The THAI Journal of SURGERY 2008; 29:32-36.
Official Publication of the Royal College of Surgeons of Thailand

Recombinant Activated Factor VII: An Addition to Replacement Therapy in Trauma Patients with Uncontrolled Massive Bleeding

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Abstract

Introduction: **Trauma patients tend to have multiple sites of bleeding, sometimes in surgically inaccessible areas of the pelvis and retroperitoneum or in an organ that is difficult to control or repair such as the liver. Massive transfusion will lead to various complications of dilutional coagulopathy, acidosis and hypothermia, which will slow the enzymatic reactions of the coagulation cascade and impair platelet function. Recently, several studies reported the effectiveness of recombinant activated factor VII (rFVIIa) in restoring hemostasis in patients with massive bleeding related to trauma and surgery. Here, we report the use of rFVIIa in addition to blood component therapy to control massive bleeding in patients with trauma.**

Materials and Methods: **Recombinant activated factor VII (rFVIIa) at the initial dose of 100 μg/kg followed by 40 μg/kg at 4-6 hour interval for 24-48 hour was given as a rescue therapy to 8 males with trauma exhibiting massive bleeding unresponsive to surgical intervention and replacement therapy. Their median age was 24 years old. Causes of trauma included gun shot (n =1), multiple stabs (n = 3) and motorcycle accident (n = 4). Each patient sustained 2-5 injured sites involving the chest (n = 5), liver (n = 3), artery and vein (n = 6) and one each at the heart, brain, spleen and kidney. Five patients underwent simultaneously exploratory laparotomy and chest exploration (n = 4), and craniotomy and thigh exploration (n = 1). The remaining 3 patients underwent neck, thigh and chest explorations.**

Results: **Two patients died and 6 patients survived. No thrombotic complication was detected.**

Conclusions: **Our small series of patients with trauma suggested the potential benefit of rFVIIa as a rescue therapy to control unresponsive massive bleeding.**

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Introduction

Traumatic injury and its sequelae are the principle causes of death in Thailand today. It was found that 53% of trauma victims died at the scene, 7.5% in the emergency room and the remaining 39.5% in the hospital.[1] Hemorrhage was responsible for 31% of death, whereas 18% of patients died from sepsis.[2] The improvement in rapid transport, prehospital care and immediate surgical treatment could reduce preventable death in trauma patients from 20%-30% to 2%-9%.[3] However, trauma patients tend to have multiple sites of bleeding, sometimes in the surgically inaccessible areas of the pelvis and retroperitoneum or in an organ that is difficult to control or repair such as the liver. Massive transfusion will lead to various complications of dilutional coagulopathy, acidosis and hypothermia, which will slow the enzymatic reactions of the coagulation cascade and impair platelet function.[4]

Recently, several studies reported the effectiveness of recombinant activated factor VII (rFVIIa) in restoring hemostasis in patients with massive bleeding related to trauma[5,6] and surgery.[7-10] Here, we report the use of rFVIIa in addition to blood component therapy to control massive bleeding in patients with trauma.

Materials and Methods

From February 2003 to August 2005, 8 male patients with a median age of 24 years who were admitted to the Trauma Unit, Department of Surgery, Khon Kaen Regional Hospital, Khonkaen, Thailand, were enrolled in the study. The indications for the use of rFVIIa included uncontrolled massive bleeding in trauma patients receiving surgical intervention and replacement of blood components of packed red cells (PRC) or whole blood (WB), fresh frozen plasma (FFP) and platelet concentrate. Massive bleeding was defined as acute blood loss of 150 ml/min or the requirement of massive blood transfusion which included the replacement of one blood volume (approximately 10 units of PRC in a 70 kg male) within a 24-hour period or the replacement of 50% of blood volume in less than a 3-hour period.[11-13] Moreover, patients were defined as having mild, moderate and severe coagulopathy, respectively if they met one, one to two and three of the following criteria:[14] 1) prothrombin and activated partial thromboplastin times >1.5 times mean normal level, 2) platelet count <50,000/μL and 3) fibrinogen level <1 g/L or a thrombin time >1.5 times the mean normal level.

