LETTER TO THE EDITOR

PROPHYLAXIS WITH rFVIIa BEFORE THIRD MOLAR EXTRACTION IN A PATIENT WITH FACTOR VII DEFICIENCY

P.C. PASSARELLI[1], V. DESANTIS[1], P. DE ANGELIS[1], G.B. PICCIRILLO[1], V. GIOVANNINI[1], P. PAPI[2], G. POMPA[2] and A. D'ADDONA[3]

[1]Department of Head and Neck, Oral Surgery and Implantology Unit, Institute of Clinical Dentistry, Catholic University of the Sacred Heart, Gemelli University Polyclinic Foundation, Rome, Italy;
[2]Department of Oral and Maxillo-facial Sciences, "Sapienza" University of Rome, Rome, Italy;
[3]Department of Head and Neck, Oral Surgery and Implantology Unit, Institute of Clinical Dentistry, Catholic University of the Sacred Heart, Gemelli University Polyclinic Foundation, Rome, Italy

Received February 5, 2020 – Accepted February 19, 2020

To the Editor,

Factor VII (FVII) is a vitamin K-dependent glycoprotein, that is produced in the liver and it participates in the extrinsic pathway of blood coagulation. Upon vascular injury, factor VII interacts with factor III which leads to the cleavage to its active form: this is the first step of the blood coagulation process. The complex formed by factor III and activated factor VII activates factors IX, X, and autocatalytically factor VII (1). Alexander et al. in 1951 (2) described for the first time the congenital deficit of factor VII. It is also known as serum prothrombin conversion accelerator (SPCA) deficiency, hypoproconvertinaemia, stable factor or proconvertin deficiency and Alexander's disease. It is a rare autosomal recessive bleeding disorder and its pathogenesis is due to mutations in the gene F7 (13q34), which produces a severe deficiency in the homozygote and moderate deficiency, sometimes even without clinical manifestations, in the heterozygote. This bleeding disorder has a prevalence rate of approximately 1/500,000 in the general population (3). Factor VII deficiency refers to both men and women in the 1:1 ratio. It is more readily recognizable in women because of the characteristic prodromal symptoms of prolonged menstruations (4). The clinical situation may be very severe, with bleeding to the gastrointestinal tract and central nervous system or early recurrent hemarthrosis, or moderate, with bleeding from the oral cavity, epistaxis, menorrhagia. Prophylaxis with recombinant activated factor VII (rFVIIa) [coagulation factor VIIa (recombinant); NovoSeven RT; Novo Nordisk, Bagsvaerd, Denmark] is indicated for the treatment of spontaneous and surgical bleeding in congenital FVII deficiency and also in patients with acquired haemophilia, Glanzmann's thrombasthenia, and congenital haemophilia A and B with inhibitors to factors VIII (FVIII) and IX (FIX) > 5 Bethesda units (BU) (5). The dose is generally in the range of 15-30 μg/kg for any injection for factor VII deficit (3).

Case report

This report describes the case of a 26-year-old woman diagnosed with factor VII deficiency who attended the Oral Surgery Unit, Policlinico

Key words: oral surgery; third molar; extraction; bleeding disorder

Corresponding Author:
Dr Pier Carmine Passarelli,
Department of Head and Neck, Oral Surgery and Implantology Unit,
Institute of Clinical Dentistry, Catholic University of the Sacred Heart,
Gemelli University Polyclinic Foundation, Rome, Italy
Tel.: +39 0630155278 - Fax: +39 0630154751
e-mail: piercarmine.passarelli@unicatt.it

0393-974X (2020)

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

Universitario Agostino Gemelli, Rome, in April 2018 for surgical extraction of the lower left third molar. The patient was sent from the Department of Medical Sciences, Haematology Unit of Policlinico Universitario Agostino Gemelli, where she was in care. She was in good general health and reported occasional epistaxis and heavy menstruation, but no spontaneous oral mucosa bleeding. The results of coagulation studies are shown in Table I.

