Recombinant factor VIIa in the management of postoperative bleeding in patients undergoing reconstruction of ruptured abdominal aortic aneurysm

Piotr Terlecki, Jacek Wroński, Tomasz Zubilewicz, Stanisław Przywara, Marcin Feldo, Wojciech Kobusiewicz, Andrzej Paluszkiewicz, Marek Iłżecki, Jan Kęsik

Chair and Department of Vascular Surgery and Angiology, Medical University, Lublin, Poland

Abstract: Recombinant activated factor VIIa (rFVIIa) (NovoSeveNovoNordisk, Bagsvaerd, Denmark) is a well-known haemostatic agent indicated for control of bleeding in patients with severe bleeding associated with hemophilia, thrombocytopenia and disseminated intravascular coagulation. The surgical literature increasingly reports the off-licence administration of rFVIIa to arrest haemorrhage refractory in other interventions. It has been successfully used to control peri-operative bleeding in trauma, cardio-vascular and neurosurgical patients. We report 10 cases of previously healthy males, without preexisting coagulopathy, who had undergone surgical procedure because of a ruptured infrarenal aortic aneurysm. Despite the administration of red blood cell concentrate, fresh frozen plasma and platelets specimens in the peri- and post-operative period, the patients were unstable and presented non-surgical bleeding. Intravenous treatment with rFVIIa was used in two doses (37-90 µg/kg) every 2 hours. In all cases, bleeding stopped. Two patients died in the period of 72 hours after operation because of multiple organ failure, a third died one month later because of myocardial infarction. We conclude that treatment with Recombinant Activated Factor VIIa for patients undergoing AAA reconstruction complicated with non-surgical, life-threatening bleeding, seems to be effective and safe.

Key words: recombinant activated factor VIIa (rFVIIa), abdominal aortic aneurysm (AAA)

INTRODUCTION

Recombinant factor VIIa (rFVIIa) (Novo-Seven; NovoNordisk, Denmark) was first developed for the treatment of hemorrhage in patients with hemophilia A or B with neutralizing auto-antibodies to factor VIII or IX [1]. In 2005, the Food and Drug Administration increased rFVIIa's license to include surgical procedures in the same patient group and patients with congenital factor VII deficiency. The molecular mechanism by which rFVIIa induces the formation of a stable haemostatic plug remain unclear. While it is generally agreed that rFVIIa enhances thrombin generation at sites of tissue injury, controversy exists regarding the mechanisms by which this comes about, particularly the source and role of the protein – Tissue Factor (TF). In physiological conditions TF is absent from vascular cells that come into contact with flowing blood, and is present as an inactive pool on sub-endothelial cells. Vessel injury exposes the TF to the blood, where it binds and activates FVII. The resulting TF-FVIIa complex catalyzes the conversion of factor X into its active form Xa. Factor Xa, in a complex with factor V, calcium and phospholipids, converts protrombin into thrombin. Thrombin induces local hemostasis by converting fibrinogen into fibrin, which polymerizes and forms a thrombus in conjunction with platelets at the site of vascular injury [2].

The surgical literature reports the off-license administration of rFVIIa to stop hemorrhage refractory in other intervention such as cardiac surgery, urology or trauma surgery [3-6]. In the European Union it is also licensed for the treatment of spontaneous and surgical bleeding in hemophilia A and B with known inhibitors to factor VIII and IX, as well as for use in the following indications: acquired hemophilia; patients with congenital factor VII deficiency undergoing surgery or invasive procedures; and patients with Glanzmann's thrombasthenia with antibodies to blood platelets, glycoprotein IIb/IIa, or HLA [7]. Although off-label use of rFVIIa within vascular surgery has been reported, this has been predominantly within case reports or series [8, 9], and thus its role in vascular surgery is currently unclear. In this paper we describe our experience related to the use of rFVIIa in a group of patients with a coagulopathy together with huge blood lost during an operation for ruptured abdominal aortic aneurysm.

MATERIALS AND METHODS

We retrospectively report 10 cases of previously healthy men without preexisting coagulopathy who had been operated because of ruptured infrarenal aortic aneurysm. Despite administration of red blood cell concentrate, fresh frozen plasma, and platelets specimens in the peri- and post-operative period, the patients were unstable and presented non-surgical bleeding. Patients and clinical characteristics are shown in Table 1.

Table 1   Group characteristics

Number	10
Sex (M/F)	9/1
Age – years (mean range)	59-80(71.4)
Weight – kg (mean range)	68-102 (84.4)
Ruptured AAA	10/10
Diabetes mellitus	2/10
PAOD	7/10
Blood loss (l) (mean)	1.-5,3 (2.9)
RBC used (units)	5-14 (8.0)
FFP used (units)	8-24 (12)
Platelets concentrates used (units)	6-12 (9.6)

All study participants were screened prior to and until 24 hours after administration of rFVIIa – mean blood product usage (RBC, FFP, platelets), coagulation tests (INR, APPT, fibrinogen).

