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# A Dose of NovoSeven - rFVIIa In Management of DIC with Sepsis.

Medicine

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## ABSTRACT

NovoSeven® is recombinant human coagulation Factor VIIa (rFVIIa), intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade. NovoSeven is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues (MW 50 K Dalton). NovoSeven is structurally similar to human plasma-derived Factor VIIa. We report a case of 32-year-old female patient of P2L2 who had oozing from suture line and per vaginal bleeding post-emergency LSCS. She was managed with massive blood transfusion of total 10-units cryoprecipitate, 6-units PRBC, 8-units FFP, 4-units RDP and 5-SDP and 1 dose of
Injection Factor VII 4 mg given 90mcg/kg - NOVOSEVEN (4500 mcg)- 4 mg bolus IV. Following which she recovered better with her parameters under normal range.

## KEYWORDS:

NovoSeven-rFVIIa, DIC, Sepsis, Post-LSCS.

**INTRODUCTION:**

NovoSeven is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues (MW 50 K Dalton). NovoSeven is structurally similar to human plasma-derived Factor VIIa. It is recombinant human coagulation Factor VIIa (rFVIIa), intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade.[1] We report a case of 32-year-old female patient of P2L2 who had oozing from suture line and per vaginal bleeding post-emergency LSCS. She was managed with massive blood transfusion of total 10-units cryoprecipitate, 6-units PRBC, 8-units FFP, 4-units RDP and 5-SDP and 1 dose of
Injection Factor VII 4 mg given 90mcg/kg - NOVOSEVEN (4500 mcg)- 4 mg bolus IV. Following which she recovered better with her parameters under normal range.

**CASE REPORT:**

A 32-year-old female patient of Para2, Life2 came to our emergency department after an emergency Lower Segment Caesarian Section(LSCS) in other outside hospital with complaints of oozing from suture line and per vaginal bleeding. She developed hematuria 2-hours prior to her arrival. Before her referral for further management she was given 3-units of Packed Red Blood Cells(PRBCs) and 2-units of Fresh Frozen Plasma(FFPs). Her obstetric history of marriage at 30-years of age, LLB-2years, 1st born child conceived spontaneously, FT-LSCS(PIH) with history of anemia during her 1st pregnancy. 2nd child conceived spontaneously, she was supplemented with Iron, Folic acid, Calcium during her course, had hypertension at 6-months for which was managed with anti hypertensives with a day of hospital admission. At 37-weeks and 5-days she complained of pain abdomen for which emergency LSCS was done. Child was born with birth weight of 2.3kg. Patient on examination was anxious with pallor, bleeding per-vaginally and had epigastric rebound tenderness. USG abdomen showed gross ascites with encirclage along mesentry, hypoechoic area at and around the abdominal incision site.

Her investigations showed Hb: 5.4, APTT:119.6, Plt count: 54,000, SGOT: 43, Urea: 32, PT:15, Creat:1.19, T.Bil: 4.01, PT: 76.5, Direct Bil: 2.82, INR 7.54. CECT abdomen showed contrast leak present, moderate hemoperitoneum anterior to uterus, bulky uterus with endometrial collection and surgical defect noted in anterior wall of lower uterine segment. Her initial management of massive blood transfusion with 4-units PRBC, 10-units cryoprecipitate , 5-units FFP, 3-units RDP, 1-unit SDP; Injection Vitamin K 2cc intravenously slow infusion for 3-days; Injection Calcium; Injection Metrogyl 500mg; injection Calcium gluconate. With Injection Noradrenaline support under sedation of Injection Fentanyl. Planned exploratory laparotomy done with bilateral

ligation of internal illiac artery and drain placement, she was intubated in OT. Post-operatively she was given Injection Factor VII 4-mg 90mcg/kg (NOVOSEVEN- 4500 mcg)- 4 mg bolus IV given with transfusion of 2-PRBC, 4-cryoprecipitate and 1-SDP. Day-2 investigation showed Hb : 10.4, TLC : 3,800, Platelet : 34,000, PT : 19.0, INR : 1.49 and APTT Test : 38.8.

Arterial line was placed for ABP monitoring and sample collection, Injection Calcium Gluconate was stopped, Injection Fentanyl infusion continued and Injection Noradrenaline stopped.

