Coll. Antropol. **35** (2011) 1: 193–196
Case report

Successful Use of Recombinant Factor VIIa in Traumatic Liver Injury – A Case Report

Senka Baranović[1], Ivan Zvonimir Lubina[2], Tatjana Nikolić[3] and Branka Maldini[4]

[1] University of Zagreb, University Hospital of Traumatology, Department of Anesthesiology and Intensive Care Unit, Zagreb, Croatia
[2] University of Zagreb, University Hospital of Traumatology, Department of Radiology, Zagreb, Croatia
[3] University of Zagreb, University Hospital of Traumatology, Department of Physical Medicine and Rehabilitation, Zagreb, Croatia
[4] University of Zagreb, »Sveti Duh« University Hospital, Department of Anesthesiology and Intensive Care Unit, Zagreb, Croatia

A B S T R A C T

The paper describe the use of rFVIIa in the management of massive bleeding in a patient with polytrauma involving liver injury. An 18-year-old girl with severe polytrauma sustained during a bus–car collision. She had multiple musculoskeletal injuries, severe concussion of the liver with amputation of the left liver lobe, disruption of the left hepatic vein from the inferior vena cava, and impaired hemostasis. Acute bleeding (>5 L) was not improved by conservative methods and a single dose of rFVIIa 90 μg/kg was administered. Infusion of rFVIIa resulted in an immediate clinical effect with rapid improvements in blood laboratory measurements and coagulation parameters. rFVIIa should be considered as an adjunctive treatment for the control of hemorrhage in severely injured patients with uncontrolled bleeding and impaired hemostasis.

Key words: *recombinant FVIIa, polytrauma, liver, coagulopathy, hemorrhage, hemostasis*

Introduction

Polytrauma is a life-threatening condition characterized by severe blunt trauma with injuries to multiple organ systems, generally including musculoskeletal and abdominal organ injuries, and extensive soft tissue injury. Individuals with polytrauma are at a high risk of systemic soft tissue inflammation, contusions and edema[1], and most require massive blood volume replacement together with implementation of treatment strategies for adequate and safe bleeding control[2,3].

Surgery followed by blood-product transfusion successfully manages hemorrhage and hemostatic instability in many polytrauma patients, but some patients continue to bleed uncontrollably. Persistent blood loss is a major cause of trauma-related deaths and the mortality risk is further increased by the inevitable consequences of hemodilution, hypothermia, acidosis and coagulopathy[4]. Initial treatment for intractable hemorrhage involves blood-component therapy (e.g. packed red blood cells PRBC, fresh frozen plasma FFP). Massive blood transfusion may be required in the most severe cases, but this is associated with serious complications such as infection and multiple organ failure[4–8]. In recent years, a number of pharmacotherapies have become available (e.g. desmopressin, tranexamic acid, aprotinin) to be used when surgery is insufficient to curb the bleeding and also to reduce transfusion requirements[9].

Recombinant factor VIIa (rFVIIa, Novo Nordisk, Bagsvaerd, Denmark) is a hemostatic agent that is approved in over 50 countries worldwide for the management of spontaneous or surgical hemorrhage in patients with bleeding disorders. Evidence from investigational research has indicated that rFVIIa may also be effective in intractable bleeding episodes of varying etiology in non-hemophilia patients[10]. Indeed, effective use of rFVIIa in a trauma situation was first reported in 1999 when bleeding was stopped in a patient with a serious rifle injury following unsuccessful surgical intervention and blood-product transfusion[11]. Successful hemorrhage control with adjunctive rFVIIa in patients with severe trauma has since been demonstrated in a number of case re-

Received for publication July 18, 2010

ports[12–20], as well as two randomized, placebo-controlled, double-blind clinical trials[21]. The present case report describes the use of rFVIIa in the management of massive bleeding in a female patient with polytrauma involving liver injury.

