Use of recombinant factor VIIa in the treatment of massive retroperitoneal bleeding due to severe necrotizing pancreatitis

Primena rekombinantnog faktora VIIa u lečenju masivnog retroperitonealnog krvarenja izazvanog teškim nekrotičnim pankreatitisom

Branislav Stefanović*, Branislava Stefanović†, Srdjan Mijatović*, Dejan Radenović*, Nada Popović†, Ana Šijački*, Vesna Lačković‡

Clinical Center of Serbia, Emergency Center, *Center for emergency surgery, †Department of Anesthesiology, Belgrade, Serbia; School of Medicine, ‡Institute for Hystology and Embriology, Belgrade, Serbia

Abstract

Background. Recently, a growing number of case reports and case series have suggested that the use of recombinant activated factor VII (rFVIIa) may be effective in treatment of patients with non-hemophilic acquired coagulopathy not responding to conventional treatment such as major surgery, major trauma, sepsis, necrotizing pancreatitis and bleeding due to cerebral arteriovenous malformations. Case report. We presented a septic patient with massive, life-threatening bleeding caused by retroperitoneal necrosis, due to severe acute necrotizing pancreatitis. As conservative treatment (blood, plasma, cryoprecipitates and platelet transfusions) failed to induce cessation of bleeding, the patient was urgently operated on. In spite of usual procedures of surgical hemostasis (ligation, suture, thermocauterisation, fibrin glue, temporary tamponade), hemorrhage could not be stopped. The patient manifested the signs of hypothermia and metabolic acidosis, and therefore, the decision was made to use recombinant activated factor VII (Novo Seven®). The application of rFVIIa resulted in significant discontinuation of hemorrhage, restoration to normal blood count as well as other relevant coagulation parameters. Conclusion. Although application of rFVIIa is still in the initial clinical phase, and the experience is based mainly on uncontrolled series as well as on individual observations, it seems that this drug can be promising, potent and attractive adjunctive prohemostatic agent. This drug may play a beneficial role in the treatment of serious and unresponsive, “nonsurgical”, life-threatening bleeding due to severe acute necrotizing pancreatitis.

Key words: factor VIIa; hemorrhage; retroperitoneal space; pancreatitis; digestive system surgical procedures.

Ključne reči: faktor VIIa; krvarenje; retroperitonealni prostor; pankreatitis; hirurgija digestivnog sistema, procedure.
Introduction

It is well known that one of the most widespread complications of severe acute pancreatitis is sepsis caused by activation of proinflammatory cascade of mediators and followed by subsequent bacterial infection. Among many systemic complications of sepsis due to severe acute pancreatitis is sepsis-induced coagulopathy. Moreover, infected necrosis of the pancreas, peripancreatic and retroperitoneal tissue, may cause direct erosion of blood vessels, bringing about the risk of massive, often uncontrollable, unresponsive, even fatal bleeding.

Standard therapy for achieving hemostasis in these bleeding cases involves supplementation of blood and blood derivatives. If hemorrhage does not cease, such conservative treatment may further compromise coagulation, introducing patient to dilutional coagulopathy, or other posttransfusion complications. In life-threatening bleeding cases, emergency laparotomy is necessary, but an attempt of surgical hemostasis is rather limited and often unsuccessful.

Recently, a growing number of case reports and case series have suggested that the use of recombinant activated factor VII (rFVIIa) may be effective in treatment of patients with non-hemophilic acquired coagulopathy, who do not respond to conventional treatment such as major surgery, major trauma, sepsis, necrotizing pancreatitis and bleeding due to cerebral arteriovenous malformations.

We reported a patient with severe acute necrotizing pancreatitis, complicated with sepsis who had life-threatening retroperitoneal bleeding irresponsible to standard blood products supplementation and surgical treatment, successfully treated with human recombinant activated factor VII (Novo Seven®; Novo Nordisk, Bagsvaerd, Denmark).

Case report

A male patient, 55 years of age, was admitted to our institution with a two-week history of gallstone-induced acute pancreatitis and with no preexisting coagulopathy. Contrast computerized tomography (CCT) performed on day 6 from the admission verified the presence of necrotic zones in the pancreas (over 50%) and peripancreatic tissue, with tendency to expand towards the left retroperitoneal space. As the patient had no clinical or laboratory signs of generalized infection and sepsis, intensive conservative treatment was initiated immediately. In addition, prophylactic antibiotic therapy was applied, while three-lumen nasojejunal tube was inserted for enteral nutritive support.

On day 15 of his stay, the abdominal pain followed by abdominal distension (abdominal compartment) was noticed, while body temperature was increased abruptly (39°C). White blood count (18 × 10^9/L) and C-reactive protein (380 mg/L) levels were increased along with aggravation of general condition. Percutaneous ultrasound-guided fine needle biopsy was performed and lavate was sent to microbiological identification. Two days later, Klebsiella and E. coli were discovered from the culture, and such evidence of infected necrosis called for immediate laparotomy. During the surgery, a large volume of ascites was evacuated while peripancreatic necrotic tissue was re-

Discussion

Operated patients with acute severe necrotizing pancreatitis may suffer from profound bleeding due to retroperitoneal necrosis, accompanied by sepsis-induced coagulopathy. The standard treatment of such bleeding is an early, vigorous and aggressive replacement therapy by administration of blood products, but it promotes a risk of further dilutional coagulopathy, massive transfusion syndrome, and other possible posttransfusion complications. Attempts of surgical hemostasis in these uncontrollable bleeding patients, such as ligation, suture, cautery, temporary packing (tamponade), use of fibrin glue, or even argon beam laser, are often ineffective.