She was given Inj Piperacillin Tazobactum 4.5 gm Thrice daily, Inj Esomeprazole 40 mg IV Twice daily, Inj Vitamin-K 2cc IV slow once daily, Inj Optineuron 3cc IV once daily, Inj Tramadol 100 mg IV thrice daily, Syp Potklor 20 ml Thrice daily.

**Day-3**
She was given IVF RL/ Plasmolyte at 100 ml/hr and was extubated. Investigations showed Hb:11.9, TB:5.31, TLC:17,200, Direct Bil: 2.78, Plt ct:53,000, PCT: 76, TP: 3.9, Urea: 77, PT: 18, Creat:1.44, INR:1.4, SGOT:71, SGPT:28.

**Day-4**
Patient was better.
Investigations:
Hb:10.8, TLC:10,500, Plt Ct:37,000, Urea:66, Creat:1.12, K:3.35, TB:6.4, DB 3.7.

To her medication Tab Ultracet thrice daily was added, 1-Unit SDP transfused, Incentive spirometry and deep breath exercises advised, 40mg Kcl in 1unit 5D given over 1-hour, Injection Piperacillin and Tazobactam 4.5 gm added Thrice daily.

**Day-5**
General conditions improved and was having minimal per vaginal bleeding.

Investigations showed Hb: 10.4, TLC: 8900, Plt ct: 34,000, SGOT:60, SGPT:25.

IVF fluid was decreased to 40 ml / hour, Tab Tranexamic acid 500 mg Thrice daily, High protein diet was prescribed and 1-unit SDP was given.

**Day-6**
She was hemodynamically stable with investigations showing Hb:10.9, TLC:9000, Plt ct: 44,000, PT:33.8, INR 1.02 and APTT: 27.5. Tab Ultracet , Tab Tranexa , Tab Lesuride were stopped and IVF RL / plasmalyte at 40 ml/hour.

**Day-7**
Investigations showed Hb : 10.2, Platelets : 62,000, S.Potassium : 4.06. Planned for drain removal and shift patient to room and adding Lascilatone 1 tab Once daily, Tab Ferronia D3 once daily, Tab Florstore once daily.

**Day-8**
Planned for discharge.
Her investigations were Hb: 11.3, Plt ct:1.06.

She was discharged on day-10 with advise of taking calcium, iron and follow-up review after 5 days.

**DISCUSSION:**
Description NovoSeven:
NovoSeven is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues (MW 50 K Dalton). NovoSeven is structurally similar to human plasma-derived Factor VIIa.

The gene for human Factor VII is cloned and expressed in baby hamster kidney cells (BHK cells). Recombinant FVII is secreted into the culture media (containing newborn calf serum) in its single-chain form and then proteolytically converted by autocatalysis to the active two-chain form, rFVIIa, during a chromatographic purification process. The purification process has been demonstrated to remove exogenous viruses (MuLV, SV40, Pox virus, Reovirus, BEV, IBR virus). No human serum or other proteins are used in the production or formulation of NovoSeven.

NovoSeven is supplied as a sterile, white lyophilized powder of rFVIIa in single-use vials.

After reconstitution with the appropriate volume of Sterile Water for Injection, USP (not supplied), each vial contains approximately 0.6 mg/mL NovoSeven (corresponding to 600 g/mL). The reconstituted vials have a pH of approximately 5.5 in sodium chloride (3 mg/mL), calcium chloride dihydrate (1.5 mg/mL), glycylglycine (1.3 mg/mL), polysorbate 80 (0.1 mg/mL), and mannitol (30 mg/mL).

The reconstituted product is a clear colorless solution which contains no preservatives. NovoSeven contains trace amounts of proteins derived from the manufacturing and purification processes such as mouse IgG (maximum of 1.2 ng/mg), bovine IgG (maximum of 30 ng/mg), and protein from BHK-cells and media (maximum of 19ng/mg).

NovoSeven is recombinant Factor VIIa and, when complexed with tissue factor can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis. This process may also occur on the surface of activated platelets.