The rFVIIa at the initial dose of 100 μg/kg followed by 40 μg/kg at 4-6 hour interval for 24-48 hours were given as the rescue therapy after obtaining informed consent from their spouses or relatives. The patients' demographics including age, gender, causes of bleeding, interval between onset and resuscitation at the emergency room, transfused blood components and coagulation testing before and after the infusion of rFVIIa were recorded.

Results

Four patients each were defined as having severe and moderate coagulopathy. Causes of trauma included gun shot (n = 1), multiple stabs (n = 3) and motor cycle accident (n = 4). The interval between onset and initial resuscitation at the Emergency Unit ranged from 15 minutes to 2 hours with a median interval of 1 hour and 18 minutes. The patients had 2 to 5 injured sites involving the chest (n = 5), liver (n = 3), artery and vein (n = 6) and one of each at the heart, brain, spleen and kidney. The injured arteries and veins included intercostal, lingual, vertebral and femoral vessels. The intercostal drain was immediately applied at the Emergency Unit for hemothorax (n = 4) and pneumothorax (n = 1) followed by chest exploration. Also, exploratory laparotomy (n = 4), thigh exploration (n = 2), neck exploration (n = 1) and craniotomy (n = 1) were performed. Simultaneous exploratory laparotomy and chest explorations were performed in 4 patients and simultaneous craniotomy and thigh exploration in 1 patient. The remaining three patients received neck, thigh and chest explorations. The rFVIIa administration, transfused blood components and outcomes are shown in Table 1. Two patients died and six patients survived. No thrombotic complications were detected.

Discussion

The rapid transport of the injured patients and prompt management by experienced medical personnel at the Emergency Unit are essential for favorable outcomes. However, the replacement of an entire blood volume leaves the patient with approximately one third of the original levels of

Table 1 Treatment of trauma patients with surgical interventions, replacement therapy and recombinant activated factor VII.

Patient Age (yr) BP (mmHg) P (/min)	Causes	Finding	Surgery	Blood component		rFVIIa				Outcome	
				Before rFVIIa	After rFVIIa	Initiation of rFVIIa after bleeding	Dose	Number	Total (μg)	Bleeding Effective	Effective
No. 1* 16 yr BP 120/70 P 124	Gun shot wound at chest	Hemothorax from large laceration of Rt. diaphragm, fracture 3 ribs, severe laceration of liver	2nd Explore laparotomy, perihepatic packing and chest exploration	PRC 3 U WB 6 U FFP 4 U in 24 hrs	PRC 2 U D1 FFP 10 U D1	24 hrs	100 μg/kg, post-operation 1	1	6,000	Bleeding slowed down for 2 hours	Ineffective
No. 2 31 yr In shock	Stab wound at chest	Hemothorax from partial tear of 4th intercostal artery	Chest exploration	PRC 3 U WB 4 U FFP 4 U Plt SD 1 U Colloid 7 L in 4 hrs	PRC 2 U D1 FFP 6 U D1 PRC 1 U D2 FFP 6 U D2 FFP 4 U D3	4 hrs	40 μg/kg at 12 & 8-hr interval, post-operation	3	12,000	Bleeding stopped	Effective
No. 3 40 yr BP 100/70 P 100	Stab wound at neck	Tear of Lt. lingual artery and vein, fracture zygoma, bleeding from lt. vertebral artery	Neck exploration and packing	PCR 12 U FFP 10 U in 3 hrs	FFP 4 U in 12 hrs	30 hrs	40 μg/kg at 6- hr interval, post-operation	8	19,200	Bleeding stopped, packing removed at 48 hrs	Effective
No. 4 24 yr BP 90/60 P 120	Multiple stab wounds at face, chest, abdomen	Bilateral hemothorax, bleeding at Psoas muscle	Exploratory laparotomy and chest exploration	PRC 24 U FFP 16 U WB 1 U Plt 10 U in 4 hrs	PRC 5 U D1 FFP 2 U D1	4 hrs	100 and 20-40 μg/kg at 4-6 hr interval, intra-and post-operation	7	18,000	Bleeding stopped	Effective
No. 5 25 yr BP 60/35 P 124	Motorcycle accident	Bilateral pneumothorax, cardiac tamponade, liver injury grade IV	Exploratory laparotomy and chest exploration	PCR 8 U FFP 6 U Plt 6 U in 4 hrs	PRC 1 U D1 FFP 2 U D1 PRC 1 U D2 FFP 5 U D2 FFP 4 U D3	5 hrs 45 mins	100 and 20-40 μg/kg at 4-6 hr interval intra- and post-operation	10	26,400	Bleeding stopped	Effective
No. 6 16 yr shock	Motorcycle accident	Complete tear of femoral vein, fracture rt. tibia and rt. wrist, intracerebral hemorrhage	Exploration of thigh and craniotomy	PRC 12 U FFP 9 U Plt 12 U in 13 hrs	***	15 hrs	100 and 20-40 μg/kg at 4-6 hr interval, post-operation	8	21,600	Bleeding stopped	Effective
No. 7** 23 yr BP 50/30 P 70	Motorcycle accident	Bitateral hemothorax, tear of liver & spleen grade I, rupture kidney grade III, fracture rt. femur	Exploratory laparotomy and chest exploration	PRC 5 U FFP 4 U in 3 hrs	PRC 3 U FFP 9 U WBC 2 U in 4 hrs	5 hrs	100 and 40 μg/kg at 4 hr-interval, post-operation	2	8,400	Bleeding slowed down for 2 hrs, followed by massive bleeding at intercostal drain	Ineffective
No. 8 16 yr BP 60/40 P 120	Motorcycle accident	Complete tear of femoral artery and vein, fracture femur	Exploration of thigh	PRC 2 U FFP 4 U WB 10 U in 7 hrs	PRC 5 U D1 FFP 2 U D1 Plt SD 1 U D1	7 hrs	40 μg/kg at 4-6 hr interval, post-operation	10	24,000	Bleeding stopped	Effective