The prothrombin time (PT) and the International Normalized Ratio (INR) were prolonged, while the activated partial thromboplastin time (APTT) was normal. Factor VII showed a deficit of 33%, compared with the normal range of 70-140%. Factors II, V and X levels were within the range. A digital panoramic radiograph was carried out (Fig. 1), which showed a greater diagnostic precision (6). The mandibular left third molar showed radiographic evidence of a deep carious lesion. After informing the patient, we agreed on the extraction of the tooth. Systemic disease that can cause dental abnormalities (7) were evaluated in order to achieve a better management of the relative contraindications to the extractions and also to avoid absolute contraindications. The study was conducted in accordance with the requirements of the Helsinki Declaration of 1975 and the patient provided the written informed consent.

Recombinant activated factor VII (rFVIIa) (NovoSeven) was transfused intravenously in a single dose of 25μg/kg body weight 30 min before surgical extraction. After oral rinsing with chlorhexidine 0.2% for 1 min, local anesthesia was administered in a standard block and infiltrative manner using 2 cartridges (3.6 mL) of 2% carbocaine with 1:100,000 epinephrine. A triangular flap was made and, after a mild osteotomy, the mandibular third molar was extracted with lever and clamp, without complication or damage of gingival soft tissue, and the alveolar socket was cleaned with a bone curette and physiological saline. Primary closure was obtained using a 3-0 silk suture. The patient had no drug allergies; betamethasone (4 mg intramuscularly) and analgesic (Ketorolac 20mg/ml; 15 drops sublingual) were administered after the extraction. Ice packs were applied locally for the first day, and antibiotic therapy with Amoxicillin + Clavulanic Acid 1g BID for five days was started the day before surgery.

Table I. *Results of coagulations studies.*

Test	***Value***	***Normal range***
Prothorombin time (PT)	15.3s	9.5-12.5 s
International Normalized Ratio (INR)	1.9	0.80-1.20
Activated partial thomboplastin time (APTT)	40.2s	20.0-39.0 s
Coagulation Factors		
Factor II	105.2%	70-140%
Factor V	137.4%	70-140%
Factor VII	33.0%	70-140%
Factor X	97.5%	70-140%

Table II. *Post-operative information*

Day	***Bleeding***	***Pain***	***Swelling***
1	Very mild	No pain	No
2	No	No pain	Mild
3	No	No pain	Mild
4	No	No pain	No
5	No	No pain	No
6	No	No pain	No
7	No	No pain	No

Oral hygiene instructions were given to the patient to enhance the healing process during the following 6 months and to obtain better results in terms of osseous defect filling and to re-establish the supracrestal tissue attachment (8).

No intensive intraoperative bleeding or hemorrhagic complications and no postoperative bleeding were observed (Figs. 2 and 3), and the patient was discharged. All the postoperative clinical outcomes, such as pain, swelling, and bleeding were recorded (9). The patient was asked to annotate from the day of surgery for one week if she had had bleeding, swelling or pain (Table II). For bleeding and swelling, we gave four options: very mild, mild,

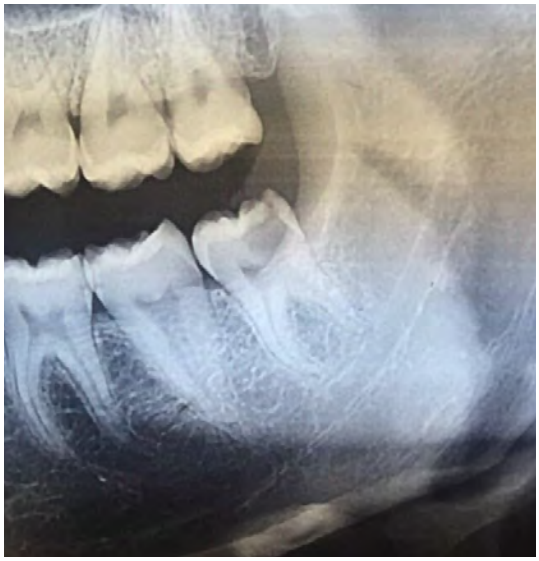

Fig. 1. *Panoramic radiograph of the mandibular left third molar shows evidence of a deep carious lesions.*