Case Report

An 18-year-old girl sustained severe polytrauma as a passenger on a bus involved in a bus–car collision, and was transferred by ambulance to the University Hospital of Traumatology in Zagreb. On admission, the patient was somnolent and amnestic of the event, with a Glasgow Coma Score (GCS) of 13, Trauma Score (TS) of 12, and she was hemodynamically unstable (tachycardia, 120 beats/min; blood pressure, 90/60 mmHg). She complained of pain in the abdomen, back and right hemithorax. Clinical examination revealed right thorax deformity and, on auscultation, there was shallow breathing on the right side with subcutaneous emphysema. Neurological status was normal with preserved motoricity of all four extremities. Peripheral venous lines were inserted for volume replacement with crystalloid and colloid infusions and analgesia was administered with morphine at a dose of 0.1 mg/kg. Emergency diagnostic assessments were conducted, including x-ray, ultrasonography and computed tomography (CT).

The patient was found to have multiple musculoskeletal injuries. Intrathoracic x-ray revealed fracture and cranial dislocation of the seventh and eighth ribs on the right, along with pleural effusion.The right side of the thorax was distorted, with a visible gap of approximately 10 cm between the inferior ribs. X-ray of the spine showed T6 fracture without fracture fragment migration to the spinal canal.The patient remained free from neurological deficit and brain CT was normal but had a severely painful, tight and distended abdomen. After admission to the intensive care unit, abdominal ultrasonography and CT scan revealed a large amount of free intraperitoneal fluid on the right, along the lateral liver margin and left liver lobe. Extensive free fluid was also observed in the pelvis minor, close to the bladder. Laboratory test results of slightly lower hemoglobin (98 g/L; normal range, 115–165 g/L) and hematocrit level (0.31; normal range, 0.36–0.47), normal prothrombin time (PT 14.6 s; normal range is usually within the range of 10–15 seconds), metabolic acidosis (with base excess of –8 mmol/L) and increased lactate levels (3.0 mmol/L; normal range, 0.5–2.2 mmol/L, Table 1).

Emergency laparotomy revealed severe concussion of the liver with amputation of the left liver lobe and disruption of the left hepatic vein from the inferior vena cava. Acute blood loss was estimated to be approximately 5 L, so replacement therapy with 4.5 L of crystalloids and 1 L of colloids plus 7.5% NaCl (4 mL/kg) was administered. The patient's marked hemodynamic instability continued, indicated by a second laboratory assessment (reduced hemoglobin 35 g/L, hematocrit 0.11 and platelets 117 x 10^9/L, prolonged PT 18.9 s and aPTT 38.2 s, low fibrinogen 0.7 g/L, Table 1) as well as systolic blood pressure of approximately 60 mmHg and tachycardia of 140 beats/min. Consequently, inotropic support with norepinephrine (0.02–0.04 μg/kg/min) was introduced intraoperatively and, prior to ligature of the blood vessels, a single dose of rFVIIa 90 μg/kg was administered. An immediate clinical effect of the rFVIIa was observed, and resection of the left liver lobe and suture of the inferior vena cava were performed. During the 3-hour surgical procedure, blood loss exceeded one circulating blood volume so massive blood transfusion was required (15 units of PRBC; 8 units of FFP, 15 mL/kg and 8 units of platelets).

Laboratory assessment 6 hours after surgery showed that blood counts had near-normalized following the administration of rFVIIa: hemoglobin increased to 110 g/L and hematocrit to 0.32 (Table 1). Similarly, improvements in coagulation parameters meant that they were close to or within the reference ranges (PT of 12.6 s; aPTT of 24 s; fibrinogen of 2 g/L). Metabolic acidosis was corrected, while the level of lactate decreased from 3 mmol/L to 1.2 mmol/L within 24 hours of trauma.

Postoperatively, the patient was connected to a mechanical respiratory device, extubated within 24 hours of the injury and the right hemithorax was drained. Coagulation factors were found to be within or close to their reference ranges 4 days after rFVIIa administration (Table 2). Posterior spondylosis of the thoracic spine was identified 12 days after the injury and corrected with surgical intervention. The patient was discharged from hospital in good general condition 20 days after admission.

A CT scan of the abdomen was performed on the eight postoperative day after liver resection. It shows the condition after resection of the left liver lobe with signs of pancreatic contusion and low level of ascites.

