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## Case Report

# Prophylactic use of NovoSeven in surgical procedures in a patient with coagulation disorders in the course of abdominal actinomycosis

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### ABSTRACT

**Introduction:** Recombinant activated factor VII (rVIIa – NovoSeven, Novo Nordisk Pharm, Denmark) is commonly used in the treatment of coagulation disorders. At present, numerous studies are being carried out with reference to expanding the indications for this drug, especially in preventing perioperative bleedings in patients at a high risk for bleeding as a result of various coagulation disorders such as hemophilia.

**Aim:** The aim of this work was to assess the effectiveness of a prophylactic use of rVIIa in patients with complex coagulation disorders before surgery or invasive procedures.

**Materials and methods:** This paper presents a case report concerning a patient with abdominal actinomycosis hospitalized at the Intensive Care Unit (ICU), who developed peritonitis and severe coagulopathy of a complex etiology and required massive transfusions of blood products. During his 200-day hospitalization, initial treatment comprised invasive procedures without the preventive use of rVIIa; however, later on due to severe bleedings accompanying treatments, NovoSeven was administered as a preoperative prophylaxis. After treatment, blood loss related to invasive procedures and transfusion requirements were assessed and compared to no drug use during the invasive procedures as well as during prophylactic NovoSeven administration.

**Results and discussion:** Preoperative use of NovoSeven resulted in reducing significant perioperative bleedings; moreover, there was a decrease in the requirement for postoperative blood transfusions.

**Conclusions:** Supplementation of morphotic blood elements and coagulation factors in the form of fresh frozen plasma and cryoprecipitate frequently does not result in obtaining the desired outcome of clinically effective hemostasis. The additional supply of rVIIa in such cases enables one to control bleeding. Preventive use of NovoSeven seems to be effective in reducing the

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frequency of perioperative bleedings that require blood products transfusions, particularly in patients with complex coagulopathy.

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## 1. Introduction

Recombinant activated factor VII (rVIIa – NovoSeven, Novo Nordisk Pharm, Denmark) is commonly used in the treatment of coagulation disorders. Originally, it was registered to be applied in congenital hemophilia, acquired hemophilia with inhibitors, factor VII deficiency, Glanzmann's thrombasthenia with antiplatelet antibodies or platelet resistance.<sup>3,8</sup> Presently, numerous studies are being carried out concerning the "off-label" use of this drug. Thus far, NovoSeven has been proven to be effective in the treatment of bleedings in patients on oral anticoagulation and heparin, in patients with liver diseases and uremia, in patients with massive bleedings triggered by injury or trauma without any pre-existing hemorrhagic diathesis, in the case of intracranial hemorrhage, post-partum bleeding, and as a prophylaxis in emergency surgery in patients treated with acenocoumarol.

NovoSeven has also been studied as a prophylactic measure aimed at reducing blood autotransfusions prior to prostatectomy, hip replacement, liver transplantation as well as in cardiac surgery.<sup>1,5,6,7,8,9,10</sup> This paper discusses an effective prophylactic use of NovoSeven in a patient with multiple organ dysfunction syndrome (MODS) in abdominal actinomycosis.

## 2. Aim

The aim of this paper is to evaluate the effectiveness of a prophylactic use of rVIIa in a patient with a complex coagulation disorder prior to surgery and invasive procedures.

## 3. Materials and methods

A 48-year old patient was admitted to the ICU due to MODS (APACHE II, score – 33, predicted mortality – 87.7%) and septic shock following numerous laparotomies due to peritonitis in the course of actinomycosis. Originally, the patient was operated on due to the perforation of a sigmoid tumor and peritonitis. Histopathological tests of the tumor revealed an *Actinomyces israelii* infection. During his hospitalization, in association with MODS, the patient developed, i.a., significant and treatment-resistant hemorrhagic diathesis, complicated with numerous mucosal bleedings, including respiratory tract bleeding, and numerous hemorrhages into the peritoneal cavity. The patient required several surgical interventions. He underwent repeated large veins and peripheral arterial cannulations; he needed massive fluid resuscitation, including blood product transfusions. In the initial period of treatment, surgical interventions were associated with massive losses of blood due to coexisting coagulation disorders. The patient required supplementation with red blood cell concentrate (RBCC), coagulation factors, and

platelets. Despite massive transfusions of blood products, there occurred clinically significant hemorrhages, necessitating the administration of NovoSeven in therapeutic doses of 90 µg/kg of body weight. The observed hemorrhagic diathesis was of multiple etiologies. It was dominated by: thrombocytopenia resistant to platelet transfusions, disseminated intravascular coagulation when severe bleeding was not observed, plasmatic diathesis associated with coagulopathy due to a depletion and deficiency in the production of coagulation factors as a result of liver failure, and thrombocytopenia associated with uremia.

Initially, NovoSeven was indicated due to the massive loss of blood occurring during invasive procedures as well as because of spontaneous hemorrhages from postoperative wounds, gastrointestinal tract, and respiratory tract – despite the supplementation of coagulation factors, controlling disorders of acid-base balance, ensuring normothermia, and eliminating uremia. During the 2nd month of the treatment, due to the aforementioned, life-threatening bleedings, it was decided to introduce a drug that would prevent them. It was resolved to put the patient on "off-label" treatment with rVIIa as a prophylactic measure before elective surgeries, large veins and arterial cannulations, and bronchoscopy. This drug was administered in a dose of approximately 30 µg/kg of body weight (2.4 mg or 2.0 mg). Once, due to the possibility of directly life-threatening hemorrhage, the dose was increased to 90 µg/kg of body weight (7 mg).

