Recombinant Activated Factor VII in Aortic Surgery for Patients With Coagulation Disorders and Hypothermic Circulatory Arrest: a Single-center Retrospective Study

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Research Article

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Abstract

Background: We aimed to identify the risk factors of uncontrollable bleeding and investigate the safety of recombinant activated factor VII (rFVIIa) in aortic surgery under hypothermic circulatory arrest (ASHCA).

Methods: The present single-center retrospective study compared the baseline characteristics of 144 patients who underwent ASHCA at our institute the total cohort. Of the 144 patients, 42 received rFVIIa (group rFVIIa), while the remaining 102 patients did not (group non-rFVIIa). Perioperative bleeding and transfusions, postoperative 30-day mortality, and adverse events (AEs) were analyzed in 29 propensity score-matched pairs.

Results: Before surgery, the rFVIIa group demonstrated a greater number of shocks (p=0.019), higher JapanSCOREx II mortality rate (p=0.033), low platelet count (p=0.015), fibrinogen (p<0.001), prolonged activated partial thromboplastin time (p=0.005), prothrombin time international normalized ratio (p=0.006), and longer aortic cross cramp (ACC) time (p=0.049). Postoperative bleeding, transfusion, 30-day mortality, and AEs were comparable between the groups.

Conclusions: Preoperative shock, higher JapanSCORE II mortality rates, low platelet and fibrinogen levels, prolonged aPTT and PT-INR, and longer ACC time might be risk factors for excessive bleeding and indicate the need for rFVIIa treatment. The present study suggests that rFVIIa can be safely used to address uncontrollable bleeding in ASHCA without inducing an increase in 30-day mortality and AEs.

Background

Management of bleeding is an important and often urgent concern for anesthesiologists and cardiac surgeons, especially during aortic surgery. Currently, hypothermic circulatory arrest (HCA) with cerebral perfusion is a safe standard strategy in thoracic aortic surgery to lower the incidence of perioperative stroke [1–4]. However, HCA causes coagulopathy because of both cardiopulmonary bypass (CPB) and hypothermia, which may result in life-threatening bleeding [5, 6]. In such cases of bleeding, massive transfusion of packed red blood cells (PRBC), fresh frozen plasma (FFP), and platelet concentrate (PC) is performed. Occasionally, the condition necessitates further administration of other hemostatic agents, such as fibrinogen concentrates, prothrombin complex, and recombinant activated factor VII (rFVIIa). However, researchers have not yet assessed the risk factors of such uncontrollable bleeding that necessitates rFVIIa treatment in aortic surgery under hypothermic circulatory arrest (ASHCA).

rFVIIa was developed as a treatment agent for bleeding episodes in hemophilia. Nonetheless, its off-label use in cardiac surgery has increased since the first report in 2000 [7]. In 2008, rFVIIa was most frequently used in cardiac surgery (29%) and trauma (29%) in the USA, compared to its use foe hemophilia A and B (2.7%) [8]. Numerous studies have investigated the efficacy and safety of rFVIIa in cardiac surgery [9, 10]. However, only few studies have focused on its off-label use in aortic surgery [1, 12]. Furthermore, these studies only included patients with acute aortic dissection (AAD) or those who underwent aortic surgery without HCA. Therefore, the safety of rFVIIa for life-threatening bleeding in ASHCA remains unclear.

Thus, we intended to identify the risk factors of uncontrollable bleeding in ASHCA and to elucidate the safety of off-label rFVIIa use for life-threatening bleeding events.

Methods

Study design and patient population

We retrospectively analyzed 162 patients who underwent ASHCA between April 2014 and March 2019 at a single institution. Cases of redo and salvage surgeries (requiring cardiopulmonary resuscitation before surgery) were excluded. Of the remaining 144 patients, 42 patients received rFVIIa (group rFVIIa), while 102 patients did not (non-rFVIIa group). We analyzed the preoperative patient characteristics, perioperative bleeding and transfusions, postoperative AEs, and 30-day mortality. Postoperative 30-day mortality and thrombosis-related adverse events (AEs) were the primary endpoints. In contrast, postoperative bleeding and transfusions were the secondary endpoints. AEs were defined as follows: disabling stroke (postoperative persistent neurological deficits caused by thromboembolic events, confirmed by computed tomography (CT) scan or magnetic resonance imaging); minor stroke (postoperative temporary neurological deficits with recovery at discharge or at transfer to another hospital), and renal failure (serum creatinine >2.0 mg/dl and doubling of the preoperative value, or the new onset of hemodialysis). Myocardial infarction (MI), pulmonary embolism (PE), deep venous thrombosis, and other AEs were comprehensively diagnosed by physical examinations, laboratory tests, CT, electrocardiography, echocardiography, or color Doppler sonography (where appropriate).