TABLE 1
LABORATORY PARAMETERS BEFORE AND AFTER rFVIIa ADMINISTRATION

	Hemoglobin (g/L)	Hematocrit	Platelets (x10^9/L)	PT (s)	aPTT (s)	Fibrinogen (g/L)	D-dimers (mg/mL)
On admission	98	0.31	277	14.6	22.7	1.9	No data
Before rFVIIa	35	0.11	117	18.9	38.2	0.7	1.2
After rFVIIa	110	0.32	118	12.6	24.0	2.0	0.6
At discharge	79	0.24	189	14.4	27.8	3.0	0.3

aPTT – activated partial thromboplastin time, PT – prothrombin time

TABLE 2
COAGULATION FACTORS 4 DAYS AFTER rFVIIa ADMINISTRATION

Coagulation factor	Day 4 after rFVIIa	Reference value (kIU/L)
Factor II	0.78	0.75–1.20
Factor V	1.27	0.75–1.20
Factor VII	0.69	0.70–1.20

Discussion

In this case study, adjunctive treatment with a single dose of rFVIIa (90 μg/kg) proved useful in the control of severe hemorrhage due to polytrauma and involving blunt liver injury. The liver plays a crucial role in the regulation of coagulation factors and injury may impair hemostasis resulting in massive bleeding, as seen in this patient[6,22]. Blunt liver trauma is a major cause of death in patients with abdominal injury, with reported mortality rates of 11–21% potentially increasing to 50–67% in severe cases; most deaths are attributed to exsanguinations[13,23–28]. As blood loss is usually severe in patients with polytrauma involving the liver, frequently exceeding one circulating blood volume, replacement therapy with high volumes of crystalloids and colloids, as well as transfusion of multiple blood products, is generally necessary in order to maintain normovolemia and to prevent hypoxemia[29]. However, such treatment causes dilution of coagulation factors and platelets, and ultimately leads to consumption coagulopathy.

The present case illustrates the typical clinical picture of polytrauma with liver injury. Despite the severity of the situation, treatment with rFVIIa in conjunction with surgical intervention led to hemorrhage control with rapid improvements in blood laboratory measurements and coagulation parameters.

The mechanism of action of rFVIIa in non-hemophilia patients is yet to be established; pharmacological doses directly activate factor IX on the surfaces of activated platelets, in the absence of tissue factor, leading to formation of additional tenase complexes, and improved thrombin generation, clot structure and clot stability at the site of injury[30].

The effectiveness of rFVIIa in our case patient adds to the evidence of its beneficial effects in blunt trauma injuries shown in clinical trials[21] and case reports[13,14,17–20].

Conclusion

This report indicates that rFVIIa may be useful as an adjunctive treatment for the control of hemorrhage in traumatized patients and may reduce the need to administer blood products; in many cases, coagulation parameters are normalized. Although associated with additional costs, early hemorrhage control through rFVIIa administration can reduce the risk of infection transmission and costs associated with blood product transfusion. Investigations to determine the optimal therapeutic use of rFVIIa in non-hemophilia patients with uncontrolled bleeding are warranted.

