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Original Article

Recombinant Factor VIIa for The Management of Uncontrollable Bleeding Following the Repair of Acute Type A Aortic Dissection

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Abstract

Background: Bleeding is a serious complication after surgical repair of acute type A aortic dissection. Recombinant factor VIIa (rFVIIa) could be used for the management of severe bleeding; however, it could lead to thromboembolic events. We aimed to report our experience in using rFVIIa in the management of severe bleeding following the surgical repair of acute type A aortic dissection.

Methods: We performed a retrospective study, including patients who had surgery for acute aortic dissection type A and received rFVIIa, in the period between January 2012 and January 2019. We reported the amount of bleeding 4 hours before and after the administration of rFVIIa, the number of blood products transfused before and after the use of rFVIIa, thrombosis of the central venous line, as well as the presence of disseminated intravascular coagulation.

Results: There were ten patients (2 females and 8 males) out of 120 patients with acute type A aortic dissection, who required the use of rFVIIa for severe postoperative bleeding. The mean age was 67.7±10.5 years. The amount of drainage decreased from 889±585.6 ml during the 4 hours prior to the infusion, to 165±73.5 ml during the following 4 hours ($p<0.001$). The patients received 2752±1362.9 ml, and 618±483.3 ml packed RBCs before and after rFVIIa administration, respectively ($p< 0.001$). The patients received 1601±693.4 and 246±419.6 ml of fresh frozen plasma before and after the use of rFVIIa, respectively ($p< 0.001$). The prothrombin time decreased after the infusion of rFVIIa (42.7±32 and 17.1±8 seconds, $p= 0.001$). There were no clinical signs of thromboembolism after its use. Mortality occurred in five patients (50%).

Conclusion: In the life-threatening situation of uncontrollable bleeding following surgical repair of type A acute aortic dissection, rFVIIa may have benefits to control bleeding. Furthers studies are recommended.

KEYWORDS

Acute aortic dissection, Activated recombinant factor VII

Article History

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Introduction

Acute type A aortic dissection is a serious and potentially fatal condition that requires urgent surgical intervention. The surgical procedure can be complicated by major bleeding, which can significantly affect the outcomes. Massive blood transfusion could lead to many complications [1]. Bleeding can be either surgical, from the multiple suture lines and the extensive tissue dissection, or medical due to a coagulation defect. Therefore, it

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is crucial to evaluate the efficacy of several medications to control bleeding, such as activated recombinant factor VII (rFVIIa).

The need for extracorporeal circulation, as well as hypothermia during surgical repair can affect the coagulation process [2]. Additionally, many patients admitted urgently to surgery are on antiplatelet medications for associated ischemic heart disease, which can also aggravate postoperative bleeding [3].

Massive postoperative bleeding requires the transfusion of blood products; however, these measures may not be able to control life-threatening bleeding, and the rFVIIa might have a role [4]. rFVIIa was initially used to treat hemophilia in patients with factors VIII and IX deficiency [5]. Moreover, rFVIIa is used for the management of uncontrollable bleeding in various clinical conditions, such as trauma, and following cardiac surgery [6].

However, rFVIIa can lead to fatal thromboembolic complications [7]. Thus, the benefits and the potential complications of its use must be carefully weighed and considered according to the severity of postoperative bleeding. In this study, we reported our experience in using rFVIIa to control severe bleeding following the repair of acute type A aortic dissection.

Patients and Methods:

We performed a retrospective study, including patients who had surgery for acute aortic dissection type A, and received rFVIIa postoperatively, in the period between January 2012 and January 2019. Acute aortic dissection was defined as any dissection involving the ascending aorta within two weeks from the beginning of the symptoms. The diagnosis was confirmed by 3D CT angiography as well as intraoperatively.

Data collection:

The demographic data, the procedures, and the perioperative results were obtained from the surgical database. We reported the amount of drainage 4 hours before and 4 hours after the infusion of rFVIIa, the number of blood products transfused before and after the use of rFVIIa, thrombosis of the central venous line, as well as the presence of disseminated intravascular coagulation (DIC). The incidence of Myocardial infarction was assessed by the presence of persistent elevation of the ST segment in electrocardiography, or an increase in the cardiac enzymes. Cerebrovascular Stroke (CVS) was diagnosed by the appearance of neurologic deficits clinically and confirmed by computed tomography.