The Asahikawa Medical University Hospital approved the off-label use of rFVIIa. The Institutional Review Board of Asahikawa Medical University approved this study (No. 19078). While the need for informed consent for enrolment in this study was waived due to the retrospective study design, written informed consent to use rFVIIa had been obtained from the participants.

Anesthetic Methods

Once in the operating room, standard monitoring was performed using five-channel electrocardiography, pulse oximetry, and direct arterial or indirect blood pressure monitoring. General anesthesia was performed using the target-controlled intravenous infusion of propofol, continuous infusion of remifentanil, and single-dose administration of fentanyl. Propofol was infused to maintain a bispectral index within the range of 40–60. Sevoflurane or Desflurane were also administrated if the attending anesthesiologist judged it to be necessary. Rocuronium was administered to facilitate endotracheal intubation and to provide adequate muscle relaxation during surgery when necessary. After intubation, a central venous catheter and transesophageal echocardiography probe were inserted. After completing the surgical procedures, the patients were sedated using the continuous infusion of propofol and dexmedetomidine while intubated and were transported to the intensive care unit.

Surgical Procedures

Median sternotomy was performed in all cases. Before CPB, we administered heparin (300 U/kg) to maintain an activated clotting time of >480 s during CPB. CPB was established using bicaval venous cannulation. Arterial cannulation is generally performed at the level of the ascending aorta or femoral artery in some AAD cases. Following CPB establishment, mild (>28°C) to moderate (20.1-28°C) hypothermia was applied. Myocardial protection was achieved by antegrade or retrograde cardioplegia in cases of thoracic aortic aneurysm (TAA) or AAD, respectively. The ascending aorta was clamped and transected during systemic cooling, and proximal anastomosis of the aorta was performed. The rectal temperature upon reaching the target temperature induced HCA. Simultaneously, retrograde cerebral perfusion was initiated and eventually switched to antegrade selective cerebral perfusion by cannulation of the supra-aortic arch vessels. Moreover, the patients underwent distal anastomosis of the ascending aorta or aortic arch during the HCA. Following the end of the distal anastomosis, perfusion of the lower body was restarted from the side branch of the prosthesis, and rewarming was initiated. Moreover, anastomoses of the supra-aortic arch vessels were performed following distal anastomosis of the aorta in case of total arch replacement. Concomitant procedures were performed when required.

Intraoperative and postoperative management of bleeding and transfusion

Following weaning from CPB, heparin was antagonized by protamine administration (1:1 ratio to the applied heparin dosage). Subsequently, a transfusion was initiated. Hemoglobin <8 g/dL resulted in PRBC transfusion. Moreover, FFP was transfused upon detecting prolonged activated partial thromboplastin time (aPTT) or prothrombin time international normalized ratio (PT-INR). PC transfusion occurred when platelets (Plt) were $<8 \times 10^9$. In addition, the patients were administered cryoprecipitate when fibrinogen was <1.5 g/L. Fibrinogen <1.5 g/L following cryoprecipitate transfusion resulted in fibrinogen concentrate administration. rFVIIa was administered on observing continuous excessive bleeding despite the correction of surgical bleeding, pH, temperature, and adequate transfusion. Cryoprecipitate, fibrinogen concentrate, and rVIIa were only used in the operating room. After achieving adequate hemostasis in the operative field, as assessed by the surgeon, the patients were transferred to the intensive care unit (ICU). Re-exploration was considered in the ICU if the total bleeding amount from the chest tubes exceeded 400 mL/h regardless of adequate transfusion.

