



Recombinant factor VIIa as an adjunct in nonoperative management of solid organ injuries in children

Laura R. Vick, Saleem Islam*

Division of Pediatric Surgery, Department of Surgery, University of Mississippi Medical Center, Jackson, MS 39216, USA

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Abstract

Background: Ongoing bleeding after blunt solid organ injury in children may require invasive therapy in the form of either angiographic or operative control. We report our experience in the use of a procoagulant, recombinant activated factor VII (rFVIIa), for controlling persistent bleeding in blunt abdominal trauma in children.

Methods: After institutional review board approval, the records of 8 children with blunt abdominal trauma, persistent bleeding, and managed nonoperatively with rFVIIa were reviewed.

Results: All 8 patients presented to our institution after sustaining blunt abdominal trauma and solid organ injury. All children had evidence of persistent bleeding with a drop in hematocrit and elevation in heart rate. Patients received a single dose of rFVIIa at 75 to 90 $\mu\text{g}/\text{kg}$ (1 patient had 24 $\mu\text{g}/\text{kg}$) and had successful control of their bleeding without any further therapeutic intervention. Only 3 patients required a blood transfusion after rFVIIa administration—2 who had subarachnoid hemorrhages and the third during pelvic fixation. There were no cases of thromboembolic events after treatment with rFVIIa.

Conclusions: Recombinant factor VIIa is a useful adjunctive therapy in pediatric patients with evidence of ongoing hemorrhage from blunt abdominal injury and may reduce the need for invasive therapeutic procedures and transfusions.

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Solid organ injury in the pediatric population leading to severe and ongoing hemorrhage can have devastating consequences, including death if not controlled. The management of solid organ injury from trauma in children has evolved over the past few decades as imaging and monitoring modalities have improved. Nonoperative management of intraabdominal organ injuries after trauma is now the gold

standard [1]. However, there is a group of patients in which the hemorrhage from the injury continues and in whom adjunctive treatments are needed. Typically, these treatments include angioembolization techniques in interventional radiology [2] or operative control of the bleeding. Recently, a hemostatic agent known as recombinant activated factor VII (rFVIIa) has been used as a noninvasive therapy for continued bleeding in the adult trauma literature [3-10] and has only been seen in a few cases of pediatric trauma [11,12].

Recombinant activated factor VII is a product that was approved by the US Food and Drug Administration in 1999 for use in bleeding episodes in patients with hemophilia A or B and as inhibitors to factors VIII or IX [13]. This product is nearly identical to human factor VIIa structurally and promotes

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* Corresponding author. Division of Pediatric Surgery, Department of Surgery, University of Florida College of Medicine, PO Box 100286, Gainesville, FL 32610-0286, USA. Tel.: +1 352 392 3718; fax: +1 352 392 9081.

E-mail address: islamsa@surgery.ufl.edu (S. Islam).

Table 1 Demographics, injuries, and outcomes

Patient no.	Age/sex	Mechanism	Injuries	Injury severity score	LOS	Follow-up
1	13/M	Bicycle handlebars	Grade III renal laceration	9	6	1 y, no issues
2	7/M	Peds vs auto	Grade IV liver laceration	25	8	14 mo, no complications
3	12/F	MVC	Grade III renal, open-book pelvic fracture with bilateral internal iliac artery injuries	41	20	10 months, slight limp
4	15/M	Football helmet	Grade III splenic laceration	16	5	8 mo, no issues
5	8/M	MVC	Grade III liver laceration, femur fracture	29	10	7 mo, no complications
6	12/F	MVC	Grade IV splenic laceration, extravasation at suprahepatic IVC	18	11	5 mo, back brace
7	12/M	MVC	Grade III liver laceration, femur fracture	34	13	2 mo, no issues
8	10/F	Tornado	Grade IV liver laceration	48	11	3 mo, no complications

LOS, length of stay; Peds vs auto, pedestrian vs automobile; MVC, motor vehicle crash; IVC, inferior vena cava.

hemostasis by 2 potential mechanisms: activating coagulation factors IX and X when complexed with tissue factor and by binding to activated platelets independent of the tissue factor pathway [14]. Both mechanisms lead to formation of thrombin and a hemostatic clot at the site of vascular injury [9,10]. This property offers significant theoretical benefits to patients with traumatic bleeding without hemophilia.