REFERENCES

1. PEPE PE, BMJ, 327 (2003) 1119. — 2. GOWERS CJD, PARR MJA, Anaesth Intensive Care, 33 (2005) 96. — 3. DUTTON RP, HESS JR, SCALEA TM, J Clin Anesth, 15 (2003) 184. — 4. SPAHN DR, ROSSAINT R, Br J Anaesthesia, 95 (2005) 130. — 5. ARMAND R, HESS JR, Transfus Med Rev, 17 (2003) 223. — 6. GROUNDS M, Blood Rev, 17 (2003) S11. — 7. HARDY JF, Can J Anaesth, 49 (2002) S4. — 8. HOYT DB, Semin Hematol, 41 (2004) 40. — 9. CHIU J, KETCHUM LH, REID TJ, Curr Opin Hematol, 9 (2002) 544. — 10. ERHARDTSEN E, Intensive Care Med, 28 (2002) S248. — 11. KENET G, WALDEN R, ELDAD A, MARTINOWITZ U, Lancet, 354 (1999) 1897. — 12. DUTTON RP, McCUNN M, HYDER M, D, ANGELO M, O, CONNOR J, HESS JR, SCALEA TM, J Trauma, 57 (2004) 709. — 13. KULKARNI R, DANESHMAND A, GUERTIN S, FATH J, ATWAL M, MELVIN J, LAFRANCE S, J Trauma, 56 (2004) 1348. — 14. MARTINOWITZ U, KENET G, LUBETSKY A, LUBOSHITZ J, SEGAL E, Can J Anaesth, 49 (2002) S15. — 15. MARTINOWITZ U, KENET G, SEGAL E, LUBOSHITZ J, LUBETSKY A, INGERSLEV J, LYNN M, J Trauma, 51 (2001) 431. — 16. O'NEILL PA, BLUTH M, GLOSTER ES, J Trauma, 52 (2002) 400. — 17. SIEGEL LJ, GERIGK L, TUETTENBERG J, DEMPFLE CE, SCHARF J, FIEDLER F, Anesthesiology, 100 (2004) 441. — 18. BECTON D, SAYLORS R, MORRIS J, Blood, 98 (2001) 11. — 19. AGGARWAL A, CATLETT J, ALCOM K, Blood, 98 (2001) 38. — 20. KAMPHUISEN PW, VAN DEN AKKERA JM, KAASJAGER KA, BLOEMEN TI, Am J Med, 112 (2002) 332. — 21. BOFFARD KD, RIOU B, WARREN B, CHOONG PI, RIZOLI S, ROSSAINT R, AXELSEN M, KLUGER Y, J Trauma, 59 (2005) 8. — 22. SILVA MA, MURALIDHARAN V, MIRZA D, Semin Hematol, 41 (2004) 132. — 23. GIRGIN S, GEDIK E, TACYILDIZ IH, Ulus Travma Acil Cerrahi Derg, 12 (2006) 35. — 24. GAO J, DU D, ZHAO X, LIU G, YANG J, ZHAO S, LIN X, Chin J Traumatol, 5 (2002) 346. — 25. GAO JM, DU DY, ZHAO XJ, World J Surg, 27 (2003) 703. — 26. GUR S, ORSEL A, ATAHAN K, HOKMEZ A, TARCAN E, Hepatogastroenterology, 50 (2003) 2109. — 27. COLOMBO F, SANSONNA F, BATICCI F, CORSO R, SCANDROGLIO I, MAGGIONI D, Di LERNIA S, FERRARI GC, MAGISTRO C, COSTANZI A, PUGLIESE R, Chir Ital, 57 (2005) 695. — 28. DUANE TM, COMO JJ, BOCHICCHIO GV, SCALEA TM, J Trauma, 57 (2004) 494. — 29. STEIN DM, DUTTON RP, Curr Opin Crit Care, 10 (2004) 520. — 30. GABRIEL DA, LI X, MONROE DM, ROBERTS HR, J Thromb Haemost, 10 (2004) 1816.

S. Baranović

University of Zagreb, University Hospital of Traumatology, Department of Anesthesiology and Intensive Care Unit, Draškovićeva 19, 10 000 Zagreb, Croatia
e-mail: senka.baranovic1@zg.t-com.hr

USPIJEŠNA PRIMJENA AKTIVIRANOG REKOMBINANTNOG FAKTORA VIIa KOD TRAUMATSKE OZLIJEDE JETRE: PRIKAZ SLUČAJA

S A Ž E T A K

Aktivirani rFVIIa je dobro hemostatsko sredstvo u zbrinjavanju krvarenja kod bolesnika sa hemofilijom i inhibitorima faktora VIII ili IX. Također se uspješno upotrebljava u kontroli krvarenja u kirurških bolesnika u traumi i »non-hemophilia« koagulopatija kod kojih je ugrožen život zbog nekontrolibilnog krvarenja. Politrauma u okviru teških ozljeda lokomotornog sustava sa pridruženim oštećenjem abdominalnih organa je za život opasno stanje, koje zahtjeva veliku nadoknadu volumena i krvnih pripravaka, te adekvatnu i sigurnu kontrolu krvarenja. Donosimo vam prikaz slučaja primjene rFVIIa u zbrinjavanju masivnog krvarenja kod politraumatizirane bolesnice sa dominantnom ozljedom jetre.