Statistical analyses

While the categorical variables are presented as numbers and percentages, the continuous variables are presented as medians. We performed propensity score matching (PSM) to balance the risk factors for outcomes between the groups. The propensity score (PS) was obtained from a logistic regression model, including variables presented in Table 1, except for concomitant surgery and JapanSCORE II. JapanSCORE II was not considered for PS because it represents the risk-adjusted mortality and preoperatively expected morbidity, based on the Japan Cardiovascular Surgery Database (JCVSD) [13]. Patients were matched 1:1 using the nearest neighbor matching method without replacement, and a caliper width of 0.2 of the standard deviation of the logit of the estimated PS. This resulted in 29 out of the possible 42 pairs. We calculated standardized mean differences before and after PSM to assess the

balance of variables between the groups. Unmatched sub-cohorts were compared using the Fischer's exact test Mann-Whitney U test for categorical and continuous variables, respectively. Following PSM, we performed the McNemar test and Wilcoxon signed rank test for the categorical and continuous variables, respectively. PSM was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [14]. All other statistical analyses were performed using SPSS for Windows (version 26.0; IBM Corp., Armonk, NY, USA). We analyzed the baseline characteristics in an unmatched population. Perioperative bleeding, transfusion, and postoperative outcomes were analyzed in the matched population. The statistical significance was defined as $p<0.05$.

Table 1
Baseline and operative characteristics

	Before matching				After matching			
Characteristic	rFVIIa (n=42)	non-rFVIIa (n=102)	p-value	SMD	rFVIIa (n=29)	non-rFVIIa (n=29)	p-value	SMD
Age (yr)	76.5 (69.5, 82.3)	73.5 (66.0, 79.0)	0.065	0.150	75.0 (65.0, 81.0)	78.0 (68.5, 80.5)	0.820	0.192
Sex (Male)	24 (57.1)	57 (55.9)	1.000	0.025	17 (58.6)	18 (62.1)	1.000	0.071
Body mass index (kg/m^2)	23.1 (19.8, 26.8)	22.8 (20.8, 26.3)	0.610	0.180	23.1 (20.4, 27.3)	21.5 (20.0, 24.7)	0.370	0.237
AAD / TAA	27 (64.3) / 15 (35.7)	53 (52.0) / 49 (48.0)	0.200	0.252	16 (55.2) / 13 (44.8)	16 (55.2) / 13 (44.8)	1.000	< 0.001
Emergency surgery	27 (64.3)	51 (50.0)	0.142	0.292	16 (55.2)	17 (58.6)	1.000	0.07
Malperfusion	5 (11.9)	9 (8.8)	0.550	0.101	3 (10.3)	2 (6.9)	1.000	0.123
Shock (requiring hemodynamic support)	6 (14.3)	3 (2.9)	0.019	0.413	3 (10.3)	2 (6.9)	1.000	0.123
Cardiac tamponade	8 (19.0)	8 (7.8)	0.077	0.333	5 (17.2)	6 (20.7)	1.000	0.088
GCS <8	1 (2.4)	3 (2.9)	1.000	0.035	1 (3.4)	2 (6.9)	1.000	0.156
Smoking	7 (16.7)	27 (26.5)	0.281	0.240	5 (17.2)	5 (17.2)	1.000	< 0.001
Hypertension	33 (78.6)	78 (76.5)	0.831	0.050	24 (82.8)	24 (82.8)	1.000	< 0.001
Diabetes mellitus	7 (16.7)	12 (11.8)	0.428	0.141	5 (17.2)	6 (20.7)	1.000	0.088
Liver dysfunction	6 (14.3)	8 (7.8)	0.234	0.206	3 (10.3)	4 (13.8)	1.000	0.106

AAD, acute aortic dissection; ACC, aortic cross clamp; APTT, activated partial thromboplastin time; AVP, aortic valvuloplasty; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; GCS, Glasgow Coma Scale; HCA, hypothermic circulatory arrest; PT-INR, prothrombin time international normalized ratio; rFVIIa, recombinant activated factor VII; SMD, standardized mean difference; and TAA, thoracic aortic aneurysm.