Initial uses of rFVIIa in children focused on the control of bleeding episodes in hemophilic patients who have antibodies to other factors [15]. Recent reports have demonstrated the effectiveness of rFVIIa in obtaining hemostasis in the pediatric population for other off-label indications including liver disorders, cardiac surgery, preterm infants with coagulopathy, and platelet disorders, such as Glanzmann's thrombasthenia [15-18]. There are a few case reports of children treated with rFVIIa for traumatic liver injuries [11,12]. In this study, we report our experience with the use of rFVIIa as an adjunctive treatment in pediatric blunt trauma patients with intraabdominal injuries being treated nonoperatively.

1. Methods

After obtaining approval from the institutional review board at the University of Mississippi Medical Center, all pediatric trauma records from October 2004 to October 2006 were reviewed. Inclusion criteria for this study were patients younger than 18 years having blunt abdominal trauma with solid organ injury, evidence of ongoing hemorrhage, nonoperative management of their intraabdominal injury, and treatment with rFVIIa. The charts were retrospectively reviewed, and data pertaining to the injury, emergency department and hospital care, blood product transfusion, dose of rFVIIa used, and outcome were noted.

2. Results

Eight patients met inclusion criteria for our study period (Table 1). Ages ranged from 7 to 15 years, with the median

age of 12 years. Five were males and 3 were females. Mechanisms of injury included motor vehicle collisions, pedestrian vs parade float, bicycle handlebar injury, football helmet injury, and one child thrown from her house during a tornado. Injuries ranged from isolated renal, spleen, or liver trauma to one patient having a grade III renal laceration, grade I liver and splenic laceration, and an open-book pelvic fracture with bilateral internal iliac artery injuries. Injury severity scores ranged from 9 to 48, with a mean of 27.5. All patients displayed a significant drop in their hematocrit (Fig. 1) with a concomitant rise in heart rate. Several of the patients also displayed a decrease in their blood pressure during this time. A single dose of rFVIIa was administered between 6 and 48 hours after injury. Five patients received a dose of 90 $\mu\text{g}/\text{kg}$, 2 patients received 75 $\mu\text{g}/\text{kg}$ of rFVIIa, and 1 patient received 24 $\mu\text{g}/\text{kg}$ (Table 2). This last patient also received one 2-mg dose of vitamin K. Two patients received packed red blood cells before being treated with rFVIIa. Four patients had transfusions of red blood cells concomitant with rFVIIa administration. After rFVIIa dosing, 4 patients received blood or blood products. All patients' hematocrits stabilized after rFVIIa dosing with the largest difference in hematocrit from the time of dosing to the lowest hematocrit recorded being 8 points. This patient had a grade IV splenic

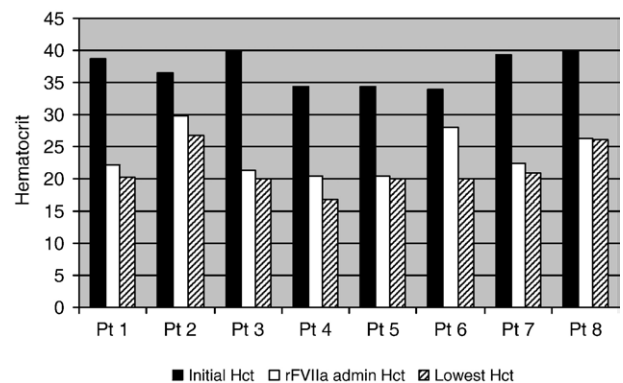


Fig. 1 Graphic representation of each patient's initial hematocrit, hematocrit at the time of rFVIIa administration, and the lowest hematocrit recorded after treatment with rFVIIa.