In a separate model, and in line with previous reports[2], escalating doses of NovoSeven in hemophilia plasma demonstrate a dose-dependent increase in thrombin generation.
The normal Factor VII plasma concentration is 0.5 g/mL. Factor VII levels of 15-25% (0.075 – 0.125 g/mL) are generally sufficient to achieve normal hemostasis.[3]

**INDICATIONS AND USAGE**
NovoSeven is indicated for:
1. Treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or
Factor IX and in patients with acquired hemophilia.

2. Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B, patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia.

3. Treatment of bleeding episodes in patients with congenital FVII deficiency.

4. Prevention of bleeding in surgical interventions or invasive procedures in patients with congenital FVII deficiency. NovoSeven should be administered to patients only under the supervision of a physician experienced in the treatment of bleeding disorders.

In our patient the indication for use of NovoSeven in view of DIC which was not resolving inspite of massive blood transfusion prior to administration. Also included treatment of bleeding episodes and prevention of bleeding episodes in surgical intervention.

**Labor and Delivery**
NovoSeven was administered to a FVII deficient patient (25 years of age, 66 kg) during a vaginal delivery (36 μg/kg) and during a tubal ligation (90 μg/kg). No adverse reactions were reported during labor, vaginal delivery, or the tubal ligation.

**CONTRAINDICATIONS**

NovoSeven® Coagulation Factor VIIa (Recombinant) should not be administered to patients with known hypersensitivity to NovoSeven or any of the components of NovoSeven. NovoSeven is contraindicated in patients with known hypersensitivity to mouse, hamster, or bovine proteins.

**WARNINGS**

The extent of the risk of thrombotic adverse events after treatment with NovoSeven in patients with hemophilia and inhibitors is not known, but is considered to be low. Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates) may have an increased risk of developing thrombotic events due to circulating TF or predisposing coagulopathy.

The extent of the risk of arterial and venous thromboembolic adverse events after treatment with NovoSeven in patients without hemophilia is also not known. A clinical study in elderly non-hemophilia intracerebral hemorrhage patients indicated a potential increased risk of arterial thromboembolic adverse events with use of NovoSeven, including myocardial ischemia, myocardial infarction, cerebral ischemia and/or infarction.[4]

Our patient was not hypersensitive to NovoSeven or it's components.

**PRECAUTIONS**

General

Patients who receive NovoSeven should be monitored if they develop signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, the rFVIIa dosage should be reduced or the treatment stopped, depending on the patient's symptoms.

Due to limited clinical studies which clearly address the effect of post-hemostatic dosing, precautions should be exercised when NovoSeven is used for prolonged dosing.

Factor VII deficient patients should be monitored for prothrombin time and factor VII coagulant activity before and after administration of NovoSeven. If the factor VIIa activity fails to reach the expected level, or prothrombin time is not corrected, or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed.

**Information for Patients**

Patients receiving NovoSeven should be informed of the benefits and risks associated with treatment. Patients should be warned about the early signs of hypersensitivity reactions, including hives, urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

**Drug Interactions**

The risk of a potential interaction between NovoSeven and coagulation factor concentrates has not been adequately evaluated in preclinical or clinical studies. Simultaneous use of activated prothrombin complex concentrates or prothrombin complex concentrates should be avoided.

Although the specific drug interaction was not studied in a clinical trial, there have been more than 50 episodes of concomitant use of antifibrinolytic therapies (i.e., tranexamic acid, aminocaproic acid) and NovoSeven.

NovoSeven should not be mixed with infusion solutions until clinical data are available to direct this use.

**ADVERSE REACTIONS**

The most serious adverse reactions observed in patients receiving NovoSeven are thrombotic events, however the extent of the risk of thrombotic adverse events after treatment with NovoSeven in individuals with hemophilia and inhibitors is considered to be low. The most common adverse reactions observed in clinical studies for all labeled indications of NovoSeven are pyrexia, hemorrhage, injection site reaction, arthralgia, headache, hypertension, hypotension, nausea, vomiting, pain, edema and rash.

**DOSAGE AND ADMINISTRATION**

Dosage

NovoSeven is intended for intravenous bolus administration only. Evaluation of hemostasis should be used to determine the effectiveness of NovoSeven and to provide a basis for modification of the NovoSeven treatment schedule; coagulation parameters do not necessarily correlate with or predict the effectiveness of NovoSeven.

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