Techniques:

All patients were assessed with CT angiography, which was used for the evaluation of the presence of coronary lesions. Transthoracic echocardiography was done to evaluate the cardiac function, the presence and severity of aortic valve regurgitation, and the presence of pericardial collection.

All patients were operated via median sternotomy. Cannulation of the femoral artery was performed, and we used a single right atrial cannula for the venous drainage. Myocardial protection was achieved by selective antegrade coronary infusion of cold blood cardioplegia following the aortotomy, with systemic cooling and topical cooling with ice slush. Venting of the left ventricle was done via the right superior pulmonary vein. The cardiologic solution was infused at 30 minutes intervals.

Administration of rFVIIa was done following a unified protocol for patients who had severe uncontrollable bleeding, without a definite surgical cause, and after initial treatment with packed red blood cells (RBCs), fresh frozen plasma (FFP) and platelet concentrates. The infusion of rFVIIa was always done after the full dose of protamine and normalization of the activated clotting time (ACT) following cardiopulmonary bypass. The dose of rFVIIa was 60 mg/kg, repeated once in case of failure of the initial dose to control bleeding. Prothrombin time and platelet count were checked before and after the use of rFVIIa.

Ethical considerations:

No informed consent was required because of the severity and urgency of the condition. The local Ethical Committee, however, approved the use of rFVIIa according to the patients' prognosis.

Statistical analysis:

SPSS (version 20; IBM, Chicago, IL) was used to perform all analyses. Continuous values were expressed as mean ± standard deviation and qualitative values as number and percentage. Normality was tested using the Shapiro-Wilk test, and a paired t-test or Wilcoxon signed-rank test was used to compare continuous variables before and after rFVIIa administration.

Results

One hundred and twenty patients had surgery for acute type A aortic dissection, rFVIIa was used in ten patients (8.3%). There were two females and eight males, with a mean age of 67.7±10.5 years. Eight patients had replacement of the ascending aorta, and two patients required additional hemi-arch replacement, with none of them requiring any intervention on the aortic root or valve.

The mean cardiopulmonary bypass time (CBP) was 262.7±87.9 min, and the mean cross-clamp time was 151.4±52.3 min. A hypothermic circulatory arrest was needed in 7 patients, selective antegrade cerebral perfusion was used for 3 of them, and retrograde perfusion for four patients. The mean total circulatory arrest time was 32±27 min.

Six patients had acute renal failure postoperatively, 4 of them required dialysis. Five patients had a severe chest infection, and one patient had a cerebral hemorrhage.

The mean intensive care unit (ICU) stay was 13.1±8 days, and the mean hospital stay was 25.3±39 days. Mortality occurred in 5 patients (50%), all due to multiorgan failure (MOSF).

The effect of rFVIIa:

rFVIIa was given to seven patients intraoperatively and three patients in ICU. All causes of surgical bleeding were excluded. The bleeding profile, the blood pH, and the body temperature were within acceptable ranges before starting rFVIIa infusion.

The severity of bleeding decreased significantly after the rFVIIa administration, as well as the number of transfused blood products. The amount of drainage decreased from 889±585.6 ml during the 4 hours prior to the infusion, to 165±73.5 ml during the following 4 hours. (Table 1) Two patients had surgical re-exploration, 6, and 7 hours postoperatively for hemodynamic instability, with suspected tamponade. No serious bleeding was found in both patients.

There was a significant decrease in the prothrombin time (PT) following rFVIIa infusion (Table 1). There were no clinical signs of DIC.

Thrombotic and hemorrhagic complications:

One patient developed massive cerebral hemorrhage postoperatively, and no apparent reason was found. This patient went into a deep coma on the third postoperative day and died 12 days postoperatively. No patient developed myocardial, cerebral, or mesenteric infarctions. There was no need to change arterial or venous lines due to thrombosis. No peripheral ischemic changes were noted in any of our patients.

Table 1: Blood products transfused and coagulation factors before and after rFVIIa infusion. Data are presented as mean and standard deviation.

