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Recombinant-activated factor VII in the paediatric cardiac surgery: Single unit experience

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ABSTRACT

Background: The control of excessive bleeding after paediatric cardiac surgery can be challenging. This may make the use of recombinant-activated factor VII (rFVIIa) in preventing this excessive bleeding, after adopted conventional methods have failed, desirable. Our aim is to highlight our experience with the use of rFVIIa in preventing excessive bleeding after paediatric cardiac surgery. **Patients and Methods:** The data for 14 patients who had rFVIIa for excessive haemorrhage after cardiac surgery from December 2009 to November 2010 was analysed. The perioperative blood loss from the chest drain before and after the administration of rFVIIa, use of blood products, international normalized ratio (INR) and activated partial thromboplastin (aPTT), before and after administration of rFVIIa, were analysed. **Results:** The rFVIIa was successful in stopping bleeding in all the patients. The mean coagulation factors before rFVIIa were as follows: INR, 2.88 (1.82–4.5); aPTT, 65 seconds (33.4–95.1); after rFVIIa, the mean INR was 1.2 (0.82–1.56), mean APTT was 38.7 seconds (25.6–54.9). No thromboembolic events or allergic reactions or deaths were recorded. **Conclusions:** rFVIIa use is not only effective in stopping excessive perioperative bleeding but also safe and indirectly reduces transfusion of blood and its products.

Key words: Coagulating factor, excessive bleeding, paediatric cardiac surgery, recombinant-activated factor VII

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INTRODUCTION

Bleeding after some paediatric cardiac surgeries can be really excessive even after conventional methods of haemostasis have been applied. This has made the use of haemostatic agents like recombinant factor VII in this kind of setting desirable.[1,2]

Perioperative bleeding following open heart surgery in the paediatric age group, especially neonates, is multifactorial in nature: it can be due to non-surgical or surgical causes. Fibrinolysis and platelet dysfunction have been implicated as leading causes of non-surgical bleeding.[1] Also, cyanosis is an important cause. Other significant haemostatic defects are largely attributed to cardiopulmonary bypass (CPB) that include thrombocytopenia, heparin effect and coagulation factor deficiency, which can result from immature clotting factors, especially vitamin K-dependent factors of which factor VII is in the groups.[3,4]

Factor VII has a central role in coagulation, promoting thrombin generation locally at the site of blood vessel injury even when there are other significant deficits in coagulation.[5]

Recombinant-activated factor VII (rFVIIa) was originally developed for prevention of excessive bleeding in perioperative period in haemophiliacs with inhibitors to factors VIII or factor IX[6] and the knowledge gained, which has largely been by "open-label" use, has led to its use in treating patients with excessive bleeding problems without haemophilia.[7]

It has been noted to be safe and effective in doubly reducing blood transfusion and the accruable risk of blood reactions and infections, especially Creutzfeldt Jakob disease.[5,8]

The mechanism of action of rFVIIa in promoting haemostasis following injury to vessel wall is by enhancing the generation of thrombin. rFVIIa complexes

with exposed tissue factors (TF) in tissue factors-bearing cells. The complex so formed activates factor X which subsequently acts with prothrombin to form thrombin. [9] This mechanism of rFVIIa in initiating haemostasis has led to serious concerns that besides acting locally at the site of vessel injury, more widespread coagulation could be possible if TF is in contact with plasma, e.g., when TF is up regulated on the surface of circulating monocytes in the setting of Gram-negative septicaemia/endotoxemia resulting in disseminated intravascular coagulation. TF is expressed within the lipid core of atherosclerotic plaques and is exposed at the sites of plaque fissure which can lead to myocardial infarction and the use of activated factor concentrates in hypercoagulability states (e.g., history of thrombotic complications, established thrombotic disorders like factor V Leiden, antiphospholipid syndrome, etc.) can led to thromboembolism or excessive bleeding.[10]

Luckily, the neonate and paediatric age groups coming for open heart surgeries are not saddled with these duo problems.

However, the problem of cost which has been consistent, but when juxtaposed to the aforementioned advantages seems to be dwarfed.

PATIENTS AND METHODS

Fourteen (2.94%) out of 477 patients who underwent open cardiac surgery in the paediatric cardiac unit from December 2009 to November 2010 received rFVIIa following excessive intraoperative bleeding and in whom intercostals drainage of average of 10 ml/kg/hr for 2 hours was noted.

The data were analysed into the biodata, cardiac lesion, cardiac surgery, CPB time, time of cessation of bleeding, complications, transfusions of blood, chest tubes draining parameters, the coagulations parameters and time of cessation of bleeding (defined as the time starting with the infusion of the rFVIIa infusion and the time significant bleeding stops).