	Before matching				After matching			
Anticoagulant treatment	5 (11.9)	10 (9.8)	0.766	0.068	2 (6.9)	3 (10.3)	1.000	0.123
Antiplatelet treatment	7 (16.7)	17 (16.7)	1.000	<0.001	6 (20.7)	7 (24.1)	1.000	0.083
JapanSCORE II 30-day mortality (%)	8.4 (5.6, 14.0)	6.1 (3.9, 10.2)	0.033	0.355	6.9 (4.3, 11.1)	7.1 (4.4, 13.5)	0.665	0.088
Hemoglobin (g/dl)	11.5 (10.0, 13.6)	12.5 (10.8, 14.0)	0.092	0.285	11.9 (10.0, 13.7)	11.7 (10.2, 13.6)	0.811	0.101
Platelet count (10^9/L)	157 (124, 188)	177 (142, 213)	0.015	0.401	158 (126, 179)	168 (130, 188)	0.787	0.074
APTT (sec)	31.2 (27.4, 37.7)	28.4 (26.2, 31.9)	0.005	0.284	31.1 (27.5, 35.2)	30.3 (27.2, 34.8)	0.795	0.190
PT-INR	1.07 (1.00, 1.24)	1.02 (0.96, 1.10)	0.006	0.314	1.05 (0.98, 1.18)	1.06 (1.00, 1.14)	0.964	0.056
Fibrinogen (g/L)	2.43 (1.62, 2.96)	2.90 (2.46, 3.91)	<0.001	0.668	2.64 (1.77, 3.29)	2.45 (2.21, 2.97)	0.922	0.053
Serum creatinine (mg/dl)	0.94 (0.72, 1.11)	0.87 (0.70, 1.10)	0.427	0.149	0.94 (0.75, 1.12)	1.00 (0.78, 1.25)	0.160	0.195
Surgery								
Primary procedure			0.146	0.274			1.000	< 0.001
Total arch replacement	19 (45.2)	60 (58.8)			14 (48.3)	14 (48.3)		
Hemiarch replacement	23 (54.8)	42 (41.2)			15 (51.7)	15 (51.7)		
Concomitant procedure	14 (33.3)	26 (25.5)	0.413	0.173	9 (31.0)	8 (27.6)	1.000	0.076

AAD, acute aortic dissection; ACC, aortic cross clamp; APTT, activated partial thromboplastin time; AVP, aortic valvuloplasty; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; GCS, Glasgow Coma Scale; HCA, hypothermic circulatory arrest; PT-INR, prothrombin time international normalized ratio; rFVIIa, recombinant activated factor VII; SMD, standardized mean difference; and TAA, thoracic aortic aneurysm.

	Before matching				After matching			
None	28 (66.7)	76 (74.5)			20 (69.0)	21 (72.4)		
AVR or AVP	3 (7.1)	4 (3.9)			2 (6.9)	2 (6.9)		
Bentall	2 (4.8)	1 (1.0)			1 (3.4)	0 (0)		
David	3 (7.1)	7 (6.9)			2 (6.9)	3 (10.3)		
CABG	7 (16.7)	11 (10.8)			4 (13.8)	3 (10.3)		
Others	0 (0)	3 (2.9)			0 (0)	0 (0)		
CPB time (min)	169 (145, 230)	169 (142, 192)	0.136	0.437	161 (136, 227)	177 (136, 216)	0.754	0.084
ACC time (min)	110 (88, 146)	97 (79, 121)	0.049	0.376	102 (80, 141)	110 (75, 123)	0.462	0.119
Lowest rectal Temperature (°C)	27.5 (25.7, 27.9)	26.1 (25.3, 27.6)	0.043	0.421	27.4 (25.6, 27.9)	26.6 (25.4, 27.8)	0.546	0.183
HCA time (min)	40 (28, 49)	39.5 (29.0, 53.0)	0.986	0.094	40 (28, 50)	36 (25, 56)	0.829	0.039

AAD, acute aortic dissection; ACC, aortic cross clamp; APTT, activated partial thromboplastin time; AVP, aortic valvuloplasty; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; GCS, Glasgow Coma Scale; HCA, hypothermic circulatory arrest; PT-INR, prothrombin time international normalized ratio; rFVIIa, recombinant activated factor VII; SMD, standardized mean difference; and TAA, thoracic aortic aneurysm.