	Before rFVIIa	After rFVIIa	P-Value
Packed RBCs (ml)	2752 ± 1362.9	618 ± 483.3	<0.001
FFP (ml)	1601 ± 693.4	246 ± 419.6	<0.001
Platelets(ml)	731.4 ± 459	111 ± 179.7	0.002
Prothrombin time (sec)	42.7 ± 32	17.1 ± 8	0.001

FFP: fresh frozen plasma; RBCs: red blood cells; rFVIIa; recombinant factor VIIa

Discussion

This study was conducted on ten patients who developed severe uncontrollable bleeding following surgical management of acute type A aortic dissection from a total of 120 operated patients. This is a surgical emergency associated with high mortality and morbidity; one of them is bleeding. Hemorrhage can be caused by preoperative antiplatelet therapy [8], and 32% of the patients operated for acute aortic dissection had platelet dysfunction at the time of surgery (14% with acetylsalicylic acid alone, and 18% via a combination of ASA and clopidogrel). Antiplatelet therapy is related to the fact that the initial presentation of most of the patients is chest pain with ST-segment depression, which mimics ischemic heart disease. These patients are normally at a higher risk of intra and postoperative hemorrhagic complications than patients with normal platelet count and function [9].

The blood flow through the false lumen is a strong activator of coagulation and fibrinolysis prior to surgery. The extracorporeal circulation with associated hypothermia also could lead to some inhibition of the coagulation cascade, decreasing the synthesis of the coagulation factors and affecting the platelet function [10]. The blood contact with the tubing system activates the anti and procoagulants, as well as the complement system [11]. All these factors can eventually lead to severe intra and postoperative bleeding, requiring massive blood transfusion with its serious complications.

In this case, achieving hemostasis via transfusion of blood products such as packed RBCs, FFP, and platelet concentrates can control bleeding in most cases. However, in our study, in 8.3% of the patients, these measures were not sufficient, and persistent, life-threatening bleeding continued despite the absence of any correctable source of surgical bleeding. In such cases, the use of rFVIIa might be of benefit. Gill and colleagues concluded that the use of rFVIIa could be of benefit in controlling intractable bleeding following cardiac surgery in a randomized trial versus placebo. They noted, however, an increase in the incidence of thromboembolic events [5].

The efficacy, as well as the complications of the usage of rFVIIa after surgical repair of acute aortic dissection, are not adequately evaluated. Tritapepe and coworkers found that rFVIIa was used with satisfactory results during and following the surgical treatment of acute aortic dissection using deep hypothermic circulatory arrest, to control massive bleeding refractory to conventional hemostatic measures, with insignificant differences in the undesirable effects [12]. Other case reports have reported successful results of its usage in the situation of refractory hemorrhagic shock following the surgical repair of acute aortic dissection [13].

It is crucial, however, to obtain the maximum benefit from rFVIIa, to optimize the hemostasis, by maintaining a satisfactory platelet count (>50g/l), and by correcting anemia, hypothermia, and hypocalcemia [14]. Management of acidosis (pH<7.1), which seriously reduces the rFVIIa activity, is also very important [6].

The use of procoagulant medications can induce thromboembolic complications, as reported by many studies [15, 16]. In our study, no thromboembolic events were reported. There was a single incidence of a cerebral hemorrhage, not related to the rFVIIa. There were no signs of DIC. The low rate of complications in our study might be attributed to the limited number of re-explorations after the usage of rFVIIa to detect thrombosis. Thus, we cannot exclude micro-embolism as a cause for acute renal failure or multiorgan system failure (MOSF), which occurred to some of the patients enrolled in the study.

The use of rFVIIa can, however, lead to activation of factor X to factor Xa through a systemic reaction. This leads to the production of a sufficient amount of thrombin, transforming fibrinogen into fibrin, leading to thrombus formation [17]. This systemic response can lead to thromboembolic events. Levi and colleagues, in their analysis of 35 controlled trials, noticed an increase in the incidence of arterial thromboembolic events with the use of rFVIIa compared to a placebo [18].

The mortality rate in patients with acute aortic dissection in our center was 27%, this operative mortality increased significantly in patients who developed major postoperative bleeding (50%), but this is not only related to the use of rFVIIa. Massive blood transfusion is known to be related to an increase in the incidence of infections, acute respiratory distress syndrome, multiorgan failure, as well as an increase in postoperative mortality [19].

rFVIIa alone cannot, however, control severe bleeding due to a surgical source. It is also crucial to adjust all other factors that may interfere with coagulation, such as hypothermia and acidosis, as well as to optimize hemostasis by transfusion of blood products such as FFP and platelet concentrates. The timing of rFVIIa infusion is very important, as waiting until the patient's condition worsens to start treatment would be of no benefit. Karkouti and colleagues noted that the early use of rFVIIa during the course of bleeding had a better outcome [20].