Such failure to control a source of bleeding often leads to consumption coagulopathy. An additional mechanism altering the process of clot formation is an activation of fibrinolytic system, excessive fibrinolysis and subsequent disruption of newly formed clots, which all make patient to be caught into a vicious cycle. Contributing effects of additional hypothermia and metabolic acidosis have negative impact on clotting process in view of further refractory coagulopathy, hypoperfusion and irreversible cellular shock.

Recombinant activated factor VII (rFVIIa) was introduced in clinical medicine more than 10 years ago and licensed as prohemostatic agent for the treatment of hemorrhagic patients with inhibitors for over 5 years. Recombinant activated factor VIIa is a 50 kDa analog of the naturally occurring serine protease. Circulating half-life of rFVIIa is 2.7 hours. Recombinant activated factor VII increases local thrombin generation at sites where the endothelium is damaged, resulting in an increased platelet activation and aggregation and enhancing fibrin deposition. Recombinant activated factor VIIa also decreases the lag-time of clot formation. Final result of such rFVIIa action is stable, insoluble fibrin “superclot”, which has stronger architecture and is much more resistant to degradation by fibrinolytic enzymes compared with normal clot.

There has been still considerable disagreement on the mechanism of action of rFVIIa, so its mode of action has not been established yet. According to current knowledge the mode of action of recombinant factor VIIa might be based on two possible alternative mechanisms.

The first mechanism, supported by Mann et al. is dependent upon and mediated by the tissue-factor pathway. Recombinant activated factor VIIa becomes active after forming a complex with tissue factor (TF), which is released from subendothelial media of damaged vessel wall. This complex (rFVIIa-TF) initiates the activation of coagulation cascade by the extrinsic pathway, activating factors X and IX – just at the site of the vessel injury, and without triggering the systemic activation of blood coagulation. In that way, rFVIIa makes "bypass", avoiding and eliminating systemic coagulation effects.

Another mechanism of action of rFVIIa revised the classical concept of coagulation cascade. This is a cell-based model, designed on the theory about dominating cell membrane role. A cell-based model emphasizes the importance of specific cell receptors for coagulation proteins and states that hemostasis takes place on two cell surfaces: TF bearing cells and activated platelet membranes. According to this hypothesis, rFVIIa initiates coagulation in the absence of tissue-factor pathway. Triggering a direct activation of factor X, rFVIIa leads to acceleration and amplification of thrombin generation on the surface of phospholipid membrane of activated platelets, adhering at the site of the injury. Final result of this action is a subsequent formation of fibrin clot.

According to the aforementioned, rFVIIa has two potential and possible sites of action in surgery and trauma: at injury site, where rFVIIa binds to tissue factor (TF), previously released from the injured vessel, and on the surface of

activated platelets, producing thrombin, independently of TF.

The only requirement for a sufficient activity of rFVIIa is
enough quantity of platelets (> 50 × 10^12/L) and enough
quantity of fibrinogen (> 50 mg/dL). According to the ex-
perience so far, rFVIIa activity has not been reduced by
hipothermia. The only limiting factor lowering the effect of
rFVIIa is metabolic acidosis.

Whatever it generally does, rFVIIa markedly stopped
the fulminant hemorrhage in our patient with severe acute
necrotizing pancreatitis. It was clear that initially ruptured
septic spleen was not the primary source of bleeding, but
diffuse altered peripancreatic and retroperitoneal veins were
the main origin of hemorrhage. The cessation of bleeding did
not occur immediately, but slowly, during the following 24 hours
from the start of rFVIIa administration. The parameters of
coaulation cascade also restored to normal during the next
days and the patient recovered coagulation status.

According to the majority of reports, timing of rFVIIa
administration have not been determined yet. Although dosage
depends on prophylactic or therapeutic use and varies in
range from 20 μg/kg to “megadose” of over 300 μg/kg, the
majority of authors advocate, suggest and recommend a dose
between 90–120 μg/kg.

According to the majority of reports, timing of rFVIIa
administration in uncontrollable life-threatening bleeding
patients with a high rate of blood loss followed by unsuc-
cessful and ineffective attempts of surgical hemostasis is – as
soon as possible, before manifestation of hypothermia and
metabolic acidosis, and before noticeable signs of irrever-
sible hemorrhagic shock.

The cost-benefit of rFVIIa use is actually not known.
Despite relatively expensive cost of its use, significantly de-
creased number of transfusion units of the whole blood and
blood-derivatives, shortened stay in the intensive care unit,
reduction of transfusion – related morbidity and bleeding –
related mortality, as well as generally improved survival of
patients treated with rFVIIa, indicate that this drug may be
quite acceptable and convenient adjunctive prohemostatic
agent.

Conclusion

We reported a septic patient with unresponsive retro-
peritoneal bleeding caused by severe acute necrotizing pan-
creatitis, successfully treated with recombinant activated
factor VII (NovoSeven; Novo Nordisk; Bagsvaerd; Den-
mark).

Although application of recombinant factor VIIa is still
in the initial clinical phase, and the experience is based
mainly on uncontrolled series as well as on individual obser-
vations, it seems that this drug can be promising, potent
and attractive adjunctive prohemostatic agent. Although our re-
port offers limited insight into the subject, it could contribute
to the establishment of some selection criteria for clinical use
of rFVIIa. This drug may play a beneficial role in the treat-
mint of serious and unresponsive, “non surgical”, life –
threatening bleeding due to severe acute necrotizing pan-
creatitis, as well as units transfused along with their compli-
cations and cut down total expenses.

Despite the fact that these results seem promising and
encouraging, randomized multicentric clinical trials are
necessary to confirm such initial observations.

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