RESULTS

All examined patients survived the operation. Mean perioperative blood loss was 2,900 ml (1,800-5,300 ml). The number of doses of rFVIIa given was 1-3, with individual doses varying from 37-90 ug/kg. In all cases, the bleeding stopped. The response to treatment was rapid. No adverse events were observed related to rFVIIa administration. Blood products usage and changes in coagulation before and after rFVIIa used is shown in Table 2. Two patients died in the 72 hour period post-operation because of multiple organ failure; a third patient died one month later because of myocardial infarction.

Table 2   Blood products usage, changes in coagulation before and after rFVIIa use

Factor	Before rFVIIa		24 hours after rFVIIa	
		Range		Range
RBC used	8.0 U	5-14	2.3 U	1-4
FFP used	12 U	8-24	4.8 U	2-7
Platelets concentrates used	9.6 U	6-12	4.2 U	0-6
Hb (g/dl)	8.0	6.3-9.1	10.8	9.7-12
INR	1.63	1.2-2.6	1.35	1.0-1.7
APTT(sec)	38	36.0-48.1	39.3	36.6-40.1
Fibrynogen (g/dl)	580	480-630	370	250-500

DISCUSSION

In numerous types of surgery rFVIIa has been used to control bleeding due to preexisting conditions or to manage severe surgical bleeding. Trauma and cardiac surgery have been one of the common situations for the treatment of surgical bleeding [10, 11]. The use of Novo Seven also has been reported during thyroidectomy in a patient with Hermansky-Pudlak syndrome [12], and posterior spinal fusion surgery in children with neuromuscular scoliosis

[13]. The preoperative use of rFVIIa in patients undergoing prostate surgery, as well as in the orthopedic procedures such as total hip arthroplasty, has been reported [5, 14] Vascular surgery lags behind the other surgical specialities in this regard. One reason for this may be the theoretical concern regarding the exacerbation of conditions mediated by TF exposure to the circulation. Atherosclerostic plaquesexpress TF, and both surgical injury and extracorporeal circulation up-regulate systemic TF expression. Recommendations for the administration of rFVIIa in major vascular surgery have been made by Shander [15]. Based on the experience of a panel of experts and a literature review, they deemed its use to be appropriate as a rescue therapy in thoracic aortic surgery, but suggested that the evidence for its use in abdominal aortic surgery was less certain. Similar recommendations were made by Goodnough who advised caution in those with a history of vascular disease [16]. The 15 articles found in a Medline Database reported on the administration of Novo Seven to a total of 273 patients, of whom 43 had undergone vascular surgery. The patients ranged from 39-83 years of age, 51% were male, 26% female, and in 23% the gender of the patients was not declared. Unsuprisingly, major thoracoabdominal or abdominal aortic (both supra- and infrarenal) surgery accounts for the vast majority of cases (75%). RFVIIa has been administered in both elective and emergency settings, to assist in the management of perioperative complications, such as evacuation of postoperative haematoma, repair of leak, and in both open and endovascular procedures [8, 17]. The frequency of rFVIIa administration was varied. While some groups prescribed only a single bolus [9, 18], others administrated further doses if bleeding failed to stop [19]. Therefore, if patients received multiple doses, their cumulative dose per kilogram body weight was recorded. The range of rFVIIa administered as a cumulative dose was large (24 ug/kg-360 ug/kg, mean 87.6 ug/kg), as was the variation in the initial dose (24 ug/kg-120 ug/kg), and the total number of doses [1-4]. 59.1% of cases within the series had documented cumulative doses of <90 ug/kg. The mode dose was 90 ug/kg, the recommended dose for haemophiliacs. The timing of administration and the criteria upon which the decision to do so was made are frequently unclear. A recent review of thromboembolic complications in patients treated with rFVIIa reported to the FDA database from 1999-2004 suggested an increased rate in those treated for unlabelled conditions, an alarming result considering that the morbidity and mortality from events such as stroke and myocardial infarction is so high [3]. Warren [19] aggregated the available data within cardiac surgical patient treated with rFVIIa and found a thromboembolic adverse event rate of 5.3% for adult patients [19]. The proportional distribution of reported thromboembolic events sites are: arterial (54.1%): cerebrovascular accidents (21.3%), acute myocardial infarctions (18.6%) and remaining 14.2% involved femoral, hepatic, renal, splenic and iliac artery occlusion. There were also deep vein thrombosis, jugular, mesenteric, portal renal and retinal vein thrombosis (22.9%), and pulmonary emboli (17.5%) [20]. The differential effect of rFVIIa on arterial and venous thromboembolic events is of interest. The increased incidence of arterial thromboembolic events is related to exposure of endothelial tissue factor attributable to rupture or ulceration of atheromatous plaques. The rFVIIa may bind to such sitesx and initiate thrombosis which can result in myocardial infarction or cerebral ischemia. On the other hand,

venous thromboses develop as a result of stasis, and thus may not be caused by- rFVIIa-initiated thrombosis [21]. A case of death from myocardial infarction described in our data seems to be a cardiovascular complication related to the big operation and concomitant diseases, rather than a late adverse event of rFVIIa administration.

CONCLUSIONS

We conclude that treatment with Recombinant Activated Factor VIIa for patients undergoing AAA reconstruction complicated with non-surgical, life-treating bleeding seems to be effective and save.

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