International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Jacob KR et al. Int J Reprod Contracept Obstet Gynecol. 2024 Jan;13(1):166-169
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20234097

Case Report

Obliterative vaginal procedure for post hysterectomy vault prolapse in severe factor 7 deficiency: a case report and literature review

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Received: 03 November 2023
Accepted: 01 December 2023

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ABSTRACT

There is a concern about perioperative bleeding with any surgical intervention in patient with congenital factor VII (FVII) deficiency. The optimum dosage regimen for recombinant activated factor VII (rFVIIa) use has been not clearly established. We report a woman with post hysterectomy vault prolapse management with congenital FVII deficiency who underwent obliterative vaginal procedure. A 50-year-women with congenital FVII deficiency was diagnosed as post hysterectomy vault prolapse and planned for partial colpocleisis. She was planned to monitor FVII activity and prothrombin time international normalized ratio (PT/NR) intraoperatively. At the start of surgery, FVII activity was 3% and PT was INR 35.3 with INR of 2.83. (0.8-1.2). Presuming the improvement of 25% activity, 5 mg (70 mcg/kg body wt.) rFVIIa was administered. The PT was improved to 28.4 sec, Surgery was successfully completed without unexpected bleeding. Post operatively there was no oozing hence FVII activity and PT-INR was not checked. An additional rFVIIa dose of 2mg was given prophylactically after 12 hours of surgery. The patient was discharged on the third day after surgery without postoperative complication. In this case, rFVIIa was used just twice and there were no bleeding events during the perioperative period. Previous reports suggested using 15-30 µg/kg of rFVIIa before surgery and subsequent every 4-6 h in the first 24 h, then increasing the interval to 8-12 h. It is necessary to evaluate optimal dose of rFVIIa based on the risk and surgical invasiveness for each case. Our patient with congenital FVII deficiency uneventfully underwent obliterative vaginal procedure.

Keywords: Pelvic organ prolapse-quantification, Rare bleeding, Disorders

INTRODUCTION

Factor VII (FVII) is an important factor in the initiation of clot formation as a part of the extrinsic pathway of the blood coagulation cascade. It is a vitamin K-dependent glycoprotein synthesized in the liver. After a vascular injury, FVII interacts with factor III as a primary event and is cleaved to its active form. The complex of factor III and activated FVII serves to activate factors IX and X and then autocatalyze and activate FVII.[1]

The most common inherited coagulation factor deficiencies are Von Willebrand disease, haemophilia A, and haemophilia B. Other rare bleeding disorders (RBD) include inherited coagulation factor deficiencies of fibrinogen as well as factors II, V, VII, X, XI, XIII, combined factor V+ VIII deficiency, and vitamin K-dependent coagulation factor deficiency.[2] Of all the Inherited deficiencies of coagulation factors only 3-5% are due to RBD.[3]

Alexander et al first described the congenital deficit of FVII also known as serum prothrombin conversion accelerator deficiency, hypoproconvertinemia, stable factor or proconvertin deficiency, and Alexander's disease.[4] The mutations in the gene F7 (13q34), a rare autosomal recessive disorder, result in a severe deficiency in the homozygote and a moderate deficiency in the

heterozygote.[5] The estimated prevalence of factor VII deficiency is approximately 1/500,000 with a similar rate in men and women.[6] The spectrum of clinical features can range from very severe, with bleeding in the gastrointestinal tract and central nervous system or recurrent hemarthrosis, to moderate, with bleeding from the oral cavity, epistaxis, and menorrhagia. The international society on thrombosis and hemostasis has reclassified FVII deficiency as severe (activity >10%) are at increased risk of spontaneous major bleeding; moderate (activity 10-20%) have a risk of mild spontaneous or triggered bleeding; and mild (activity 20-50%) are mostly asymptomatic.[4] However, the plasma FVII activity level weakly correlates with bleeding risk, even within the same individual over time.

There is scanty data available in the literature about the surgical management and outcome of factor VII (FVII) deficiency. The STER (Seven treatment evaluation registry) is a multi-centre, prospective, observational, web-based study protocol providing the frame for structured and detailed data collection. The recommended methods to prevent intra-operative haemorrhages are fresh frozen plasma, prothrombin complex concentrate, plasma-derived factor VII concentrate, and recombinant activated factor VII (rFVIIa).

