Brief Communication

Thrombosis incidence after recombinant active factor VII administration in paediatric cardiac surgery

INTRODUCTION

Bleeding following complex congenital cardiac surgery under cardiopulmonary bypass (CPB) is a serious problem. It results from long durations of CPB, hypothermia and the complex anastomoses involved in these procedures.[1,2] The outcomes of intraoperative administration of recombinant activated factor VII (rFVIIa) during paediatric cardiac surgery have not been extensively studied. We aimed to review paediatric cardiac operations involving rFVIIa administration performed at our hospital and compare the incidence of postoperative thrombosis with or without rFVIIa.

METHODS

This retrospective observational study was approved by our institutional ethics committee. We reviewed the electronic anaesthesia records (FortecORSYS®; Philips Japan Ltd, Tokyo, Japan) of patients >6 years who underwent open heart surgery and received rFVIIa (NovoSeven®; Novo Nordisk, Bagsbaerd, Denmark) between April 2011 and March 2015 (treated group) at our institution. We also identified patients who underwent the same procedure without rFVIIa administration (untreated group).

The following data were extracted from the anaesthetic and/or medical records: (1) preoperative data: age, weight, past sternotomy, results of coagulation tests including prothrombin time (PT), activated partial thromboplastin time (APTT) and platelet count; (2) intraoperative data: infusion volume, blood transfusion volume, operation time, anaesthesia time, CPB time and rFVIIa dosage and (3) postoperative data: results of coagulation tests, postoperative transfusion volume and drainage volume from the chest drain over 24 h after the surgery.

For CPB, anticoagulation was achieved by heparin administration to attain an activated coagulation time of 400 s. At the end of CPB, heparin was neutralised with protamine. rFVIIa was administered when haemorrhage persisted 2 h after protamine administration despite surgical haemostatic procedures and coagulation management by transfusion. The initial dose was 90 μg/kg, and if haemostasis was not achieved within 2 h, the same dose was repeated. Haemostasis was evaluated based on visual inspection of bleeding in the surgical field by the surgeon. Postoperative thrombotic complications were routinely evaluated by clinical examination, transthoracic echocardiography on postoperative day 1 and computed tomography after extubation. Early postoperative computed tomography of the chest was only performed in a patient with suspected pulmonary embolism on transthoracic echocardiography. Thrombosis was diagnosed based on clinical symptoms or imaging findings. The primary outcome was the incidence of thrombosis, whereas the secondary outcomes were re-thoracotomy for bleeding, duration of postoperative intensive care unit (ICU) and hospital stays, and 30-day mortality rates. Statistical analysis was performed using SPSS Statistics version 23® (IBM Japan, Ltd., Tokyo, Japan). Patient characteristics and perioperative data were compared using Mann–Whitney *U*-test and χ^2 test using cross tabulation. A P value <0.05 was considered statistically significant. The values are expressed as mean ± standard deviation.

RESULTS

Preoperative examination showed significantly longer PT ($P = 0.002$) and APTT ($P = 0.048$) in the treated group [Table 1]. The treated group had a lower platelet count at the end of CPB ($P = 0.030$), required a longer time to achieve haemostasis after CPB ($P < 0.001$) and received larger volumes of intraoperative FFP ($P < 0.001$) and platelet concentrate [$P < 0.001$; Table 2] transfusions. Of the 275 patients who underwent surgery under CPB, 12 (4.4%) received rFVIIa and 17 did not. The postoperative thrombosis rates in the treated and untreated groups were 1/12 (8.3%) and 4/17 (23.5%), respectively.

One patient in the treated group showed cerebral infarction on imaging studies without symptoms. The patients with thrombosis in the untreated group included one with pulmonary embolism with SpO_2 reduction, one with pulmonary embolism on transthoracic echocardiography and computed tomography without clinical symptoms and two with cerebral infarction on imaging with no clinical symptoms. rFVIIa administration did not increase the postoperative thrombosis rate ($P = 0.168$), duration

Table 1: Preoperative characteristics and comparison between recombinant activated factor VII-treated and -untreated groups

	Treated group (*n*=12)	Untreated group (*n*=17)	*P*
Age (days)	182±443	80±65.1	0.679
Weight (kg)	4.0±2.1	3.9±1.4	0.845
Male (%)	7 (58)	7 (41)	0.829
Previous sternotomy (%)	5 (42)	10 (59)	0.362
Surgical procedure or type of CHD			
Jatene procedure	2	5	
Norwood procedure	3	6	
Truncus arteriosus	2	0	
TAPVC	1	4	
Coarctation of the aorta	2	2	
VSD patch closure	1	0	
Glenn procedure	1	0	
PT (s)	17.6±4.0	14.0±1.6	0.002
Prothrombin activity (%)	52.1±16.0	75.7±19.3	0.002
APTT (s)	51.3±23.6	38.4±9.3	0.048
Control value of APTT (s)	34.9±15.9	29.0±1.7	0.711
Platelet count (×10⁴/μL)	34.5±28.1	40.5±16.0	0.097

APTT–Activated partial thromboplastin time; CHD–Congenital heart disease; PT–Prothrombin time; TAPVC–Total anomalous pulmonary venous connection; VSD–Ventricular septal defect. Data are presented as mean±standard deviation

of postoperative ICU ($P = 0.913$) and hospital stays ($P = 0.211$), re-sternotomy rate ($P = 0.286$) or the 30-day mortality rate ($P = 0.348$) [Table 2]. The coagulation activity in the treated group was significantly higher in terms of PT ($P < 0.001$) and APTT ($P = 0.012$) at ICU admission. There was no significant difference in blood transfusion volume in the ICU and during postoperative extracorporeal membrane oxygenation (ECMO) support [Table 2]. There were no cases of thrombosis that required the introduction of ECMO or resuscitation for cardiac arrest.