Table 2 Blood/blood product administration and rFVIIa dose given during hospital course

Patient no.	rFVIIa dose ($\mu\text{g}/\text{kg}$)	rFVIIa administration ^a	pRBC before rFVIIa	pRBC with rFVIIa	pRBC after rFVIIa	Other products given
1	90	24	0	0	0	0
2	75	48	4 U	0	0	0
3	75	24	0	2 U	0	0
4	90	6	0	0	0	4 U FFP
5	90	48	0	1 U	0	0
6	90	6	0	1 U	1 U	0
7	24	6	0	0	2 U	0
8	90	6	2 U	1 U	1 U	2 U FFP, 1 U platelets

pRBC indicates packed red blood cells; FFP, fresh frozen plasma.

^a Hours after injury.

laceration (Fig. 2) with active extravasation on abdominal computed tomography and was given rFVIIa 6 hours after injury at a hematocrit of 28. One patient underwent a pelvic angiogram after rFVIIa was given for bilateral internal iliac artery injuries. At the time of angiography, no active bleeding was noted. The right internal iliac artery was transected at the gluteal branch with spasm/thrombosis preventing major hemorrhage. The left internal iliac artery showed signs of past bleeding as well. Interventional radiology placed gelfoam in bilateral internal iliac arteries, with an embolic coil in the right internal iliac artery also to ensure hemostasis. Pelvic fixation was performed on hospital day 9 without complications or further transfusions.

No adverse thromboembolic events were seen in our patients after treatment with rFVIIa. All patients were discharged home anywhere from 5 to 20 days, with the mean and median length of stay of 10.5 days. Follow-up ranges from 7 to 24 months, with no patients having any complications from their intraabdominal solid organ injuries.

3. Discussion

The first report of using rFVIIa as an off-label therapy for trauma in adults was in 1999 [3], and since then, there have been an increasing number of articles reporting on its use in traumatic injuries [4-10]. A multicenter, prospective, randomized trial compared the effects of rFVIIa with placebo in trauma patients [9]. In this study, rFVIIa was not given until 8 U of blood had been transfused. Blunt trauma patients had a reduced need for transfusion, especially massive transfusion, and post hoc analyses revealed a lower incidence of acute respiratory distress syndrome [10]. The rate of thromboembolic events was the same between the treated and placebo groups. This is an important point, as other authors have suggested that off-label use of rFVIIa would result in a higher incidence of thromboembolic complications [19]. In a retrospective study by Como et al [20], the amount of red blood cells transfused significantly correlated to the mortality in trauma patients with a 20% increase in death in patients receiving more than 20 U of blood. It has

been shown that reducing the patient's exposure to excessive transfusion of blood products decreases the risk of morbidity and potentially fatal complications associated with hemorrhage [10]. There are intrinsic risk factors for immunologic and infectious risks associated with transfusions, and the risk of developing acute respiratory distress syndrome and multiorgan failure after trauma correlates with increasing transfusion requirements as well [20,21].

Although the adult literature is well on its way in supporting the use of rFVIIa for traumatic injuries, there are only a few reports of its use in children [11,12]. In our study, we used rFVIIa when we felt that the hemorrhage was continuing despite our conservative resuscitative measures. We also felt that the patients might require an intervention such as an operative procedure or organ removal if nothing else was done. After rFVIIa administration, all patients appeared to have their hemorrhage controlled, as evidenced by normalized vital signs and stabilized hematocrits.