Recombinant activated coagulation factor VII (rFVIIa; Novoseven® RT; Novo Nordisk A/S, Bagsvrd, Denmark) is a highly purified recombinant protein approved by the US food and drug administration.[7] It is used for the treatment of bleeding episodes and the prevention of bleeding in surgical interventions or invasive procedures in patients with haemophilia A or B, congenital FVII deficiency (C7D), Glanzmann's thrombasthenia (GT), and acquired haemophilia.[3,8] The dose is usually in the range of 15 to 30 g/kg mc for any injection.[9]

CASE REPORT

A 53-year-old woman presented with progressive increasing bulge per vagina for two years. Initially, the bulge appears only after prolonged standing or straining and did not affect the quality of life. However, it gradually worsened, and the bulge persists in lying down.

She also has a complaint of increased frequency of urination and a feeling of incomplete voiding. There was no urge or stress incontinence. She was evaluated elsewhere and diagnosed with post-hysterectomy vault prolapse. The preoperative evaluation showed abnormal coagulation parameters so referred for further management.

There was no history of heavy or prolonged menstrual bleeding, had three uneventful vaginal deliveries. There was no medical comorbidities and she had undergone abdominal hysterectomy two years back. She was not on any medication that decreases the activity of factor -VII or factor -VII inhibitors.

Coagulation parameter was abnormal with prolonged prothrombin time (35.3 seconds, normal range 11.7-16.1 seconds), and the time-international normalized ratio (PT-INR) was prolonged (normal: 2.83) and the APTT was 25.8 seconds. She has stage three pelvic organ prolapse (POP) according to the international continence society POP quantification system (POP-Q) (Figure 1 and 2). As she did not have the desire to retain sexual function and hence wished to go ahead with the obliterative vaginal surgery as colpocleisis.

Investigation

In the coagulation workup, factor VII activity was decreased to 3%. The absence of activity was diagnosed as congenital deficiency; as there was no medication history or underlying liver dysfunction. As a part of diagnostic evaluation, oral vitamin K (Phyto menadione/Kenadione) was given for 3 days. Prothrombin time was persistently prolonged, with INR of 2.83. As there was no improvement in coagulation parameters despite of Vitamin K correction, deficiency of Factor VII was confirmed. As factor VII assay showed persistently low activity of 3%, she was hence classified as having a severe factor VII deficiency.[4]

Perioperative management

Vaginal obliterative procedure was planned for vault prolapse, i.e., Partial colpocleisis. In conjunction with haematologists planned to monitor FVII activity and PT-INR intraoperatively and to be maintained at more than 10% FVII activity. At the start of surgery, FVII activity and PT-INR were 3% and 35.3 sec, respectively (Table 1). Presuming the improvement of 25% activity, she was administered 5 mg (70 mcg/kg body wt.) (Novoseven) intravenously prior to induction for the general anesthesia.[9]

Partial colpocleisis was done, there was no intraoperative difficulty or unexpected bleeding or oozing. The duration of surgery was 60 minutes, and the total blood loss was 100 ml. Postoperatively, a vaginal pack was kept for compression for 6 hours and inj. Tranexamic acid was given for 24 hours. An additional rFVIIa dose of 2 mg was given prophylactically after 12 hours of surgery.

In view of absence of bleeding or oozing from the surgical site, no further testing was done. On 3rd postoperative day she was discharged and had no post operative complication. The whole perioperative course of PT-INR and FVII activity and the timing of administration of rFVIIa are shown in Figure.

Outcome and follow-up

On follow up after surgery after 10 days and 2 months, there was no bleeding or oozing from the surgical site. The repeat investigations were found to be normal.

Table 1: Liver function tests and coagulation profile- pre- and peri-operatively.

