

Jonathan R. Egan
Ahti Lammi
David N. Schell
Jonathan Gillis
Graham R. Nunn

Recombinant activated factor VII in paediatric cardiac surgery

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J. R. Egan (✉)
Paediatric Intensive Care Unit,
The Children's Hospital at Westmead,
Locked Bag 4001 Westmead NSW,
2145, Sydney, Australia
e-mail: jonathoe@chw.edu.au

A. Lammi
Department of Haematology,
The Children's Hospital at Westmead,
Locked Bag 4001 Westmead NSW,
2145, Sydney, Australia

D. N. Schell · J. Gillis
Paediatric Intensive Care Unit,
The Children's Hospital at Westmead,
Locked Bag 4001 Westmead NSW,
2145, Sydney, Australia

G. R. Nunn
Department of Paediatric Cardiac Surgery,
The Children's Hospital at Westmead,
Locked Bag 4001 Westmead NSW,
2145, Sydney, Australia

Abstract *Objective:* To review the use of recombinant activated factor VII in paediatric cardiac surgery. *Design:* Retrospective chart review. *Setting:* Paediatric intensive care unit in a stand-alone university-affiliated children's hospital. *Patients and participants:* Cardiac surgical patients who received recombinant activated factor VII (rFVIIa, NovoSeven; NovoNordisk, Copenhagen, Denmark) between June 2002 and June 2003 at The Children's Hospital at Westmead. *Results:* Six children undergoing cardiac surgery received rFVIIa. Recombinant activated factor VII was administered if bleeding was excessive and persisted despite appropriate investigation and attention to haemostasis by surgical and medical staff. An intravenous dose of 180 µg/kg was given and repeated 2 h later. All of the six patients responded well to rFVIIa

with achievement of haemostasis. No adverse events were noted. *Conclusions:* Recombinant activated factor VII achieved haemostasis in six paediatric cardiac surgical patients. Good outcomes and no adverse events were noted in these children.

Keywords Factor VIIa · Haemostasis · Cardiac surgery · Paediatric

Introduction

Recombinant activated factor VII (rFVIIa) was developed for the prevention of spontaneous bleeding episodes and for minimising intraoperative blood loss for the 15–25% of haemophilia patients with inhibitors to clotting factors VIII or IX [1]. In this setting rFVIIa has been found to be effective and safe [2, 3]. Increasingly it is being used in managing haemostasis in patients without haemophilia [4].

Intravenous therapy with rFVIIa acts by creating supra-physiological factor VIIa concentrations, which saturate tissue factor binding sites, activate factors IX

and X, activate platelets and develop a full thrombin burst with development of a stable fibrin-impregnated plug [1]. As tissue factor is required for the induction of rFVIIa, it produces only a localised effect, without systemic activation of coagulation [5]. It has proved useful in various bleeding disorders, including fibrinolysis and platelet dysfunction [5, 6].

Bleeding following cardiac surgery is multifactorial in nature. Both fibrinolysis and platelet dysfunction have been implicated as leading causes of non-surgical bleeding [7]. Other significant haemostatic defects largely attributable to cardiopulmonary bypass include thrombocytopenia, heparin effect and coagulation factor deficiency

cies [5]. Excessive bleeding following cardiac surgery may persist despite conventional medical therapy and, thus, rFVIIa may have a role in achieving haemostasis.

The use of rFVIIa in cardiac surgery has not been widely described. There are reports of five adults and two children at separate centres in the literature [5, 8, 9]. There are concerns that rFVIIa could precipitate an acute cardiac ischaemic event in adult patients, as is described in two adult patients with haemophilia [10, 11]. In paediatric cardiac surgical patients concern exists that synthetic shunts may be liable to thrombose with rFVIIa therapy [4].

We present a case series of rFVIIa in six paediatric patients following cardiac surgery.

Method

A retrospective review was made of the medical records of patients undergoing cardiac surgery, who received recombinant activated factor VII (rFVIIa, NovoSeven; NovoNordisk, Copenhagen, Denmark). This was performed following approval by the ethics committee of The Children's Hospital at Westmead.

