Adjunct use of NovoSeven (recombinant factor VIIa) for penetrating cardiac trauma


Abstract

Background: Uncontrolled bleeding leads to 40-86% of preventable deaths due to trauma. Use of NovoSeven (rFVIIa) in trauma is promising, although data supporting its utilization are limited.

Case report: We report the case of a patient who sustained a penetrating grade V cardiac injury (AAST-OIS) and presented postoperative massive coagulopathic bleeding arrested by the administration of platelet pools and NovoSeven.

Discussion: This report represents our initial experience and the very first case of successful use of NovoSeven for the treatment of traumatic coagulopathic hemorrhage at the Central Military Hospital in Mexico City. A further prospective trial justifying its use in our institution is warranted.

Key words: recombinant factor VIIa, hemorrhage, trauma, coagulopathy.

Introduction

Uncontrolled bleeding causes 40-86% of preventable deaths due to trauma. Surgical hemorrhage and coagulopathy (hemodilution, consumptive coagulopathy, hypothermia and metabolic derangement) are the principal factors.1-4 For the trauma surgeon, having the ability to control bleeding is a valuable tool in order to reduce mortality. With this in mind, new techniques, devices and medications have been developed to be used in the continuum of trauma care.1,3-5

Throughout history, penetrating cardiac trauma is a challenge for the trauma surgeon7 and the best example of the pathophysiology of uncontrollable traumatic hemorrhage.3,4 Bleeding is not only due to injury of the central circulatory organ, but also to the physiological exhaustion secondary to the metabolic disorder generated by the surgical procedure, pharmacological interventions and massive fluid and blood derivatives required for patient stabilization. Classically this is dramatically manifested in the immediate postoperative period as a coagulopathic hemorrhage.6

Recombinant factor VII-a [NovoSeven (rFVIIa), Novo Nordisk A/S, Bagsvaerd, Denmark] is indicated in various regions of the world for treatment of bleeding episodes in the case of hemophilia A/B, factor VII deficiency and Glanzmann thrombasthenia refractory to hemotherapy.2,6 Recombinant factor VII-a, by forming a complex with the tissue factor at the site of the lesion, promotes hemostasis through extrinsic coagulation routes, activating factors IX and X. Factor X-a combined with other factors converts prothrombin to thrombin and generates a hemostatic seal for the conversion of fibrinogen to fibrin.2 Although the use of recombinant factor VII-a in trauma appears to be promising, data establishing its use are very limited.1,4,6-8,13
We report the case of a patient with a penetrating grade V cardiac lesion according to the degree scale for organ lesions classified by the American Association for Trauma Surgery (AAST-OIS)\(^7\) and admitted by the Trauma Surgery Service of Hospital Central Militar. Patient presented incoercible bleeding during the first postoperative hours, effectively controlled with recombinant factor VII-a. To the best of our knowledge this represents the first report of successful use of this medication in our institution and in Mexico and is a stimulus for developing prospective studies directed to the design of an institutional protocol for use of recombinant factor VII-a in patients with non-surgical uncontrollable traumatic bleeding.

**Clinical Case**

We present the case of a 26-year-old male who was admitted to the emergency service with multiple wounds from a sharp object. On admission he was tachycardic (104/min) and hypotensive (90/50 mmHg) and was treated in the trauma/shock care unit according to the manual of the American College of Surgeons. The following were found: psychomotor agitation, alcoholic breath, four chest wounds from a sharp object (two of them in the precordium) and three penetrating abdominal wounds. Decrease of ventilation in both pulmonary bases was detected and resonance of the left hemithorax. A pleural tube was inserted in each hemithorax and almost 1 liter of bright red blood was obtained. There were also signs of unmistakable peritonism. Ultrasound reported abundant intrapericardiac fluid. The patient was transferred to the operating room for urgent surgical treatment. An anterolateral left thoracotomy was done in which a grade V AAST-OIS cardiac lesion was detected (3-cm transmural laceration of the left ventricle) along with active bleeding, and massive hemothorax. The lesion was repaired with “U” sutures of 2-0 polypropylene reinforced with Teflon pledgets. The patient presented with transoperative ventricular fibrillation successfully managed with cardiac massage and vasoactive substances. The only finding on exploratory laparotomy was a vascular abdominal lesion (grade I AAST-OIS). Thoracotomy was approached with a definitive repair technique and the abdominal wall was managed with temporary prosthetic closure using a plastic bag.

