Journal of Pediatric Sciences

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Journal of Pediatric Sciences 2011;3(2):e81

How to cite this article:

Mabora B, Avci Z, Orhan B, Arda S, Ozbek N. Succesful use of recombinant factor VIIa (Novoseven®) during apendectomy in an adolescent patient with congenital factor XI deficiency. Journal of Pediatric Sciences. 2011;3(2):e81

CASE REPORT

Succesful use of recombinant factor VIIa (Novoseven®) during apendectomy in an adolescent patient with congenital factor XI deficiency

Baris Malbora[1], Zekai Avci[1], Betul Orhan[2], Serdar Arda[3], Namik Ozbek[1]

Abstract:
Factor XI (FXI) deficiency is a rare inherited bleeding disorder caused by a mutation in the FXI gene, which is located on the distal arm of chromosome 4 (4q35). Factor XI (FXI) deficiency is defined when the activity of FXI in plasma is less than 15 U/dL. We report our experience about perioperative use of recombinant activated factor VII (rFVIIa) in a 17 year-old with congenital FXI deficiency and appendicitis. After appendectomy, the first intravenous dose of rFVIIa was administered. This same dosage was repeated and he was discharged on postoperative 72nd hour without complications.

Keywords: appendectomy, factor XI deficiency, recombinant factor VIIa
Received: *18/02/2011; Accepted: 30/03/2011*

Introduction

Factor XI (FXI) deficiency is an injury-related bleeding tendency that commonly occurs when trauma involves tissues rich in fibrinolytic activators. Severe FXI deficiency is defined when the activity of FXI in plasma is less than 15 U/dL [1,2]. The disorder is inherited as an autosomal recessive trait manifesting in homozygotes or compound heterozygotes, infrequently in heterozygotes.

Factor XI deficiency is most notable for its variable clinical phenotype. Unlike the hemophilias, FXI deficiency is rarely manifested as spontaneous bleeding. Bleeding typically occurs after trauma, surgery or other hemostatic challenges and varies considerably between patients with similar FXI levels. It may also vary over time within the same individual [3]. Bleeding tendency also appears to be influenced by the type of surgery and levels of von Willebrand factor and platelet F-XI [4]. Here, we report our experience with the use of rFVIIa during appendectomy in a child with factor XI deficiency.

Baris Malbora[1], Zekai Avci[1], Betul Orhan[2], Serdar Arda[3], Namik Ozbek[1]

[1]Baskent University Faculty of Medicine, Department of Pediatric Hematology, Ankara, Turkey
[2]Baskent University Faculty of Medicine, Department of Pediatrics Ankara, Turkey
[3]Baskent University Faculty of Medicine, Department of Pediatric Surgery, Ankara, Turkey

Correspondence author:
Baris Malbora, MD

Baskent University, Department of Pediatrics,
6. Cadde, No: 72/3, 06490, Bahcelievler, Ankara, Turkey
Tel : +90 312 2130776
Fax: +90 312 2157597
E-mail: barismalbora@gmail.com

Case Report

A 17-year-old male patient was admitted with right lower quadrant pain. Physical examination showed body weight 124 kg (>97 percentile), height 186 cm (>97 percentile), blood pressure 130/90 mmHg. Tenderness was evident in the lower right abdominal quadrant. There was no defense or rebound. His history revealed that he was diagnosed with factor XI deficiency in Switzerland where he was residing since his birth. At the moment he was visiting Turkey. His family history revealed that his younger brother was diagnosed with factor XI deficiency when he had been evaluated for nose bleeding at the age of 4. Parents, two sisters and a brother were healthy. Complete blood count were as follows: hemoglobin 14.5 g/dL, white blood cell count 12.7 x $10^3/mm^3$, platelet count 247 x $10^3/mm^3$, prothrombin time: 12.8 sec (normal range; 11-15 sec), INR: 1, activated partial thromboplastin time (aPTT) 110.6 sec (normal range; 24-40 sec), fibrinogen level 632 mg /dL (normal range; 200-400 mg/dL), fibrin degradation products: 0 µg/mL (normal range; 0-5), D-dimer level 0.188 µg/ml (normal range; 0-0.5), bleeding time with epinephrine 83.74%, and with ADP 80.55% (normal ranges; 60-90 for both), FXI 12.5% (normal range; 70-110%). A mixed aPTT test revealed no antibody. Anti-nuclear antibody, direct Coomb's test, anti-double stain-DNA, anti-cardiolipin IgM and IgG were negative, but lupus anticoagulant screening test was 183 sec [(normal range; 20-60 sec) Lupus anticoagulant confirmation test was performed]. Abdominal ultrasound was unable to rule out appendicitis due to excessive fatty tissue. Contrast abdominal computed tomography revealed appendicitis, appendix diameter was 10 mm and mucosal edema was established. On peri-appendixial tissue increased density related with inflammation and a few lymph nodes on periceacal region, the biggest one's diameter 1 cm, was obtained.