After the completion of the treatment, blood loss associated with invasive procedures and the perioperative volume of transfused blood products (RBCC) were compared concerning the periods with and without NovoSeven prophylaxis.

Initially, the drug was used intraoperatively on 5 occasions as a life-saving measure following hemorrhage; 4 of these surgeries were elective (3 laparotomies, 1 wound revision following laparotomy). During these procedures 25.6 mg of NovoSeven (on average 6.4 mg) were administered. In total, postoperatively within the first 24 h 22 units of RBCC (on average 5.5 units per procedure) were transfused (Table 1).

**Table 1 – Procedures with emergency administration of rVIIa – elective.**

Procedure	Quantity of administered NovoSeven (mg)	Quantity of transfused RBCC units
Laparotomy – replacement of drains in the peritoneal cavity	9.6	10
Wound revision following laparotomy	6.0	4
Laparotomy – evacuation of interloop abscesses	6.0	4
Laparotomy – evacuation of subphrenic abscess	4.0	4
Total	25.6	22

**Table 2 – Procedures with prophylactic administration of rVIIa (30 µg/kg of body weight).**

Procedure	Quantity of administered NovoSeven (mg)	Quantity of transfused RBCC units
Bronchoscopy	7.0	0
Laparotomy – cholecystectomy	2.0	0
Thoracentesis	2.4	0
Thoracotomy	2.0	0
Laparotomy – evacuation of interloop abscesses	2.0	0
Thoracotomy – decortication of the right lung	2.0	2
Removal of drains from the thorax	2.0	0

Following the decision concerning “off-label” use of NovoSeven, the patient received 8 prophylactic doses of the drug 15–30 min prior to surgeries (in total 21.4 mg of NovoSeven per 8 procedures, on average 2.675 mg). These procedures included: 2 laparotomies, 1 thoracotomy – decortication of the right lung, 2 thoracenteses, bronchoscopy, replacement of central cannules, removal of drains from the thorax. No clinically significant bleedings were observed postoperatively. In all procedures preceded with a prophylactic administration of the drug, only 2 units of RBCC were transfused (following the decortications of the right lung) (Table 2).

#### 4. Results and discussion

Severe coagulation disorders observed in patients treated at the ICU due to MODS have various causes. These causes may be associated with the clinical picture of the underlying disease, or have resulted from developing organ dysfunctions (kidneys or liver); they can also be caused by the applied treatment, including massive fluid transfusions.<sup>8,10,12</sup> Activities aimed at reducing the loss of blood and the number of autotransfusions frequently turn out to be extremely difficult in a patient with hemorrhagic diathesis and a grave general condition. A typical supplementation of morphotic blood elements and coagulation factors in the form of fresh frozen plasma and cryoprecipitate often does not lead to the expected outcome, i.e., clinically effective hemostasis.<sup>2,5,8,10</sup> Ineffective conventional treatment is associated with the fact the transfused elements (even if all types are used), can never achieve the coagulation effectiveness comparable to that effected by the patient's whole blood. At best, the effectiveness of transfused elements does not exceed 50% of whole blood effectiveness. Moreover, the older the transfused elements are, and the cooler at the time of transfusion, the lower the efficiency of activating coagulation in the patient's organism. Another factor contributing to the difficulty of ensuring normal coagulation in a patient with a massive hemorrhage is the necessity to control blood pressure in order to ensure adequate organ perfusion, in particular with reference to the heart and brain. This frequently requires large volume transfusions of crystalloids or colloids which exacerbate a “dilution” bleeding tendency and frequently trigger

unintentional hypothermia, additionally reducing the activity of plasma coagulation factors. A vicious circle appears: a massive bleeding leads to hemostasis disorders; whereas treating these disorders reduces the effectiveness of the coagulation system and exacerbates the bleeding.<sup>2,5,8,10</sup> Hence it seems viable to apply treatment that allows for a controlling of such bleeding in the shortest possible time in order to prevent coagulopathy due to a dilution and deficiency of coagulation factors. Controlling severe bleedings is not always possible by surgical means or a less invasive embolization of the bleeding vessels. This problem occurred in the described case. Consequently, it was decided to begin “off-label” use of rVIIa. This drug, even in the case of a deficiency of coagulation factors, triggers a massive release of thrombin causing clotting (whilst fibrinogen is still available). Prophylactic use of this drug can facilitate hemostasis directly following blood extravasation and prevent the aforementioned problems. In the reported case, when NovoSeven was administered preventively, a significant reduction of bleedings associated with invasive procedures was observed as compared to the no drug procedures. A prophylactic use of this drug also resulted in a significant reduction in transfused RBCC on the day surgery was performed.<sup>1,2,3,4,5,6,7,8,9,10,11,12</sup>

#### 5. Conclusions

1. Supplementation of morphotic blood elements and coagulation factors in the form of fresh frozen plasma and cryoprecipitate frequently does not result in obtaining the desired outcome of clinically effective hemostasis.
2. The additional supply of rVIIa in such cases enables one to control the bleeding.
3. Preventive use of NovoSeven seems to be effective in reducing the frequency of perioperative bleedings that require blood products transfusions, particularly in patients with complex coagulopathy.

#### Conflict of interest

None declared.

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