The patient presented hemodynamic stability in the first 6 postoperative hours in the intensive care unit. During this time the average output from the left pleural drain was 95 ± 27 ml/h (50-120) and from the right 12 ± 11 ml/h (0-30). However, in the 6 h postoperatively, output from the left pleural drain reached a magnitude of 930 ml and continued with 830 ml (Figure 1). Fluid and blood derivative requirements increased and vasopressors were initiated to stabilize gasometric variables and mean arterial pressure between 60 and 80 mmHg. Laboratory studies performed in the intensive care unit showed a hemoglobin of 9.1 g/dL, hematocrit 26.8%, leukocytes 8600/µL and platelets 15,000/µL. Correction of these parameters was attempted with fresh plasma, concentrated erythrocyes and platelets without clinical response. Even though the possibility that the source of the hemorrhage could be dehiscence of the cardiorrhaphy was not excluded, the trauma surgeon, along with the critical medicine and hematology services, took into consideration as a first diagnostic option coagulopathic bleeding and decided to use platelet pools and recombinant factor VII-a as a one-dose (90 µg/kg as a bolus [8.1 mg] or two vials of 4.8 mg to round off the quantity to the next vial as is indicated in the pharmacopea). The result was the abrupt drop of left pleural tube output to 450 ml in the next hour (Figure 1), maintaining an average flow of 97 ± 73 ml/h (mean 80, range: 20-170) the rest of the day and a decrease in fluid requirements and blood products administered (Figure 2). The patient evolved favorably in the following days, with decreasing output via the pleural tubes, mainly on the left side. The abdominal wall was closed by deferred primary intention without use of a prosthesis and without cavitary bleeding. The patient was discharged from the intensive care unit on the 9th hospital day, hemodynamically stable and without pleural tubes. Echocardiogram showed normal cardiac structure. Outpatient follow-up at the 6th week did not show any residual or persistent thoracic bleeding.

**Discussion**

It is currently known that uncontrollable hemorrhage is one of the main causes of perioperative mortality in a critically injured patient, as well as in those patients with sepsis and with multiple transfusions. These entities have in common microvascular damage
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...pathophysiologically characterized by deficient synthesis of thrombin due to a decrease in the levels of factors I, V, VII, IX, XI and platelets, resulting in the formation of a secondary clot, friable and sensitive to fibrinolysis. Carrillo-Esper, in an excellent literature review, reported that the process of coagulation is actually conceptualized not as a humoral phenomenon in which soluble proteins control physiological events, considering cells only as providers of phosphatidylserine residue that activate the pro-coagulation complexes, but as a cellular model that upon breaking away from the previous paradigm establishes that coagulation is regulated by the interaction of the complex comprised by activated/tissue factors VII and properties of the platelet cell surface and not by different humoral routes (extrinsic and intrinsic).

...A large number of historical, clinical and military series have reported on the serious effects on an injured patient’s coagulation profile caused by heroic resuscitation measures. Ledgerwood, in a series of 22 trauma patients with hemorrhagic shock, determined the platelet count, coagulation time and platelet aggregation activity in vitro at the time of initial surgical intervention and at 5, 15, 36, 84 h and 26 days postoperatively in order to estimate the effect of resuscitation on primary hemostasis (platelet cluster), secondary hemostasis (fibrin clot) and fibrinolysis. The author found a significant decrease in platelet count and PTT, PT and partial thromboplastin due to reduced fibrinolysis. The quantity of fibrin degradation products was also determined with the finding that fibrinolysis was not seriously affected in patients. With these parameters the author objectively demonstrated that the dilutional and immunological effect of massive infusion of fluids and blood products, rheological consequence of bleeding/acute anemia, and the deleterious metabolic effects of hypothermia and acidosis in the activity and cell vitality alter the critically injured patient’s capacity to achieve an adequate hemostasis.