Variables	Pre-operative investigation	Peri-operative investigation
Hb (gm/dl)	11.5	11.2
PT (sec)	35.3	28.4
APTT (sec)	25.8	--
INR	2.83	2.27
Factor VII	3%	--
Total bilirubin (mg%)	0.1	0.14
Bilirubin direct (mg%)	0.33	0.29
Protein total (mg%)	6.9	6.7
Albumin (%)	4.4	4.1
SGOT (U/L)	20	21
SGPT (U/L)	16	13
ALP(U/L)	119	99

PT: prothrombin time, PT-INR: International Normalized Ratio of Prothrombin Time,

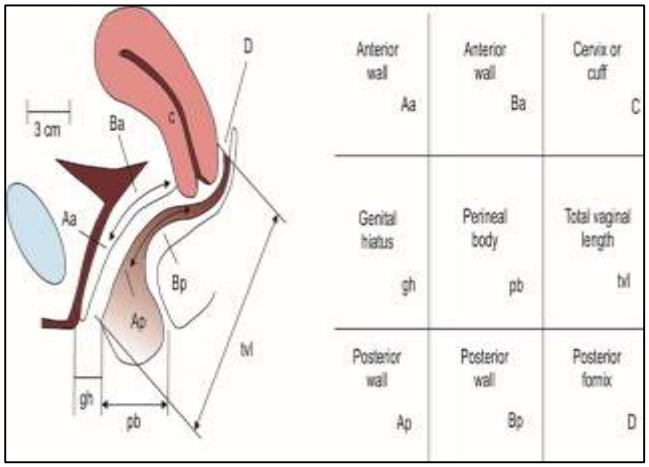

Figure 1: POP quantification system (international continence society).

Figure 2: Stage 3 vault prolapse.

DISCUSSION

With any surgical intervention there is an increased risk of intraoperative or post operative hemorrhage in a patient with FVII deficiency without replacement therapy. Recommended approach for the replacement therapy as maintenance therapy/ continuous infusion during surgery.

Maintenance therapy is used in patient with a history of recurrent bleeding and FVII activity between 10-15%. Menegatti et al reported that the half-life of rFVII is 4-6 h and the peak level of activity reached up to 10-15%. It was suggested to use 15-30 µg/kg rFVIIa before surgery and subsequently every 4-6 h in the first 24 h, then to increase the interval to 8-12 h (10).

Successful results with the use of recombinant activated FVII (rFVIIa, Novoseven; Novo Nordisk health care AG, Zurich, Switzerland) have been reported in many cases, but there is no clear optimal treatment regimen. The common approach is to administer rFVII at a dose of 15-30 µg/kg at 4-hour intervals.[11,12]

Other dosing schedule suggested by Tran et al as continuous infusion during surgery.[13] In a systemic review, the dosing reported were ranging from 0.2-30 µg/kg/h. But consistent rate derived from dividing the recommended bolus dosing of 15–30 mcg/kg by the recommended 4-6-hour dosing interval.[14]

Although rFVII helped in preventing bleeding events during the perioperative period, however it also increases the risk of thrombus formation and the development of inhibitory antibodies.[13] Levi et al reported that use of high-dose rFVIIa on- and off-label basis increased the risk of arterial thromboembolic events.[15]

Deciding the appropriate amount of rFVIIa through careful monitoring in the perioperative period is therefore necessary. In our patient, we planned to check FVII activity every 4-6 h and used rFVIIa to maintain FVII activity above 10%.

Considering this bolus dose of 70 µg/kg rFVIIa was given with the expectation to maintain the peak plasma level to be at least 25% and last for at least 6-8 hours. During the perioperative period, FVII activity and PT-INR were monitored. The duration of surgery was 60 min, with minimal blood loss, therefore another dose of 2 mg of rFVIIa was given. On the second day after the surgery, the vaginal pack was removed, and there was no extra bleeding. We used rFVIIa only twice, and there were no bleeding events during the perioperative period. It is therefore necessary to evaluate the optimal dose of rFVIIa based on the risk and surgical invasion of each case.

Learning points

Factor VII deficiency is a rare congenital bleeding disorder-that needs to be managed with a multi-

disciplinary approach, for peri-operative patients, and to assess bleeding risk based on the type pf surgery ad prior bleeding history.

Organized management and dosing algorithm is yet to be standardized, and hence, an individualized approach needs to be considered.

The patient and relatives need to be made aware of the extensive investigations, need for expensive therapies in the form of Rfvii and need for further transfusions and possibility of ICU care, following which their consent for the above needs to be obtained.

CONCLUSION

Our patient with congenital FVII deficiency uneventfully underwent obliterative vaginal procedure.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Jacob KR, Kumari M. Obliterative vaginal procedure for post hysterectomy vault prolapse in severe factor 7 deficiency: a case report and literature review. Int J Reprod Contracept Obstet Gynecol 2024;13:166-9.