In patients with intercostal drains, losses were the average of a 2-h period immediately prior to the first dose of rFVIIa, i.e. millilitres lost over two consecutive hours, divided by 2, divided by patient weight and expressed as millilitres per kilo per hour. Thus the amount of chest drain losses (in ml/kg per h) is an average over 2 h. Chest drain losses after the 1st and 2nd doses of rFVIIa were likewise the average of the corresponding 2-h period.

The Wilcoxon signed rank test for paired samples was used for non-parametric data to compute *p* values, with *p* less than 0.05

being considered significant. The STATA 8.0 statistics package (Texas, USA,) was utilised for statistical analysis.

Results

From June 2002 until June 2003, 281 children underwent cardiopulmonary bypass for cardiac surgery, 5 received rFVIIa. There were also 201 non-bypass cardiac cases and 1 of these children had rFVIIa. Administration of rFVIIa followed consultation with the haematology staff and required institutional drug committee approval prior to its use in each patient.

Conventional medical therapy to achieve haemostasis involved aprotinin administered during cardiopulmonary bypass. Then, after bypass, protamine, aprotinin, platelets and fresh frozen plasma (FFP) were given. Vitamin K, cryoprecipitate and subsequent blood products were given according to coagulation studies.

If postoperative bleeding persisted at greater than 10 ml/kg per h for 2 h or intraoperative haemostasis could not be achieved with conventional therapy, rFVIIa was given. All patients received an intravenous bolus dose of 180 µg/kg rounded to optimise the use of the 1.2 mg vials. This dose was repeated 2 h later in all patients apart from patient 6, who had minimal bleeding after the 1st dose.

Six patients received rFVIIa. In three patients postoperative chest drain losses persisted at greater than 10 ml/kg per h for 2 h, despite conventional measures to manage haemostasis. In one patient a recurrent haemothorax

Table 1 Patient details and indications for recombinant activated factor VII (rFVIIa)

Patient no.	Age (months)	Weight (kg)	Cardiac lesion	Cardiac operation	Indication for rFVIIa
1	60	17	Pulmonary atresia, VSD	Complete repair	Intraoperative bleeding
2	96	19	Ebstein's anomaly	Redo systemic pulmonary shunt	Recurrent haemothorax
3	48	16	Pulmonary atresia, VSD	Complete repair	Postoperative bleeding
4	0.5	3	dTGA	Arterial switch	Postoperative bleeding
5	0.5	3	dTGA	Arterial switch	Postoperative bleeding
6	15	10	dTGA, VSD	Arterial switch	Intraoperative bleeding

VSD ventricular septal defect, dTGA d-transposition of the great arteries

Table 2 Average chest drain losses over 2 h in relation to recombinant activated factor VII (rFVIIa)

Patient no.	1	2	3	4	5	6	Median and inter-quartile range	Reduction after rFVIIa (ml/kg per h)	<i>p</i> value ¹ (* < 0.05)
Chest drain loss - prior to rFVIIa, (ml/kg per h)	25	B	16	30	50	75	30 (25–50)		
– after 1 st dose, (ml/kg per h)	A	5	8	3	12	3	5 (3–8)	25	0.07
– after 2 nd dose, (ml/kg per h)	2	2	1	1	2	3	2 (1–2)	28	0.04*

¹*p* value calculated by the Wilcoxon signed rank test for paired samples.

A: 1st dose was given in the operating theatre and subsequent losses were not recorded.

B: Chest drain losses were absent, but 800 ml was removed from a haemothorax.

Note. (1) Chest drain losses are expressed in ml/kg per h, which is the average over the 2 h immediately before, between and after the doses of rFVIIa.