...With knowledge of the cellular theory of coagulation, Novoseven has been used successfully in the management of microvascular bleeding in gravely ill patients and as therapy in episodic bleeding due to a great variety of coagulopathies. As previously mentioned, its consistent action in the local promotion of hemostasis at the site of the lesion without inducing systemic hypercoagulability as well as being effective 10 min after administration suggests that it can be a valuable adjunct to control coagulopathic hemorrhage in trauma patients. Multiple experimental studies, isolated or anecdotal cases, and limited clinical series have attempted to endorse the use of this medication in trauma. Martinowitz reported the use of recombinant factor VII-a in seven multi-trauma victims multi-transfused due to massive bleeding, finding a statistically significant difference in the need for blood products, prothrombin time, partial thromboplastin and serum levels of factor VII before and after administration of the drug. Similarly, the author pointed out a mortality rate of 43% due to continuous hemorrhage or thromboembolism. In Dutton’s series, recombinant factor VII-a was administered to five trauma patients with a noticeable difference in the requirement for erythrocyte concentrates and plasma during pre- and postadministration of the drug. The author also pointed out the inability of recombinant factor VII-a to stop hemorrhage in 40% of the cases (n = 2), victims of critical seriousness. Boffard, on the basis of two parallel randomized studies (double-blind and controlled with placebo that integrated a series of 301 trauma patients), reported that recombinant factor VII-a drastically decreased and in a statistically significant manner the need for erythrocyte concentrates and massive transfusion in the group in which the drug was administered, when compared with the group of patients who received the placebo. Martinowitz reported the use of recombinant factor VII-a in 36 trauma patients and found statistically significant differences in the magnitude of acidosis and of bleeding, as well as prothrombin time and partial thromboplastin before and after its administration. Barletta, in a review of the literature relative to the use of recombinant factor VII-a, gathered data from 26 trauma patients demonstrating that the use of the drug achieved hemostasis in 77% of the cases. It is noteworthy that in a recent poll of unpublished results by Martinowitz two thromboembolic complications were revealed only in 4/5522 patients treated with recombinant factor VII-a between 1996 and 2000.

**Figure 2.** Requirements of fluid, blood derivatives and vasopressor drugs (mL) before and after administration of factor VII-a. Yellow line points to the time during which recombinant factor VII-a was used (4:00 P.M.). (x-axis = time; y-axis = quantities in mL).
For the effects of evidence-based medicine, the Orlando Regional Medical Center has provided the following recommendations (all level III):

1. Consider the use of recombinant factor VII-a only when bleeding is refractory to all modalities of conventional treatment (surgical control of hemorrhage, correction of hypothermia, and coagulation parameters).

2. Avoid the use of recombinant factor VII-a in patients at high risk of thromboembolic disease (history of thromboembolism, crush injury, advanced atherosclerosis, cerebral trauma) and lethal lesions with a high index of gravity.

3. The following should be observed in order to administer recombinant factor VII-a: (a) assure an appropriate platelet count before administration and (b) administer 90 µg/kg—rounding off the quantity to a complete vial—during a lapse of 2-5 min. Recombinant factor VII-a (NovoSeven) is available in vials of 1.2 mg (1200 units) and 4.8 mg (4800 units).

We know that demonstrating hemostatic effects of a drug during a major traumatic hemorrhage presents with great difficulty. According to the levels of evidence and although all the information provided does not offer conclusive results, we establish a clear temporary correlation among the use of platelet pools and use of recombinant factor VII-a and control of thoracic bleeding. We consider that these were the critical interventions in which to control coagulopathic bleeding. The initial experience obtained in the institution with the use of recombinant factor VII-a deserves full attention from the Service of Trauma Surgery and prompts us to design an institutional prospective study to justify use of this adjuvant treatment for coagulopathic hemorrhage due to trauma.

References