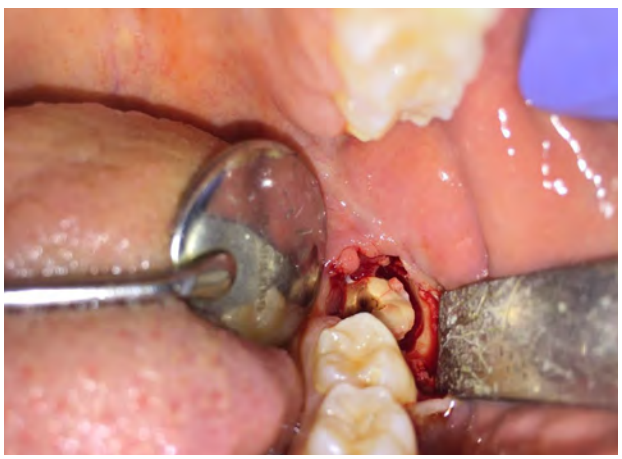

Fig. 2. *Intraoperative photo shows a good hemostasis.*

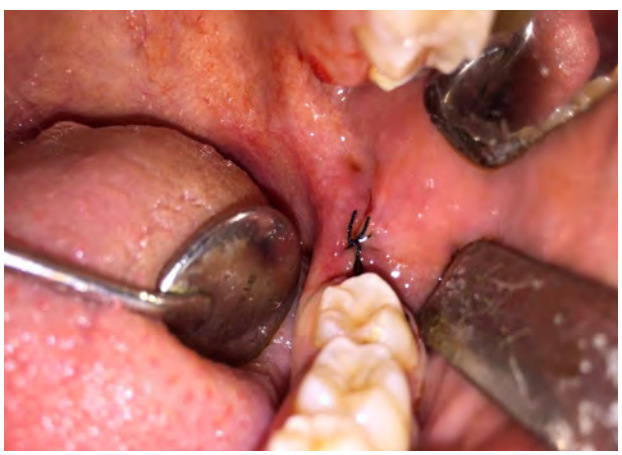

Fig. 3. *Postoperative photo shows no postoperative bleeding and the good health of the site*

moderate and severe. The pain was registered with VAS scale. She reported very mild bleeding only on the day of surgery, a mild swelling during the second and the third days and no pain in the days after wisdom tooth extraction. She did not take analgesics and antihemorrhagic during the week. The extraction site showed excellent healing at the time of suture removal, 7 days after the surgery. No thromboembolic complications following this single administration of rFVIIa were observed.

DISCUSSION

Management of patients with factor VII deficiency requiring tooth extraction involves close cooperation between the oral surgeon and the hematologist (10). The hematologist characterizes the patient's bleeding risk and determines an appropriate prophylactic regimen to prevent excessive local bleeding during and after oral interventions. Incorrect treatment of patients with factor VII deficiency who must undergo surgery may result in uncontrolled intraoperative and postoperative bleeding and hemorrhagic complications (11).

It is very important to consider the risk of bleeding and serious infections associated with invasive oral cavity procedures, and some protocols underline the importance of evaluating hematologic indices (12). In the present study, the laboratory tests included Prothrombin Time (PT), International Normalized Ratio (INR) and the Partial Thromboplastin Time (aPTT).