Results

Baseline and operative characteristics

Table 1 summarizes the baseline and operative characteristics. Before PSM, the number of shock patients (p=0.019) and JapanSCORE II 30-day mortality rates (p=0.033) were significantly higher in the rFVIIa group. While Plt (p=0.015) and fibrinogen (p<0.001) were significantly lower, aPTT (p=0.005) and PT-INR (p=0.006) were prolonged in the rFVIIa group. The rFVIIa group demonstrated longer ACC time (p=0.049) and higher lowest body temperature (p=0.043). Following PSM, none of the characteristics were significantly different between the groups.

Perioperative bleeding and transfusion

Table 2 summarizes the perioperative amounts of bleeding and transfusion. Intraoperative bleeding (p=0.012), PRBC transfusion (p=0.048), and FFP (p=0.021) were significantly higher in the rFVIIa group. Patients in the rFVIIa group received a significantly greater amount of fibrinogen concentrate (p<0.001). The median intraoperative dose of rFVIIa was 56 μg/kg. In addition, the postoperative amount of bleeding and transfusion was comparable between the groups.

Table 2
Perioperative bleeding and blood products in the propensity-score matched populations

Characteristic	rFVIIa (n=29)	non-rFVIIa (n=29)	p-value
Bleeding intra-operation (ml)	6773 (4019, 10185)	3639 (2399, 6627)	0.012
PRBC intra-operation (unit)	26 (19, 34)	20 (12, 24)	0.048
FFP intra-operation (unit)	34 (20, 46)	24 (18, 32)	0.021
PC intra-operation (unit)	55 (40, 60)	40 (40, 60)	0.472
Cryoprecipitate intra-operation (unit)	12 (12, 24)	12 (12, 12)	0.405
rFVIIa (μg/kg)	56 (32, 83)	-	
Fibrinogen concentrate (g)	3 (0, 3)	0 (0, 0)	<0.001
Bleeding until 12hr (ml)	790 (490, 1470)	740 (540, 1233)	0.071
PRBC until 12hr (unit)	2 (0, 6)	2 (0, 5)	0.370
FFP until 12hr (unit)	6 (4, 9)	6 (4, 8)	0.576
PC until 12hr (unit)	0 (0, 20)	0 (0, 10)	0.967
FFP: fresh frozen plasma, PC: platelet concentrates, and PRBC: packed red blood cells.			

Mortality and postoperative adverse events

Table 3 outlines the postoperative outcomes. The rFVIIa group manifested significantly lower Plt (p<0.001) and shorter PT-INR (p<0.001). There were no significant differences between the groups, with regard to the primary and secondary endpoints. Thirty-day mortality rate was 3.4% in both the groups. We observed stroke in one patient (3.4%) in both groups. There were no cases of MI or PE. The re-exploration rate was comparable (13.8% vs. 10.3%).

Table 3
Postoperative data and complications in the propensity-score matched populations

Characteristic	rFVIIa (n=29)	non-rFVIIa (n=29)	p-value
Hemoglobin (g/dl)	10.6 (9.0, 11.5)	10.5 (9.5, 11.8)	0.381
Platelet count (10^9 /L)	97 (73, 137)	142 (106, 169)	<0.001
APTT (sec)	45.2 (33.6, 55.1)	37.1 (33.4, 44.0)	0.206
PT-INR	0.86 (0.81, 1.03)	1.13 (1.08, 1.18)	<0.001
Fibrinogen (g/L)	2.10 (1.79, 2.59)	2.39 (2.06, 2.69)	0.846
Serum creatinine (mg/dl)	1.21 (0.94, 1.72)	1.10 (0.83, 1.63)	0.226
Intubation time (h)	25 (12, 96)	16 (10, 42)	0.991
Deep sternal wound infection	1 (3.4)	0 (0)	1.000
Septicemia	0 (0)	1 (3.4)	1.000
Renal failure	1 (3.4)	3 (10.3)	0.500
Paraparesis	1 (3.4)	1 (3.4)	1.000
Deep venous thrombosis	0 (0)	1 (3.4)	1.000
Pulmonary embolism	0 (0)	0 (0)	
Myocardial infarction	0 (0)	0 (0)	
Stroke	1 (3.4)	1 (3.4)	1.000
Minor stroke	1 (3.4)	0 (0)	1.000
Disabling stroke	0 (0)	1 (3.4)	1.000
Cardiac tamponade	0 (0)	1 (3.4)	1.000
Re-exploration	4 (13.8)	3 (10.3)	1.000
30-day mortality	1 (3.4)	1 (3.4)	1.000

