 1 and < 10 IU/dL)
Pre-surgery	15 - 25 µg/kg
On the surgery day (8 and 16 h, respectively)	10 - 20 µg/kg
Rest of the days admitted in hospital	15 - 20 µg/kg

Materials and Methods

This study included patients undergoing various arthroscopic surgeries in Kasturba Hospital, Manipal, from 2008 to 2015. Patient details were collected retrospectively from medical records department of our hospital. Our study was comprised of six patients, four men and two women, aged 25 - 60 years with inherited FVIId.

Sysmex (CS-2000i) coagulator was used to check prothrombin time (PT) and concentration of FVII. FVII assay was confirmed by using human thromboplastin. This method is also called as one stage method. rFVII (NOVO-SEVEN, Novo Nordisk, Denmark) coverage was given to all the patients who underwent the surgery. Administration of three doses of rFVII at every 8 h on the day of surgery, and then every 12 or 24 h was given till the patient was in the hospital. Three potencies (1, 2 and 5 mg bottle) of rFVIIa were available and used during surgical intervention. The doses were calculated up or down on individual basis. rFVII doses given were not less than 30 µg/kg before surgery in patients with factor VII concentration (FVIIC) ≤ 2 IU/dL and about 20 µg/kg in patients with FVIIC ≥ 2 IU/dL. The subsequent doses were about 15 µg/kg. rFVII doses were not adjusted as the FVIIC was assured twice during the surgery and PT results were measured daily. Preoperative clinical courses like loss of blood and hematoma were the parameters used in monitoring the treatment. American College of Chest Physician guidelines were used for thromboprophylaxis [10]. Antifibrinolytic was not used in the treatment of patients.

Results

Patient 1

A male patient aged 60 years diagnosed with moderate FVIId presented with spontaneous and traumatic bleeds in left knee and hip which were treated with infusions of FFP and PCC. He then showed limitation in movement of his left hip, and X-ray examination showed degeneration of joint. Arthralgia was treated with narcotic analgesics. He was also suffering from other co-morbid disorders like hypertension and ischemic heart disease and undergone a coronary angioplasty without stent placement 15 years before and currently with anti-thrombotic therapy. A complete hip replacement surgery was performed where a cemented implant was used and the procedure was done from the posterior side. Examination of cartilage and synovium specimen for pathological test showed idiopathic COX arthritis rather than blood-induced arthropathy. First dose of 30 µg/kg of rFVII was given at 15 min before the surgery and further 12 µg/kg doses were given at 8 and 16 h after first dose. rFVII treatment was continued till he was admitted in the hospital and a dose of 12 µg/kg was given for next 12 days at every 12 h (Table 2). Plasma levels of FVII were checked after surgery and were found to be 8 IU/dL. Enoxaparin 40 mg (low molecular weight heparin) was started 24 h after surgery and continued till 12 days. No bleeding complication was seen during the surgical procedure and there was a loss of 600 mL of blood, thus no blood transfusion was required. On 14th day after surgery, patient was discharged. Follow-up after a year showed there was no pain in the hip and his walking ability has improved.

Patient 2

A male patient aged 34 years was diagnosed with moderate FVIId. Patient history showed episodes of spontaneous and traumatic bleeds at different joints like knee, shoulder and hip which were treated by FFP and PCC infusions and rFVII. Patient had shoulder arthropathy due to recurrent bleeding but the main reason for his admission was pain in left hip. There

Table 2. Details of Patients, Surgery, Dosing and Outcome

Patient no.	Severity of disease	Surgical procedure	Treatment duration	No. of doses	Total dose of rFVII on surgical day (µg/kg)	Total dose of rFVII on subsequent days (µg/kg)	Dosing range (µg/kg)	Total amount of rFVII consumed (mg)
1	Moderate	Complete hip replacement	13	29	54	288	12 - 30	22.23
2	Moderate	Complete hip replacement	14	31	40	280	10 - 20	23.04
3	Moderate	Complete hip replacement	13	29	35	260	10 - 15	22.42
4	Moderate	Arthroscopy of shoulder	10	16	45	195	15	16.8
5	Moderate	Arthroscopy of ankle	10	16	60	285	20 - 25	21.39
6	Moderate	Arthroscopy of knee	12	16	35	130	10 - 15	9.57

was no co-morbid disease. Total hip replacement with cement less articulation was done. First dose of 20 μg/kg of rFVII was given at 15 min before the surgery and further 10 μg/kg doses were given at 8 and 16 h after the first dose. rFVII treatment was continued till he was admitted in hospital and a dose of 10 μg/kg was given for next 14 days at every 12 h (Table 2). The FVIIC in the plasma was 7 IU/dL checked on day 12. During the procedure, 540 mL blood was lost, thus no blood transfusion was required. Enoxaparin 40 mg (low molecular weight heparin) was started 24 h after surgery and continued till next 14 days. On day 15, the wound completely healed and patient was discharged.