Recombinant factor VIIa can be used successfully to prevent copious bleeding in a patient with factor VII deficiency requiring oral surgery (11). The dose and administration frequency should be adjusted to the patient's need and the assessment of each patient before surgery should include such factors as: the risk of hemorrhage, hemorrhagic complications and infections, duration of surgery, scope and range/ extent of surgery, level of inherited FVII deficiency, as well as preoperative clinical symptoms related to FVII deficiency. Percentage of FVII plasma levels is used to estimate the risk of bleeding and hemorrhagic complications in surgical patients: very high risk for FVII plasma levels below 1%; high risk for FVII plasma levels 1-10%, medium risk for 10-25% and

low risk for >25% (3).

In the present case, a single intravenous dose of 25µg/kg body weight 30 minutes before surgical extraction was administered to the patient which prevented excessive intraoperative and postoperative bleeding, reassuring the patient who had given great concern due to her recent diagnosis of deficit of FVII. She had no need of analgesics or antihemorrhagics in the postoperative period, and reported only very mild bleeding on the day of surgery, and a light swelling on the second and third days.

In conclusion, surgical extractions appear to be safe procedures in patients with factor VII deficiency when appropriate prophylaxis with rFVIIa, prescribed by the hematologist, is used and an appropriate protocol for surgical extraction is followed, minimizing postoperative bleeding, swelling and pain.

REFERENCES

1. Wei DC, Wong RW, Robertson EP. Congenital factor VII deficiency presenting as delayed bleeding following dental extraction. A review of the role of factor VII in coagulation. Pathology 1997; 29:234-37.
2. Alexander B, Goldstein R, Landwehr G, et al. Congenital SPCA deficiency. A hitherto unrecognized coagulation defect with haemorrhage rectified by serum and serum fractions. J Clin Invest 1951; 30:596.
3. Wiszniewski A, Szczepanik A, Misiak A, Bykowska K, Szopiński P. Prevention of bleeding and hemorrhagic complications in surgical patients with inherited factor VII deficiency. Blood coagul fibrinolysis 2015; 26:324-30.
4. Perry DJ. Factor VII deficiency. Blood Coagul Fibrinolysis 2003; 14:547-54.
5. Kubisz P, Stasko J. Recombinant activated factor VII in patients at high risk of bleeding. Hematology 2004; 9:317-32.
6. Saccomanno S, Passarelli PC, Oliva B, Grippaudo C. Comparison between two radiological methods for assessment of tooth root resorption: an in vitro study. Biomed Res Int 2018; 2018:5152172.
7. Passarelli PC, Pasquantonio G, Manicone PF, Cerroni L, Condo' R, Mancini M, D'Addona A. Orofacial signs and dental abnormalities in patients with Mulvihill-Smith syndrome: A literature review on this rare progeroid pathology. Medicine (Baltimore) 2018; 97: e0656.
8. Passarelli PC, Lajolo C, Pasquantonio G, D'Amato G, Docimo R, Verdugo F, D'Addona A. Influence of mandibular third molar surgical extraction on the periodontal status of adjacent second molars. J Periodontol 2019; 90:847-55.
9. Passarelli PC, De Angelis P, Pasquantonio G, Manicone PF, Verdugo F, D'Addona A. Management of single uncomplicated dental extractions and postoperative bleeding evaluation in patients with Factor V deficiency: a local antihemorrhagic approach. J Oral Maxillofac Surg 2018; 76:2280-83.
10. Weinstock RJ, Onyejiuwa A, Shnayder G, Clarkson EI. Use of recombinant factor VII for tooth extractions in a patient with severe congenital factor VII deficiency: a case report. J Am Dent Assoc 2015; 146(4):271-75.
11. Passarelli PC, Pasquantonio G, D'Addona A. Management of surgical third lower molar extraction and postoperative progress in patients with Factor VII Deficiency: a clinical protocol and focus on this rare pathologic entity. J Oral Maxillofac Surg 2017; 75:2070.e1-2070.e4.
12. Bollero P, Passarelli PC, D'Addona A, Pasquantonio G, Mancini M, Condò R, Cerroni L. Oral management of adult patients undergoing hematopoietic stem cell transplantation. Eur Rev Med Pharmacol Sci 2018; 22:876-87.