APTT, activated partial thromboplastin time; PT-INR, prothrombin time international normalized ratio; and rFVIIa, recombinant activated factor VII.

Discussion

Few studies have reported on the off-label use of rFVIIa in aortic surgery, with no previous study focusing on the safety of rFVIIa in ASHCA.[10,11] However, the high possibility of massive bleeding necessitates an evaluation of the safety of off-label rFVIIa use in ASHCA. The crucial findings of the present study were as follows: (i) preoperative shock, coagulopathic state in laboratory tests, higher JapanSCORE II 30-day

mortality rate, and longer ACC time might be associated with excessive bleeding in ASHCA and (ii) rFVIIa application did not result in a significant increase in the postoperative 30-day mortality and AEs in ASHCA.

Preoperative shock and coagulopathy increased the risk of intraoperative bleeding, which might require rFVIIa administration. Preoperative shock in our patients was primarily caused by AAD or ruptured TAA. The aforementioned pathologies cause coagulopathy. Guan et al. reported that intense prothrombin generation and excessive systemic fibrinolysis occur in AAD before surgery, thereby leading to prolonged consumption coagulopathy, excessive bleeding, and complications [15]. Researchers have also described coagulopathy in aortic aneurysms with increased intensity upon rupture [16]. The rFVIIa group demonstrated significantly lower Plt and fibrinogen levels, prolonged aPTT, and PT-INR before PSM. This resulted in a significantly greater amount of intraoperative bleeding and transfusion.

JapanSCORE II is a calculated operative risk similar to EuroSCORE. However, it is based on JCVSD. JapanSCORE II more precisely reflects operative risk in Japan than EuroSCORE [17]. In the present study, the higher frequency of AAD, emergent surgery, and shock might result in higher operative risk in the rFVIIa group. Despite a lower actual mortality rate than the calculated value, JapanSCORE II appeared to be a reliable risk predictor.

The clinical impact of HCA-induced coagulopathy is well known. However, the underlying mechanism is still unclear. Hypothermia and CPB are factors that cause coagulopathy. However, several studies have reported that the lowest body temperature is not associated with bleeding [2, 4]. In the present study, the lowest temperature was significantly higher in the rFVIIa group. Nevertheless, intraoperative bleeding was significantly higher in the rFVIIa group than that in the control group. In other words, the lowest temperature was not strongly associated with coagulopathy. Meanwhile, the ACC time in the present study was significantly longer and supposedly associated with excessive bleeding. There are few reports on the relationship between coagulopathy and ACC. Moreover, longer ACC reportedly causes both fibrinogen consumption and accumulation of tissue plasminogen activator. Nonetheless, the underlying mechanism is unclear [18].

The efficacy of off-label rFVIIa use has been repeatedly reported. However, most of the latter studies involved patients who underwent cardiac surgery [7–10], where the efficacy was demonstrated with respect to the amount of perioperative bleeding, transfusion, and re-exploration [7–10]. However, a previous study on AAD surgery reported on significantly greater perioperative bleeding, transfusion, and re-exploration, following rFVIIa administration [11]. In the present study, the rFVIIa group demonstrated significantly higher intraoperative bleeding and transfusion, in addition to significantly lower postoperative Plt. The severity of coagulopathy in ASHCA is expectedly much higher than that in general cardiac surgery. Therefore, consumption coagulopathy may have persisted even after rFVIIa treatment. According to Paparella et al., intense thrombin generation in patients with AAD stimulates platelet activation and dysfunction, and promotes coagulation factor consumption and excessive fibrinolysis, which collectively result in excessive bleeding [19]. Consumption coagulopathy and platelet dysfunction

have been not only reported in AAD but also in TAA [20]. Patients in the rFVIIa group in ASHCA might continue to suffer from life-threatening bleeding and require a greater amount of transfusion if not treated with rFVIIa. Therefore, rFVIIa in ASHCA plays an important role in rescue therapy.