Patient 3

A male patient aged 45 years was diagnosed with moderate FVIId. Patient history showed episode of spontaneous and traumatic bleeds on knee and hip which were treated with FFP and PCC. Frequent join bleeds led to arthropathy in knee but the main concern was pain and reduced range of movement of hip. There was no co-morbid disease. Arthralgia was treated with narcotic analgesics. Total hip replacement with cement less articulation was done. He was given first dose of 15 μg/kg rFVIIa at 15 min prior to the surgery followed by 10 μg/kg rFVII at 8 and 16 h after the first dose. Till next 13 days, he received 10 μg/kg rFVII every 12 h (Table 2). FVIIC in plasma was 7.5 IU/dL on day 12. There was a loss of 640 mL blood, thus no blood transfusion was required. Enoxaparin 40 mg (low molecular weight heparin) was started 24 h after surgery and continued till day 13. On day 14, the wound healed completely and patient was discharged.

Patient 4

A male patient aged 25 years was diagnosed with moderate FVIId. Three years earlier, patient had a traumatic episode leading to fracture of left humeral neck. He underwent a surgery and was fixed by using rush pins. The surgery became complicated due to uncontrollable bleeding after surgery and was diagnosed with hypoproconvertinemia. Surgical intervention was required even after healing of fracture because of stiff shoulder caused due to rush pins in subacromial space. Shoulder arthroscopy was done for removal of rush pins from subacromial space and excision of scar tissue. First dose of 15 μg/kg of rFVII was given at 15 min prior to surgery and further same dose was continued at 8 and 16 h. Till next 4 days, he received 15 μg/kg of rFVII on 12 h and every 24 h from day 5 to day 9 (Table 2). FVII level in plasma was 45 IU/dL on 10th day. There was a loss of 25 mL blood. No thromboprophylactic agent was given. On 11th day after surgery, the patient was discharged with healed wound.

Patient 5

A female patient aged 30 years was diagnosed with moderate FVIId. Medical history of patient showed episode of spontaneous and traumatic bleeds during childhood. She used to have recurrent bleeding at left ankle and joint movement was reduced. FFP, PCC and rFVII were the agents used for her earlier treatment. Her complaints on admission were left ankle swelling and reduced mobility of the joint. The radiographic test of her leg showed presence of periarticular cyst on distal tibia which may have led to possible penetration to the ankle joint. Substitution of bone and removal of cyst were done by performing an ankle arthroscopy. During arthroscopic inspection, it was surprising to see an unaffected joint cartilage and synovium. First dose of 20 μg/kg rFVII was given at 15 min prior to the surgery followed by 20 μg/kg dose of rFVII every 8 and 12 h for 4 days. A dose of 25 μg/kg rFVII was given on every 24 h from day to day 9 after surgery (Table 2). FVIIC in the plasma was 30 IU/dL after surgery. No bleeding complication was seen. There was a loss of 35 mL blood. No thromboprophylactic agent was given. Physiotherapy helped in resolving the pain as patient had mild pain after surgery. On day 11, patient got discharged. Upon follow-up after 6 months of surgery, the ankle movement was completely resolved and no pain was reported by patient even after strenuous activity.

Patient 6

A female patient aged 60 years was diagnosed with moderate FVIId. She had no history of unprovoked bleeds and undergone several surgeries under hemostatic cover using various FVII containing preparations like FFP, PCC and rFVII. Hypertension and ischemic heart disease were the concomitant diseases present. She came with complaints of pain in her left knee which might have appeared due to injury that took place several months before. X-ray examination showed no changes but magnetic resonance imaging reports showed articular cartilage tear in right knee. A knee arthroscopy with partial meniscectomy and shaving of cartilage deficit with microfractures was performed. First dose of 15 μg/kg of rFVII was given at 15 min prior to the surgery. On the same day, additional doses of 10 μg/kg of FVIIa were given at 8 and 16 h. A dose of 10 μg/kg rFVII was given at every 12 h till the fourth day and every 24 h from day 5 to day 9 after surgery (Table 2). FVIIC in plasma was 25 IU/dL after the surgery. There was a loss of 120 mL blood. Thromboprophylactic therapy was not given. Physiotherapy was started immediately. On 12th day after surgery, patient got discharged. Upon follow-up after 6 months of surgery, patient said she was able to move the knee without pain.

