Is recombinant activated factor VII effective in the treatment of excessive bleeding after paediatric cardiac surgery?

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Abstract
A best evidence topic in paediatric cardiac surgery was written according to a structured protocol. The question addressed was whether recombinant activated factor VII was effective for the treatment of excessive bleeding after paediatric cardiac surgery. Altogether 150 papers were found using the reported search; 13 papers were identified that provided the best evidence to answer the question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these studies were tabulated. A total of 311 children experienced excessive bleeding following cardiac surgery that was refractory to the conventional methods of achieving haemostasis. One hundred and ninety-two patients received the rFVIIa while 116 were in control arm from five studies. The primary end-point was on chest tube drainage, the plasma prothrombin time, the activated partial thromboplastin time after the administration of rFVIIa and the secondary end-point was reduction of blood products transfusion. Thrombosis was a complication in 8 patients (4.2%); three deaths (1.6%) but not attributable to thromboembolic events following the use of rFVIIa. Most of the studies failed to clearly state the doses but the extracted doses ranged between 30 and 180 µg/kg/dose, the interval between doses ranged between 15 and 120 min with a maximum of four doses. However, most of the patients had 180 µg/kg/dose with interval between dose of 2 h and maximum of two doses with dosage moderated with respect to weight, prior coagulopathy and responsiveness. There were two randomized studies with good sample size. One showed no significant differences in the secondary end points between the two arms and noted no adverse complications. However, the rFVIIa was used prophylactically. The other observed that there were no increase in thromboembolic events rather rFVIIa was effective in decreasing excessive bleeding that may complicate cardiac surgery in children. In conclusion, the studies were in support of the notion that the use of rFVIIa was effective in decreasing excessive bleeding which may complicate paediatric cardiac surgery, and care should be exercised when using it in the children on ECMO circuit.

Keywords: Recombinant activated factor VII · Excessive bleeding · Paediatric cardiac surgery

INTRODUCTION
A best evidence topic was constructed according to a structured protocol. This protocol is fully described in the ICVTS [1].

THREE PART QUESTION
In [patients with excessive bleeding (EB) after paediatric cardiac surgery] does [recombinant activated factor VII] reduce [bleeding without causing significant complications].

CLINICAL SCENARIOS
You have just performed a long Norwoods operation on a young child. It was a difficult procedure and there was a long bypass time. Separation from bypass was eventually performed but the child was profoundly coagulopathic. You give him a large amount of FFP and platelets and cryoprecipitate and return him to the intensive care unit having meticulously looked for surgical causes for the bleeding. He continues to bleed in the ICU. Colleagues have used factor VIIa in adults in similar situations and you wonder whether there is evidence to support its safe use in children and the dosages that have been used.

SEARCH STRATEGY
The literature search was done by MEDLINE from 1966 through February 2012 using the PubMed interface recombinant [All Fields] AND ('factor viia' [MeSH Terms] OR 'factor viia' [All Fields]) AND ('paediatrics' [MeSH Terms] OR 'paediatric' [All Fields]) AND ('cardiac' [All Fields] OR 'cardiac surgery' [All Fields] OR 'cardiac surgical procedures' [MeSH Terms] OR 'cardiac' [All Fields]). The
<table>
<thead>
<tr>
<th>Author, date, journal, country, reference</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments/weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egan et al., 2004 Intensive Care Med, Australia [2] Retrospective study (level 4)</td>
<td>Six children who underwent cardiac surgery received rFVIIa for EB</td>
<td>All the patients achieved haemostasis</td>
<td>The dose was 180 µg/kg</td>
<td>Small patient size</td>
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<tr>
<td>Kylasam et al., 2006 Intensive Care Med, Australia [3] Retrospective study (level 2)</td>
<td>Twenty-five children for EB. A single dose (180 µg/kg) of rFVIIa given to 11 patients, Group A Two doses to 14 patients, Group B</td>
<td>Haemostasis achieved in all 25 patients after rFVIIa was given.</td>
<td>The maximum dose was 2</td>
<td>Randomized on dosage</td>
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<tr>
<td>Pychynka-Pokorska et al., 2004 Paediatr Crit Care Med, Poland [4] Prospective study (level 3)</td>
<td>Eight children with EB after cardiac surgery and who did not respond to optimal transfusions of blood products</td>
<td>The use of rFVIIa controlled EB and prevented re-exploration in all 7 patients. No adverse seen</td>
<td>The dose was 180 µg/kg</td>
<td>Good sample size</td>
</tr>
<tr>
<td>Tobias et al., 2004 Intensive Care Med, USA [5] Prospective study (level 2)</td>
<td>Nine children had rFVIIa with CTO of 4 ml/kg/h for the initial 3 postoperative hours. CTO for the 3 h before and after rFVIIa was compared using a paired t-test. In addition, CTO for the initial 3 postoperative hours and the 3 h following rFVIIa was compared to 8 control patients</td>
<td>No adverse effects were noted. rFVIIa decreased CTO following cardiac surgery in children</td>
<td>The CTO for the 3 h before and the 3 h after rFVIIa was compared to 8 control patients who did not require rFVIIa using a paired t-test</td>
<td>Good comparative study between pre- and post-rFVIIa use in the same group and the group with control</td>
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<tr>
<td>Niles et al., 2008 J Extra Corpor Technol, USA [6] Retrospective study (level 3)</td>
<td>Fifteen patients receiving rFVIIa for EB refractory to conventional blood component therapy</td>
<td>There were no complications noted. The rate of bleeding (ml/kg/h) was improved in patients &lt;30 kg for the first 2 h</td>
<td>The doses ranged from 76 to 282 µg/kg (Group A &lt;30 kg) and 26 to 956 µg/kg (Group B &gt;30 kg)</td>
<td>Randomized with respect to the weight of the children</td>
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Table 1: Continued