The safety of rFVIIa is still unclear and depends on several factors, such as patient characteristics, transfusion, and the dose of rFVIIa applied. A randomized trial reported on no significant increase in mortality, rather a numeric increase in AEs [9]. Alferevic et al. reported on higher mortality and renal morbidity in the rFVIIa group [21]. The aforementioned studies focused on complex cardiac surgery. Other studies on AAD or aortic surgery demonstrated no significant increase in postoperative mortality or AEs [11, 12]. Intense thrombin generation in ASHCA causes platelet dysfunction, consumptive coagulopathy, and excessive fibrinolysis. Based on the above-mentioned factors, a low frequency of thromboembolic AEs might result from rFVIIa therapy in aortic surgery.

The safety dose or optimal protocol for rFVIIa in cardiac surgery is still unknown. Researchers have reported on the safety and efficacy of a dose ranging between 35 μg/kg to 70 μg/kg in general cardiac surgery [22]. Several studies have described the efficacy of low-dose rFVIIa <20 μg/kg [10]. However, considering the severity of coagulopathy in ASHCA, a higher dose may also be acceptable. A dose <90 μg/kg is considered safe in patients without hemophilia [23]. In the present study, the median dose of rFVIIa was 56 μg/kg, and patients did not demonstrate an increase in mortality or thromboembolic AEs. We administered rFVIIa following the correction of other hemostatic parameters, which was in compliance with current recommendations [22].

Our study had several limitations. This was a single-center, retrospective, observational study with a small sample size. We performed PSM based on different characteristics before rFVIIa treatment. Nevertheless, there were several unmeasured confounders. In addition, we observed a difference in intraoperative transfusions, which might have affected the amount of intraoperative bleeding and rFVIIa administration. However, it was impossible to equalize the number of intraoperative transfusions because of the retrospective observational study design. Despite the aforementioned limitations, this is the first study to focus on the use of rFVIIa in ASHCA.

Conclusion

Preoperative shock, higher JapanSCORE II mortality rates, low Plt and fibrinogen, prolonged aPTT and PT-INR, and longer ACC time might be risk factors for excessive bleeding, thus necessitating rFVIIa treatment. The present study suggests that rFVIIa can be safely used for uncontrollable bleeding in ASHCA, without an increase in 30-day mortality and AEs. Further prospective randomized studies are required.

List Of Abbreviations

AAD, acute aortic dissection; AEs, adverse events; aPTT, activated partial thromboplastin time; ASHCA, aortic surgery under hypothermic circulatory arrest; CPB, cardiopulmonary bypass; CT, computed

tomography; FFP, fresh frozen plasma; HCA, hypothermic circulatory arrest; ICU, intensive care unit; JCVSD, Japan Cardiovascular Surgery Database; MI, myocardial infarction; PC, platelet concentrate; PE, pulmonary embolism; Plt, platelets; PRBC, packed red blood cells; PS, propensity score; PSM, propensity score matching; PT-INR, prothrombin time international normalized ratio; rFVIIa, recombinant activated factor VII; TAA, thoracic aortic aneurysm.

Declarations

- **Ethics approval and consent to participate**

The Institutional Review Board of Asahikawa Medical University approved this study (No. 19078). While the need for informed consent for enrolment in this study was waived due to the retrospective study design.

- **Consent for publication**

Not applicable

- **Availability of data and materials**
- **Competing interests**

The authors declare that they have no competing interests.

- **Funding**

None.

- **Authors' contributions**

HI contributed to data collection and drafting of the manuscript. RU contributed to data collection. HK (Hirotsugu Kanda) conceived the study and revised the manuscript. FK contributed to data interpretation. YS provided expert consultation on statistical analysis. PA and AL contributed to conception of the study design and data interpretation. HK (Hiroyuki Kamiya) supervised the project. All authors read and approved the final manuscript.

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