Our institution approved the use of rFVIIa in the setting of life-threatening bleeding after cardiac surgery. The family consent was obtained indirectly by telling them about the use of blood and its product in event of excessive bleeding after surgery and there was consensus amongst the paediatric cardiac surgeon, Anaesthetist and the Intensivist.

We defined postoperative haemorrhage as that bleeding which results in the sternotomy wound not immediately being able to close after completion of CPB and heparin reversal because of continuing blood loss or the need for surgical re-exploration or bleeding from the chest drain of >10 ml/kg/1hr for the first 2 hours, the need for non-red cell blood product support: Fresh Frozen Plasma (FFP), platelets, Cryoprecipitate (CPP), and we defined cessation of haemorrhage as no further need of blood products or surgical re-exploration.[11]

RESULTS

The conventional methods to achieving haemostasis were intraoperative administration of protamine, post-operative use of protamine (repeated), platelets and FFP, Vitamin K, CPP and subsequent blood products according to coagulation studies.

The median age was 3.5 months (range, 23 days - 21 years), 7 males and 7 females, median weight was 4.8 kg (range, 2.3–33 kg), the median CPB Time was 315.5 minutes (range, 120–555 minutes), the median time for cessation of bleeding median time for cessation of bleeding was 52 min (range, 30-90 min). Eight patients had Transposition of great artery (d-TGA), 3 had tetralogy of Fallot (TOF), 1 had Double outlet Right Ventricle, 2 had Truncus arteriosus, 2 had redo intracardiac repair for TOF, 8 had arterial switch operation, 3 had I-packed cell transfused each for the correction of anaemia concomitantly with the administration of the rFVIIa. All the patients have some degree of cyanosis. There was no systemic impact of the drug noted [Table 1].

The dose of recombinant factor VII administered was 90 mcg/kg, which was repeated an hour if the chest drainage was still greater than 10 ml/kg/hr.

The decision to administer rFVIIa was made by the surgical team after consideration of the following four general criteria: (1) exclusion of all surgical causes of bleeding; (2) failure to reverse coagulopathy with adequate pharmacologic and blood product replacement defined as evidence of normalisation of coagulation laboratory values (international normalized ratio <1.5; (3) correction of the patient's core body temperature to normal (>36.5°C) and (4) adequate heparin reversal with protamine defined as an activated clotting time of 120 s or less, or an activated partial thromboplastin of less than our laboratory control (45 seconds) and patients in whom the chest tube drainage was greater than 10 ml/kg/hr, which was used in all the patients.

The drainage from the chest tube before administration of the rFVIIa was greater than 10 ml/kg/hr in all the

patients, which reduced to less than 8 ml/kg in 8 patients after hour of the administration of the activated factor VII. In 6 patients, the drainage remained greater than 10 ml/kg/hr and a repeated dose was given with subsequent drop in drainage to less than 7 ml/kg/hr in them [Table 2].

There was an improvement in the coagulating parameters after the administration of the drugs in the entire patients [Table 3], the transfusion which averages about 3 to 6 units in these patients with excessively post-operative bleeding was observed to have dropped to 0-3 units in this study. All the patients were discharged alive.

DISCUSSION

Although rFVIIa was initially used for the treatment of haemorrhage in haemophiliacs after surgery,[10] it has now been seen as a panacea in an area such as paediatric cardiac surgery where haemorrhage associated with coagulopathy is a common event.[12] However, the use of rFVIIa requires consultation with the Paediatric cardiac surgeon, Anaesthetist and the Haematologist to help in appropriate selection of patients who meet the criteria for excessive bleeding post-operative.[13]

This drug was used in conjunction with the convention methods in 14 patients who had excessive bleeding

Table 1: Showing Biodata, cardiac lesion, cardiac surgery, cardiopulmonary bypass (CPB) time, bleeding time, complications and transfusion after rFVIIa administration

Age	Sex	Weight (kg)	Cardiac lesion	Cardiac surgery	Cpb Time (Min)	Time of cessation of bleeding (Min)	Complications	Total transfusion after administration of Rfviia
21 yrs	M	33	TOF	Redo-ICR	120	90	Non	3unit PC
4 yrs	F	10	TOF	Redo-ICR	346	40	Non	Non
4.9 yrs	M	11	TOF	ICR	555	60	Non	Non
2.7 yrs	M	9.5	DORV+VSD+RMBTS	ICR	303	65	Non	Non
1 month	M	4.6	d-TGA/VSD	ASO	218	45	Non	Non
1 month	F	4.9	d-TGA/ intact IVS	ASO	356	35	Non	I unit PC
5 months	M	6.7	Truncus Arteriosus	Repair Conduit	312	50	Non	Non
15 days	F	4.3	d-TGA+VSD	ASO	228	30	Non	1unit PC
1 month	F	5	d-TGA intact IVS	ASO	301	45	Non	Non
23 days	M	3.9	d-TGA	ASO	319	45	Non	Non
1 month	F	2.3	d-TGA	ASO	347	60	Non	Non
9 months	F	3.2	d-TGA	ASO	410	75	Non	Non
9 months	F	3.8	d-TGA	ASO	345	60	Non	Non
2 months	F	3.4	Truncus Arteriosus	Repair Conduit	257	30	Non	Non