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<thead>
<tr>
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<tr>
<td>Veldman et al., 2007 Paediatr Anaesth, Germany [7] Retrospective study (level 4)</td>
<td>Seven children were treated with rFVIIa for ED while three were not treated</td>
<td>Three patients died and four survived (deaths not due to thrombus formation). Four patients had thrombosis: two have occlusion of the oxygenator and other two noticed after discontinuation. No thromboembolic events observed</td>
<td>A reduction in PT ($P = 0.001$) and PTTK ($P = 0.02$) was noted in patients &lt;30 kg</td>
<td>Small patient size</td>
</tr>
<tr>
<td>Agarwal et al., 2007 Ann Thorac Surg, USA [8] Retrospective study (level 1)</td>
<td>Twenty-four children who had EB were treated with rFVIIa while 22 children were treated with blood products</td>
<td>Two patients developed thrombotic complications—clots in the ECMO circuit and thrombosis at arterial line site resulting in limb ischaemia. Four patients had mediastinal clots. 6/24 (25%) had thrombosis</td>
<td>The threshold to using rFVIIa was low</td>
<td>No follow-up</td>
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<tr>
<td>Singh et al., 2012 Asian Cardiovasc Thorac Ann, India [9] Retrospective study (level 4)</td>
<td>Twenty children &lt;15 years who underwent cardiac surgery and received rFVIIa for EB</td>
<td>Primary end-point was the reduction in CTO. The secondary end-point was reduction in transfusions of blood products</td>
<td>The mean dose was 43 ± 22.9 µg/kg/dose. Reduction in CTTD from 52.3 to 18.8 ml/kg/h $P = 0.0003$. Reduction of blood products transfusion $P &lt; 0.001$</td>
<td>Good sample size too</td>
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<td>Razon et al., 2005 Paediatr Anaesth, Israel [10] Retrospective study (level 4)</td>
<td>Five patients received rFVIIa after cardiac surgery for EB. The blood loss, blood product and coagulation test results were recorded before and after rFVIIa administration</td>
<td>The use of rFVIIa eliminated the need for additional blood products and normalized the prolonged PT. No side effects noted</td>
<td>The blood loss decreased considerably after rFVIIa administration (mean 7.8 ml/kg/h)</td>
<td>No follow-up</td>
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<tr>
<td>Guzzetta et al., 2009 Paediatr Anaesth, USA [11] Retrospective study (level 4)</td>
<td>Eight neonates undergoing complex congenital cardiac surgery received rFVIIa, either intraoperatively or postoperatively, for EB</td>
<td>The bleeding significantly reduced and transfusion requirements. A high mortality was found in neonates exposed to both rFVIIa and ECMO</td>
<td>The mean amount of some transfused blood product decreased significantly after the administration. The cryoprecipitate tended toward a decrease but did not reach statistical significance</td>
<td>Small size</td>
</tr>
<tr>
<td>Karsies et al., 2010 Ann Thorac Surg, USA [12] Prospective study (level 3)</td>
<td>Twenty-five children received rFVIIa and 50 controls were matched</td>
<td>The use of rFVIIa did not increase thrombotic complications but decreased EB in the small cohort</td>
<td>The dose was 70 µg/kg/dose. There was no significant difference in the rate of thrombosis between patients who received rFVIIa and controls (8% vs 4%). After</td>
<td>Randomized study with good sample size</td>
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reference citations of the articles found through these searches were also reviewed for relevant articles.

SEARCH OUTCOME

One hundred and fifty papers were found using the reported search. From these, 13 were identified that provided the best evidence to answer the question. The results are tabulated in Table 1.