Table 3 Coagulation parameters in relation to recombinant activated factor VII (*rFVIIa*)

Patient no.		1	2	3	4	5	6	Median and inter-quartile range	Change after rFVIIa	<i>p</i> value ¹ (*<0.05)
INR (normal range 1–1.2)	Pre VIIa	2	2.3	2.1	1.7	1.6	1.7	1.9 (1.7–2.1)		
	Post VIIa	1.2	1.4	1.7	1.3	1.1	1	1.3 (1.1–1.4)	–0.6	0.03*
APTT (normal range 22–39 s)	Pre VIIa	94	45	73	72	64	54	68 (54–73)		
	Post VIIa	67	43	50	56	63	40	53 (43–63)	–15	0.03*
Fibrinogen (normal range 2–5 g/l)	Pre VIIa	2.1	3.2	2.1	2.2	2.3	2.3	2.3 (2.1–2.3)		
	Post VIIa	2.4	3.1	3.3	1.9	2	2.4	2.4 (2–3.1)	+0.1	0.67

INR international normalised ratio, APTT activated partial thromboplastin time

¹*p* value calculated by the Wilcoxon signed rank test for paired samples.

resolved with rFVIIa following the 2nd repeat thoracotomy, after it had failed to resolve following the initial re-exploration when rFVIIa was not used. Two other patients received rFVIIa for intraoperative blood loss that was not manageable with conventional medical therapy. The median age of the patients was 32 months, (interquartile range 2 weeks to 60 months) and the median weight 13 kg, (interquartile range 3–17 kg). See Table 1 for details of the cases.

There was a statistically significant reduction in volume of bleeding after the 2nd dose of rVIIa had been completed. There was also a statistically significant reduction in the international normalised ratio (INR) and activated partial thromboplastin time (APTT) following the 2nd dose of rFVIIa. See Tables 2 and 3.

Discussion

We have used rFVIIa in six paediatric patients following cardiac surgery. In all these patients there was excessive bleeding that persisted despite conventional therapy, but which resolved after rFVIIa. There were no adverse reactions to rFVIIa and all the patients had good outcomes. This is the largest single institutional report of the use of rFVIIa in this patient population. However, it is a small and retrospective study and, thus, the findings are limited by this.

Bleeding warranting consideration of rFVIIa should be significant. In our practice this equated to greater than 10 ml/kg per h for 2 h that did not resolve with conventional measures in the early postoperative period. The other setting for the use of rFVIIa is intraoperatively when haemostasis cannot be achieved by conventional means—including protamine, aprotinin, platelets, FFP and cryoprecipitate.

An intravenous bolus of 180 µg/kg was given over 1 min and repeated after 2 h. This dosage was based on institutional experience with haemophilia patients. Previous studies in children have used a range of doses, from 40–200 µg/kg [12, 13]. A maximal thrombin burst was sought with the use of a relatively large, repeated dose to ensure that haemostasis occurred. This dose achieved statistically significant reductions in chest drain losses, INR and APTT in these patients when conventional therapy had not.

One patient in this series had a systemic to pulmonary shunt and two patients had polytetrafluoroethylene (Gore-Tex) conduits from the right ventricle to main pulmonary artery. In these patients there was no evidence of thrombotic occlusion of shunt or conduits, which has been raised as an issue previously [4, 8]. Importantly, in the three patients who had arterial switch repairs, the re-implanted coronary arteries were not affected by factor VIIa therapy.

The use of rFVIIa could potentially reduce the need for repeat thoracotomy and the inherent risks and costs involved, which are considerable and have been associated with adverse outcome in patients [14]. However rFVIIa is expensive, costing approximately US\$ 972 per 1.2 mg vial [4]. Thus two doses of rFVIIa at 180 µg/kg for a 10 kg child, 3.6 mg, would cost almost US\$ 3000. This is likely to restrict its indication to instances of persistent and unrelenting bleeding, such as those we describe.

In this small retrospective study, rFVIIa was safe and haemostasis was achieved following its use in all six patients. There is possibly a role for rFVIIa in the management of haemostasis in the postoperative paediatric cardiac surgical patient. And, as a consequence of this study, further investigation is justified into a potential role for rFVIIa in this setting.

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