*Fatal case at 72 hours after surgery due to sepsis, **Fatal case at 4 hours after admission due to massive bleeding, ***data were missing
PRC = packed red cells; FFP = fresh frozen plasma; WB = whole blood; Plt SD = single donor platelet concentrate; Plt = random donor platelet concentrate

coagulation factors. Patients in this report had moderate to severe coagulopathy which aggravated excessive bleeding during and after the operation.

The administration of rFVIIa in addition to the blood component therapy showed effectiveness in ceasing bleeding. The rFVIIa initiates fibrin formation through interaction with exposed tissue factor at the injured site as well as through direct binding of rFVIIa on the surface of activated platelets allowing coagulation to proceed through conversion of fibrinogen to fibrin.[15] The replacement is essential because certain levels of coagulation factors are required to allow clot formation. Using rFVIIa provides the potential advantage of a small volume, easy-to-use preparation and no risk of transfusion-transmitted diseases.

The dose regimen of rFVIIa in patients with massive bleeding has not been well established. In this study, an initial dose of 100 μg/kg imitated the dose for hemophiliacs with inhibitor. However, the subsequent dose was reduced to 40 μg/kg which has also shown effectiveness in decreasing blood loss among patients undergoing retropubic prostatectomy.[16] The data in this report showed effectiveness in reducing the bleeding until complete cessation. The required blood component decreased dramatically, similar to other reports.[17,18] However, a protocol violation in the initial dose of rFVIIa of 40 μg/kg occurred in two patients (No. 3 & 8). Both of them had an effective response. Also, one patient (No. 1) received the initial dose of 100 μg/kg of rFVIIa without receiving the subsequent dose. His bleeding significantly slowed down for 2 hours and then continued to ooze from the drain. He succumbed to sepsis at 72 hours. Another succumbed patient (No. 7) had bleeding decreased for 2 hours followed by massive bleeding in the intercostal drain. Although the second dose of rFVIIa was given at 4 hours, he died due to massive bleeding. Unfortunately, an autopsy was not performed in these two succumbed patients. Since the half life of rFVIIa is rather short at 2.72 hours in adults, the second and/or third dose of rFVIIa should be given at 2-hour intervals before postponing to 4 hr in the subsequent doses.