RESULT

In Egan et al. [2] described six children who received recombinant activated factor seven (rFVIIa) for EB despite appropriate attention to haemostasis. The dose was 180 µg/kg, which was repeated after 2 h with no complications.

Kylasam et al. [3], used rFVIIa in 25 patients with EB after cardiac surgery. A single dose of rFVIIa at 180 µg/kg given to 11 patients and two doses to 14. The chest tube output (CTO) was reduced following one dose and successive reduction in those who had two doses. Also, the plasma prothrombin time (PT) and the activated partial thromboplastin time (PTTK) decreased in the same fashion with no adverse events noted.

Pychynska et al. [4] used rFVIIa in 8 patients at a dose of 30 µg/kg increasing to 60 µg/kg in preoperative coagulopathy and if the bleeding had decreased but still exceeded 10 ml/h for body weight ≤5 kg or exceeded 2 ml/kg/h for body weight >5 kg; another dose was repeated 2 h later. They concluded that rFVIIa may prevent re-exploration with no adverse events.

Tobias et al. [5] analysed nine children receiving rFVIIa for EB with CTO of 4 ml/kg/h for the initial 3 h postoperative. CTO for the 3 h before and after rFVIIa was compared. In addition, CTO for the initial 3 h postoperative and the 3 h following rFVIIa was compared to eight controls who did not require rFVIIa. The CTO for the initial 3 h postoperative before the administration of rFVIIa decreased after the administration with no complications.

Niles et al. [6] reviewed 15 patients receiving rFVIIa at a dose range from 76 to 282 µg/kg (Group 1 <30 kg) and 26–956 µg/kg (Group 2 >30 kg). The bleeding rates for the first 2 h after admission to the ICU remained statistically unchanged but increased for those time periods >3 h in patients <30 kg. A significant reduction in PT and PTTK was also noted in patients <30 kg with no complications recorded.

Veldman et al. [7] reviewed 7 patients with respect to the variations in CTO and transfusion requirements, thrombosis in the
ECMO circuit and thromboembolic events. In the 2 patients who developed occlusion of the oxygenator; the thrombus was observed in the ECMO system on inspection after discontinuation with no thromboembolic events recorded.

Agarwal et al. [8] reviewed 46 patients with EB. Patients treated with rFVIIa (study group) were compared with patients treated with blood products alone (control group). Twenty-three of 24 patients in the study group responded to rFVIIa at a dose of 43 µg/kg/dose. Two patients developed thrombotic complications; one in ECMO circuit and the other in the arterial line site resulting in limb ischaemia.

Singh et al. [9] reviewed 20 children who underwent re-exploration before rFVIIa was administered at a dose of 83.33 µg/kg per episode and 154.16 µg/kg with interval between doses of 2 h with no complications observed.

In Razon et al. [10] account, 5 patients blood loss, blood product consumption and coagulation test results were recorded before and after rFVIIa administration. The result showed that blood loss decreased considerably after rFVIIa administration and the prolonged PT normalized with no adverse reactions.

Guizette et al. [11] retrospectively reviewed eight neonates for EB. The transfusion trends and (PT) were assessed both pre- and post-rFVIIa administration. The CTO were recorded pre- and post-rFVIIa administration in postoperative neonates in the ICU. The amount of transfusion of blood products and PT values significantly decreased after the administration of rFVIIa with higher mortality found in neonates exposed to both rFVIIa and ECMO.

Karsies et al. [12] retrospectively matched a case–control study of 25 patients who had rFVIIa at a dose of 70 mcg/kg to 50 controls. There was no difference in the rate of thrombosis between two groups. However, after administration of rFVIIa, there was a reduction in transfusion volume of blood and its products.

In Ekert et al. [13] randomized controlled study for the effective prophylactic use of rFVIIa at a dose of 40 µg/kg for 40 in rFVIIa group and 36 in placebo group and showed no benefit of prophylactic rFVIIa. Similarly, there were no significant differences in the secondary end-points and adverse events were similar in both groups.

In Warren et al. [14] meta-analysis, they observed that postoperative haemorrhage was a recognized complication in paediatric cardiac surgery because of the immature coagulation system and increased susceptibility to haemodilution when compared with adults [15, 16] and concluded that there was an increased use of rFVIIa in treating EB after congenital cardiac surgery with proven efficacy. A previous best evidence topic performed in the adult population showed that the incidence of thrombotic episodes was low (1%) [17].

**REFERENCES**


**CLINICAL BOTTOM LINE**

In conclusion, rFVIIa was effective in stopping EB after paediatric cardiac surgery with adverse reactions rarely encountered; however, caution should be exercised when using it with ECMO circuit [7, 8, 11]. The limitations of the study include the lack of homogeneity in age and few randomized studies.

**Conflict of interest:** none declared.