One hour before operation, the first intravenous dose of rFVIIa (80 µg/kg; NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) was administered. During operation, there was no significant bleeding. At the second hour after appendectomy, PT, INR and aPTT levels were 11 sec, 1, and 62.4 sec, respectively. The same dosage of rFVIIa was repeated four hours after the operation and PT, INR and aPTT were 12 sec, 1, and 53 sec, respectively. No further treatment with rFVIIa was given after that point. His aPTT was 57.8 and 70.9 sec at 6th and 15th hours after operation.

Postoperative drainage was within normal limits. He was discharged on postoperative 3rd day without complications.

Discussion

FXI deficiency has been described in most populations, but is particularly common in Jews. The deficiency is inherited as an autosomal recessive trait [5]. So far 219 mutations in the FXI gene have been described and most of them are listed in a database (http://www.factor.xi.com). Molecular genetics has an important role in the clinical management of FXI deficiency. For example, definitive diagnosis of FXI deficiency is only possible using molecular techniques, since some heterozygotes have FXI levels very similar to those seen at the lower end of the normal range. It is also difficult to distinguish between type II homozygotes and compound heterozygotes on the basis of plasma levels of FXI alone.

Bleeding in patients with severe FXI deficiency can start at the time of injury or is delayed for several hours. In the severe deficiency, bleeding is injury-related, particularly when trauma involves tissues rich in fibrinolytic activators such as the oral mucosa, nose and urinary tract [2]. It persists until specific treatment is provided. As a result patients with severe FXI deficiency require replacement therapy before a surgical procedure, even if they have never bled before [6]. Usually replacement therapy consists of fresh frozen plasma with a target level of 30-40 U/dL. To achieve this goal one should start treatment with an infusion of 15 ml/kg day of fresh frozen plasma maintaining these FXI levels for 7 days. Another option is FXI concentrate which is safer with regard to transmission of infections agents. However, use of FXI concentrate is safer with regard to transmission of infections agents [7].

This is the first report concerning appendectomy in Factor XI deficient patients. There are a few reports on pre- and perioperative treatment in these patients [6,8-10]. Tooth extractions can be managed only by tranexamic acid without plasma replacement therapy

and skin biopsy can be treated similarly. Epidural anesthesia is not recommended in patients with severe FXI deficiency without replacement therapy although anecdotal cases have been reported [10]. Recombinant activated factor VII has been approved for clinical use in patients with inhibitors against factor VII or factor IX as well as in severe platelet function disorders [11]. Our patient's recent history did not reveal spontaneous bleeding. Since bleeding tendency may vary over time within the same individual, we decided to give rFVIIa during appendectomy. However, we restricted treatment to two doses by close observation. Another patient treated in our hospital was a patient with congenital cardiac disease and F XI deficiency. In this patient, we administered intravenous dose of rFVIIa (90 μg/kg; total, 800 μg) one hour before cardiac operation, then the same dosage was repeated eight more times, at 2- to 4-hour intervals postoperatively [8]. Operations were successful in both of our patients who undergone cardiac or abdominal operations. There was no adverse event related to rFVIIa.

In summary, we suggest use of rFVIIa in patients with FXI deficiency who undergoes major operations. However, we advice restrictive treatment adjusted by the patient's postoperative findings in order to minimize treatment costs.

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