Conclusions

Our small series of trauma patients suggested the potential benefit of rFVIIa as an adjuvant therapy to control unresponsive massive bleeding. Further randomized, double-blind, placebo-controlled study to determine the optimal dose of rFVIIa is warranted.

Acknowledgement

The authors would like to express their gratitude to the staff of the Emergency, Surgery, Anesthesiology and Nursing Departments, Khon Kaen Regional Hospital, who provided excellent care for the patients.

REFERENCES

1. Baker CC, Oppenheimer L, Stephens B, Lewis FR, Trunkey DD. Epidemiology of trauma deaths. Am J Surg 1980;140:144-50.
2. Hoffman MR, Martinowitz U, Tobias JD, Dutton RP. Excessive bleeding in surgery and trauma: new concepts in coagulation theory and an updated treatment paradigm. Surgical Rounds (Special Supplement); 2002. p. 5-24.
3. Broos PL, Janzing HM, Vandermeeren LA, Klockaerts KS. Life saving surgery in polytrauma patients. Przegl Lek 2000;57(Suppl 5):118-9.
4. Ferrara A, MacArthur JD, Wright HK, Modlin IM, McMillen MA. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. Am J Surg 1990;160:515-8.
5. Kenet G, Walden R, Eldand A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. Lancet 1999;354:1879.
6. Martinowitz U, Kenet G, Segal E, Luboshitz J, Lubetsky A, Ingerslev J, et al. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. J Trauma 2001;51:431-8.
7. White B, McHale J, Ravi N, Reynolds J, Stephens R, Moriarty J, et al. Successful use of recombinant FVIIa (NovoSeven®) in the management of intractable post-surgical intra-abdominal haemorrhage. Br J Haematol 1999;107:677-8.
8. Al Douri M, Shafi T, Al Khudairi D, Al Bokhari E, Black L, Akinwale N, et al. Effect of the administration of recombinant activated factor VII (rFVIIa; NovoSeven) in the management of severe uncontrolled bleeding in patients undergoing heart valve replacement surgery. Blood Coagul Fibrinolysis 2000;11(Suppl 1):S121-7.
9. Hedriks HG, van der Maaten JM, de Wolf J, Waterbolk TW, Slooff MJ, van der Meer J. An effective treatment of severe intractable bleeding after valve repair by one single dose of activated recombinant factor VII. Anesth Analg 2001;93:287-9.

10. von Heymann C, Hotz H, Konertz W, Kox WJ, Spies C. Successful treatment of refractory bleeding with recombinant factor VIIa after redo coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2002;16:615-6.
11. Rutledge R, Sheldow GF, Collins ML. Massive transfusion. Crit Care Clin 1986;2:791-805.
12. Hewitt PE, Machin SJ. Massive transfusion. In: Contreras M, editor. ABC of transfusion. Rugby: BMJ Publishing Group; 1992. p. 38-40.
13. Fakhry SM, Sheldon GF. Massive transfusion in the surgical patient. In: Jefferies LC, Brcher ME, editors. Massive transfusion. Bethesda: American Association of Blood Banks; 1994. p. 17-38.
14. Clark AD, Gordon WC, Walker ID, Tait RC. "Last-ditch" use of recombinant factor VIIa in patients with massive haemorrhage is ineffective. Vox Sang 2004;86:120-4.
15. Hedner U. Mechanism of action of recombinant activated factor VII: an update. Semin Hematol 2006;43(Suppl 1):S105-7.
16. Friederich PW, Henny CP, Messelink EJ, Geerdink MG, Keller T, Kurth KH, et al. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomized trial. Lancet 2003;361:201-5.
17. Martinowitz U, Kenet G, Lubetski A, Luboshitz J, Segal E. Possible role of recombinant activated factor VII (rFVIIa) in the control of hemorrhage associated with massive trauma. Can J Anaesth 2002;49:S15-20.
18. Dutton RP, McCunn M, Hyder M, D'Angelo M, O'Connor J, Hess JR, et al. Factor VII for correction of traumatic coagulopathy. J Trauma 2004;57:709-19.