Several studies have reported giving multiple doses of rFVIIa several hours apart until hemostasis is achieved for the treatment of traumatic bleeding [11,15]. This is also recommended in patients with bleeding associated with hemophilia [13,14]. Each of our patients received a single



Fig. 2 Grade IV splenic laceration.

dose of rFVIIa, with 5 of 8 doses being considered a “standard hemophilia” dose of 90 $\mu\text{g}/\text{kg}$. One patient received 24 $\mu\text{g}/\text{kg}$ of rFVIIa after receiving 2 mg of Vitamin K. We speculate that the lower dose was used after vitamin K administration because information on rFVIIa administration and adverse effects in pediatric trauma patients is very limited. Of our 8 patients, 1 required no blood products despite a drop in hematocrit of 19 points. Two patients received blood before administration of the procoagulant factor VII. These transfusions were given at the outside treating facility before the patient’s arrival at our institution. The patients receiving blood transfusions after rFVIIa administration were given at the advice of other services because of concomitant injuries and were not related to the initial injury resulting in the continued hemorrhage. Fresh frozen plasma was given after rFVIIa dosing in one patient to correct a laboratory value (elevated prothrombin time), not for ongoing bleeding. The patient who was dosed with the procoagulant before angiography was found to have thrombus without active extravasation at both arterial injuries. This finding during angiography may likely have been from the rFVIIa administration before the intervention.

The expense of controlling bleeding with rFVIIa is significant. The patient charge for a 2700- μg dose (90 $\mu\text{g}/\text{kg}$ in a 30-kg child) is approximately \$15,000. There have been 2 cost-effectiveness analyses carried out for this drug, and both showed an advantage to its use in controlled circumstances [22,23]. We do not recommend that rFVIIa should supplant appropriate surgical care when needed nor do we suggest that it should be used in patients in whom the bleeding would have likely stopped spontaneously. Rather, selective use as in our series would be most cost-efficient.

Further studies on the efficacy of rFVIIa for the control of bleeding and for reducing transfusion requirements need to be performed in the pediatric trauma population. A prospective, randomized, double-blinded study is called for in this patient population to validate the use of rFVIIa in children with traumatic intraabdominal injuries. For this study, a set protocol would be devised that would have the same dose to all patients initially and would also have parameters laid out for multiple dosing if further therapy is warranted as well as protocols for transfusion. We suggest that the use of rFVIIa should be considered as an adjunctive therapy in children with traumatic bleeding from blunt injury.

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Discussion

Darrel Cass, MD (Houston, TX): I guess the obvious question is, have you learned anything from your 8 patients that might guide us as to when this therapy may be useful?

The rate of ongoing bleeding in our pediatric patient population is very low, and this is a very, very expensive product. In what population of patients do you think it will be useful?

Laura Vick, MD (Jackson, MS): I think it would be useful in patients that have continued bleeding. Obviously the earlier you can administer it—probably within 6 hours of their injury—the better. I think it also depends on your experience with factor VII. In regards to its cost, we found that from the pharmacy at our institution, the patient cost is \$15,000, but if you consider that it possibly prevents them from going to the operating room and also prevents them from having further blood and blood products as well as a risk of blood-borne pathogens. We think in certain instances it is warranted.

Ricardo Superina, MD (Chicago, IL): I found your paper very interesting because I am not sure how your factor VII works. Obviously the hypothesis would be that you have a factor VII deficiency in these patients, so I was wondering if you probably should measure the factor VII levels and see how factor VII administration alters those levels. The liver is very good at making factor VII, plus you are giving factor VII when you are giving fresh

frozen plasma, so it would be very interesting to know exactly what impact factor VII has on your serum levels to see if it actually—you do not need a lot of factor VII to form clot. You only need about 10%-15% of normal.

Laura Vick, MD (response): Thank you. I think that would be very interesting to look at. We did not look at that.

Nelson Rosen, MD (New Hyde Park, NY): I just wanted to know how many patients you tried recombinant factor VIIa in that ended up needing an operation or needing angioembolization or some other further measure to stop their bleeding that was not included in this group?

Laura Vick, MD (response): We had one patient that had factor VII given. She had to go to the operating room for other injuries. She had a pancreatic transaction. Of these 8 patients, one patient did require angiointervention that actually had angioembolization after factor VII administration and at the time they already found that the bleeding had stopped, but since they were there, the interventional radiologist decided to insert a coil. She had bilateral internal iliac artery injuries, but they coiled them anyway, although there was no active bleeding.