Discussion

Preoperative treatment protocol is present for patients diagnosed with hemophilia A and B [11, 12]. Literature on preoperative treatment protocol is scarce as FVIId comes under rare bleeding disorders. Moreover, the available data are not consistent [5, 8, 13]. Mariani et al [14] in her study reported of using rFVIIa successfully in seven patients of severe FVIId who underwent major surgeries. They were given rFVIIa at 2 - 3 h

interval on the day of surgery and longer intervals during the postoperative period. Mean dose/procedure ranged from 13.85 to 26.29 μg/kg and the number of doses/procedure varied from 30 to 112. Other results from different groups showed that 20 - 25 μg/dL of rFVII should be given at every 4 - 6 h in combination with tranexamic acid which was seen to be effective in surgical settings for FVIId patients but treatment duration is not well defined [5, 8, 9, 15].

Pharmacokinetic studies of rFVII helped in choosing the dose and time interval between the subsequent infusions, but it is still not defined about minimum requirement for FVII in plasma to attain hemostasis [15, 16]. According to UK guidelines, the management of rare bleeding disorder in patients with FVIId undergoing surgery requires plasma level of 20 IU/dL with FVII plasma derived concentrate [5]. Ingerslev et al [15] in his study of two patients diagnosed with severe FVIId, showed rFVII cover was used for homeostasis and concentration of FVII was kept at 30 IU/dL. Al Dieri et al [17] had a contrasting result as he postulated that 2 IU/dL concentration of FVII is sufficient for normal thrombin generation but the drawback is it was an observation in one patient who had a normal thrombin potential value. Giansly-Blaizot et al [18] suggested that FVIId patients are at a low bleeding risk during surgery as patient should be given rFVII for any bleeding complication and not for preventive therapy. Further controversies have been raised by different authors because only 30% of FVIId patients undergoing surgery had bleeding complication [19]. French authors had to change their opinion after an extensive study was conducted on 83 patients who were given 5 IU/dL as the median FVII level in plasma undergoing surgery and concluded that only minor procedure or clinical hemorrhage can be performed asymptomatic even with patients with FVII levels ≥ 10 IU/dL without replacement therapy [20].

Another issue is the lab assay used for treatment monitoring [20]. FVIIC, the most widely used assay, is the most appropriate monitoring tool in which FVII concentrates are given as plasma derived FVII infusions are considered as simple substitution in FVIId patients [5]. The hemostatic efficacy mechanism of rFVIIa in patients is not yet clear and a probable mechanism can be binding of rFVII with platelets which delivers high concentration of rFVII at any site of injury and platelet activation [21]. Therefore, the laboratory assay used for monitoring rFVII in patients might not be accurate [21-23].

Our study is the first on rFVII treatment regimen done in India and the results indicate that patients who are FVIId undergoing surgical intervention are administered with rFVII with their frequency limited to 1 - 3 injections on the day of surgery and 1 - 2 injections on rest of the days. Mean dose of rFVIIa administered on day of surgery is 17 - 16 μg/kg and on following days, it is 18 - 49.3 IU/dL. These results were not different significantly from the other studies conducted. In one article, it is stated that two patients with FVIId underwent hip and knee replacement surgery and total dose of rFVII administered was 263 and 241 IU/kg, respectively [9]. Our patients received a much higher dose than the above mentioned study, i.e. 412.9 - 444.4 IU/kg of rFVIIa. However, the patients in the above mentioned study as well as Mariani's study stated that bleeding complication was experienced during the postoperative period. Even though FVIIC came back to the baseline on the first operative days, none of our patients have any episode of excessive bleeding. In comparison to other studies, we did not use any homeostatic agent in our patients, so results obtained in our study are not biased.

Limitation of our study is there were very few patients. Nevertheless, we wanted to share our observation with the physicians who treat hemophilia as there is a requirement of standardized regimen for FVIId patients undergoing surgical procedures. Further refinement is required of treatment protocol stated here. Further answers are required in the aspect of rFVII dosing and dosing frequency, rFVII treatment monitoring assays which are accurate and requirement of thromboprphylaxis.

Conflicts of Interest

All authors declare no conflicts of interest.

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