DISCUSSION

We investigated the outcomes of rFVIIa administration in paediatric patients undergoing cardiac surgeries. Generally, rFVIIa serves as a rescue therapy for bleeding that cannot be controlled with standard haemostatic therapy. A great concern is whether off-label rFVIIa administration can increase the incidence of perioperative arterial or venous

Table 2: Comparison of intraoperative data and postoperative outcomes between recombinant activated factor VII-treated and -untreated groups

	Treated group (*n*=12)	Untreated group (*n*=17)	*P*
Intraoperative infusion volume (mL/kg)	38.4±21.8	43.5±19.7	0.586
Intraoperative blood transfusion volume			
RBC (mL/kg)	58.1±67.9	12.4±13.9	0.066
FFP (mL/kg)	44.1±36.3	12.9±7.1	<0.001
PC (mL/kg)	35.5±21.5	13.2±8.1	<0.001
Platelet count after CPB (10⁴/μL)	4.0±1.7	6.4±3.3	0.03
Operation time (min)	529±113	465±83	0.097
Anaesthesia time (min)	645±136	600±116	0.444
CPB time (min)	220±85	230±61	0.419
Time from the end of CPB to the end of surgery (min)	210±43	131±22	<0.001
Postoperative result of coagulation test			
PT (s)	10.1±0.9	16.7±2.0	<0.001
Prothrombin activity (%)	176.6±41.1	53.8±10.7	<0.001
APTT (s)	41.2±14.0	69.1±50.6	0.012
Control value of APTT (s)	29.2±1.6	28.8±1.5	0.679
Platelet count (10⁴/μL)	17.0±5.8	14.2±4.5	0.211
Postoperative thrombosis	1	4	0.168
30-Day mortality	2	1	0.348
Postoperative ICU stay duration (days)	49±55	44±56	0.913
Postoperative hospital stay duration (days)	121±108	67±75	0.211
Re-sternotomy	1	4	0.286
Postoperative ECMO	1	1	0.798
Transfusion volume within 24 h after operation			
RBC (mL/kg)	7.8±8.4	6.1±9.0	0.711
FFP (mL/kg)	99.3±91.8	57.0±45.0	0.166
PC (ml/kg)	19.7±21.1	15.8±13.8	0.948
Drainage volume of chest drain within 24 h after surgery (mL/kg)	38.4±18.9	32.1±15.0	0.263

APTT–Activated partial thromboplastin time; CPB–Cardiopulmonary bypass; ECMO–Extracorporeal membrane oxygenation; FFP–Fresh frozen plasma; ICU–Intensive care unit; PC–Platelet concentrate; PT–Prothrombin time; RBC–Red blood cell. Data are presented as mean±standard deviation

thrombosis.[3-6] The increased risk of thrombosis after rFVIIa administration during paediatric cardiac surgery has been reported previously.[5,6] However, the high rates of ECMO use in the rFVIIa-treated groups may be related to the incidence of thrombosis.[5,7,8] The difference between our study and previous studies is the reduction in serious symptoms due to thrombosis and the low rates of postoperative ECMO. ECMO is used after poor surgical reconstruction or for attenuated cardiac function during surgery. Slowing or pooling of blood may promote thrombogenesis. In this study, administration of rFVIIa might not have increased the risk of thrombosis because the postoperative rate of ECMO use was equivalent in both groups. Our study population may thus have been at a lower risk of thrombosis.

Cardiopulmonary reserve is limited in children, especially after CPB, and they cannot tolerate volume overload. Once factor VII levels fall secondary to acute massive bleeding, they are difficult to correct using general transfusion therapy.[9] The advantages of rFVIIa over blood transfusion include more effective restoration of blood factor VII level, less probability of infection, smaller volume loads, and rapid preparation and administration.

There are several limitations to this study. First, this was a retrospective study conducted at a single facility. Propensity score matching could not be performed due to the small sample size. In our country, rFVIIa is used in an off-label manner and is extremely expensive. Therefore, it is difficult to increase the number of cases performed using it. Second, there is a possibility that asymptomatic thromboses were missed, despite evaluation using CT and transthoracic echocardiography.

CONCLUSION

rFVIIa administration during paediatric cardiac surgery did not increase the incidence of postoperative thrombosis or the 30-day mortality rate.

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Conflicts of interest

There are no conflicts of interest.

Contributors

Keitaro Tachi acquired the data and prepared the article. Shinji Takahashi designed the study and analysed the data. Maiko Ishigaki acquired the data and reviewed the article. Shin Nakayama acquired the data and reviewed the article. Soichiro Yamashita acquired the data and reviewed the article. Yuji Hiramatsu reviewed the article. Makoto Tanaka reviewed the article. The article has been read and approved by all the authors.

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