Limitations

Our study has several limitations. The small sample size, being a single-center study, as well as the bias related to the retrospective study, concerning the patients' recruitment. Due to the rarity of these cases, a randomized study to evaluate the advantages and benefits of the use of rFVIIa to control severe bleeding in patients operated for acute aortic dissection would be very difficult.

Conclusion

This study suggests that in the critical, life-threatening situation of uncontrollable bleeding following surgical repair of type A acute aortic dissection, rFVIIa may have benefits to control bleeding with low clinically evident thromboembolic complications. Further studies to confirm our findings are recommended.

Disclosure

We used NovoSeven (Novo Nordisc Inc.), and the use of this medication was only guided by the clinical condition and the prognosis. There were no conflicts of interest.

Conflict of interest: Authors declare no conflict of interest.

References

1. Paparella D, Rotunno C, Guida P et al. Hemostasis alterations in patients with acute aortic dissection. Ann Thorac Surg. 2011; 91: 1364-9.
2. Lau P, Ong V, Tan WT, Koh PL, Hartman M. Use of Activated Recombinant Factor VII in Severe Bleeding – Evidence for Efficacy and Safety in Trauma, Postpartum Hemorrhage, Cardiac Surgery, and Gastrointestinal Bleeding. Transfusion medicine and hemotherapy. 2012; 39: 139-50.
3. Barua A, Rao VP, Ramesh B, Barua B, El-Shafei H. Salvage use of activated recombinant factor VII in the management of refractory bleeding following cardiac surgery. J Blood Med 2011; 2: 131-4.
4. Bui JD, Despotis GD, Trulock EP, Patterson GA, Goodnough LT. Fatal thrombosis after administration of activated prothrombin complex concentrates in a patient supported by extracorporeal membrane oxygenation who had received activated recombinant factor VII. J Thorac Cardiovasc Surg 2002; 124: 852-4.
5. Gill R, Herbertson M, Vuylsteke A, et al. Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. Circulation. 2009; 120: 21-7.
6. Meng ZH, Wolberg AS, Monroe III DM, Hoffman M. The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. J Trauma. 2003; 55: 886-91.
7. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med. 2010; 363: 1791-800.
8. Yorgitis BK, Ruggia C, Dujon J. Antiplatelet and anticoagulant medications and the surgical patient. Am J Surg 2014; 207: 95-101.
9. HO PM, Peterson ED, Wang L. Incidence of death and acute MI associated with stopping Clopidogrel after acute coronary syndrome. JAMA. 2008;299:532-9.

10. Liu Y, Han L, Li J, Gong M, Zhang H, Guan X. Consumption coagulopathy in acute aortic dissection: Principles of management. J Cardiothoracic Surg. 2017; 12: 50.
11. Tanaka M, Kawahito K, Adachi H, Isawa H, Ino T. Platelet damage caused by the centrifugal pump: Laser-Light scattering of aggregation patterns. Artif Organs. 2001;25(9):719-23.
12. Tritapepe L, De Santis V, Vitale D et al. Recombinant activated factor VII for refractory bleeding after acute aortic dissection surgery: a propensity score analysis. Crit Care Med 2007; 35: 1685-90.
13. Yan W, Xuan C, Ma G. Combination use of antiplatelets and recombinant activated factor VII for increased hemostasis during type A aortic dissection operations. J Cardiothoracic Surg. 2014; 9: 156.
14. Vincent JL, Rossaint R, Riou B, Ozier Y, Zideman D, Spahn DR. Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding–a European perspective. Crit Care. 2006;10: R120.
15. Mitra B, Phillips L, Cameron PA, Billah B, Reid C. The safety of recombinant factor VIIa in cardiac surgery. Anaesth Intensive Care. 2010; 38: 671-7.
16. White MC, Pryn SJ, Monk CR. Thrombogenic side-effects of recombinant factor VIIa after use in coronary artery bypass surgery. Anaesth Intensive Care. 2006; 34: 664-7.
17. Hedner U. Mechanism of action of recombinant activated factor VII: An update. Semin Hematol. 2006;43 (1 suppl 1): 5105-7.
18. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med. 2010; 363: 1791-800.
19. Kristen CS, Lena MN. Complications of massive transfusion. Chest.2010;137(1):209-20.
20. Karkouti K, Yau TM, Riazi S et al. Determinants of complications with recombinant factor VIIa for refractory blood loss in cardiac surgery. Can J Anaesth. 2006; 53: 802-9.