TOF - Tetralogy Of Fallot; DORV - Double Outlet Right Ventricle; VSD - Ventricular Septal Defect; ICR - Intracardiac Repair, ASO - Arterial Switch Operation; d-TGA – dextro-Transposition of Great Artery; RMBTS - Right Modified Blalock Taussig Shunt; PC - packed cell

Table 2: Showing the patient's chest tube drainage before and after rFVIIa administrations

Patients number	1a	2	3a	4a	5	6	7	8	9	10	11a	12a	13a	14
Chest drain before the dose (ml/kg)	15.	15	11	23	22.8	42.8	28.4	13	20	43.6	36.1	11.5	26	26
Chest drain after the 1st hr (ml)/first dose	13	4.2	11.2	11.1	6.5	4.1	7.5	4.6	8	7.1	11.6	20	13.3	3.2
Chest drain after the 2nd hr (ml)/2nd dose	0.2	0.4	0.1	5	0.7	2	5.2	3	6.2	6.7	3.1	3.6	1.1	0.7

Patients with alphabet- "a" had a repeated (second) dose

Table 3: Showing the patients' coagulation profile before and after administration of rFVII a

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	mean
INR	PRE	2.68	2.38	3.72	2.43	3.20	2.0	4.5	3.9	3.1	1.88	3.25	1.8	2.57	2.56	2.88
	POST	1.56	1.13	1.24	1.04	1.43	1.24	1.	1.8	0.82	1.01	0.90	1.20	1.32	0.90	1.21
aPPT	PRE	36.3	80	86	66	60.2	76	80	92	49.1	60.4	33.4	50.2	45.3	59.1	65
	POST	25.6	28.7	42	39	54.2	38	43	42	37.7	43.2	25.6	34.5	33.2	37.7	38.7

INR - International Normalized Ratio; aPPT - Activated partial thromboplastin time

after an open cardiac surgery, in whom the initial conventional medical methods to achieve haemostasis failed. The monitored chest tube drainage which was noticed to be significant, in the patients, dropped in all of them after the second dose of rFVIIa and the coagulating parameters also improved too [Tables 2 and 3].

A dose of 90 mcg/kg was given by Egan *et al*. in Sidney to 7 patients based on the institutional experience with its use in haemophiliacs and that was, then, reported as the largest single institutional experience.[14] The dose of rFVIIa (90 mcg/kg) used was similar to the initial dose used in our experience in achieving haemostasis. Kenet *et al*. observed better efficacy with a higher dose of 300 mcg/kg bolus dose followed by continuous infusion.[15] Al Douri *et al*. showed that lower dose of 30 mcg/kg dose was also effective[16] and Martinowitz *et al*. used a median dose of 120 mcg/kg (range, 120–210 mcg/kg) to achieve haemostasis in 7 cases of trauma.[17]

In 8 patients (57.1%), rapid haemostasis was achieved following a single dose of rFVIIa while 6 patients had repeated dose with achievement of haemostasis [Table 2]. DiDomenico *et al*. reported 70% success in achieving rapid haemostasis[9] and if haemostasis was not achieved within 30 to 60 minutes, consideration may be given for a second dose.

There was no adverse event such as systemic thromboembolic episodes or adverse reactions, which has been the main fear entertained by previous studies.[11,18,19]

We chose the drastic decrease of chest tube drain, the improvement in the coagulation parameters and blood-product administration as the surrogate measure of bleeding control and rFVIIa effectiveness as these could be convenient and expediously measured.

LIMITATIONS

The issue of cost has continuously hampered its use in many of the paediatric cardiac surgery patients as most of the patients cannot afford it and thus was used in a small number of patients which obviously affected the results.

Also, our inability to measure the platelet count and fibrinogen levels for immediate clinical use.

Direct consent as to the use of the drugs was not obtained preoperatively because of the "open-label" use of the drug and lack of established protocol on the use of the drug.

CONCLUSION

In our experience, the use of rFVIIa had not only showed effectiveness in stopping intractable bleeding but also safe in usage and indirectly drastically reducing blood transfusion. The use of factor VI I has not been associated with any side effect in our study.

The high cost is actually offset by the avoidance of morbidity from increased exposure of the patients to blood and blood products transfusions.

Prospective studies are necessary to determine optimal patient selection, dose and timing of rFVIIa administration.

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