Recombinant activated factor VII in cardiac surgery: a systematic review

CRD summary
This review assessed the efficacy and safety of human recombinant factor VIIa (rFVIIa) in cardiac surgery. The authors suggested that rFVIIa may reduce refractory post-operative bleeding while limited evidence supports rFVIIa in a prophylactic role. These conclusions have to be interpreted with extreme caution as they are based on small poor-quality studies.

Authors' objectives
To evaluate the efficacy, safety and costs of human recombinant activated factor VII (rFVIIa) in cardiac surgery.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched up to July 2006; the search terms were reported. The bibliographies of retrieved articles were screened for additional articles. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
The inclusion criteria were not defined in terms of study design, but it appears that any type of study design was eligible.

Specific interventions included in the review
Studies evaluating the use of rFVIIa were eligible for inclusion. rFVIIa was provided most often to treat refractory post-operative bleeding. In some studies rFVIIa was given as a prophylactic haemostatic agent. The dose of rFVIIa varied across the studies.

Participants included in the review
Studies of adult or paediatric patients undergoing cardiac surgery were eligible for inclusion. Studies reported on mixed patient groups were also included, but data were only included for cardiac patients. Most studies were restricted to cardiac patients; six were conducted in mixed populations. A quarter of the patients were children ranging from neonates to older children; within this subgroup, cardiac surgery consisted of septal defect repairs, correction of transposition of great vessels, and the treatment of congenital abnormalities. Coronary artery bypass grafting, valve replacement, or a combination of the two were the most frequent types of surgery performed on adult patients. One fifth of the adult patients were reoperations.

Outcomes assessed in the review
Studies that reported clinical data were eligible for inclusion. The outcomes evaluated were blood loss, adverse events (including stroke, myocardial infarction and other thromboembolic event) and mortality.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Study quality was not formally assessed, but data on study design and blinding were reported.

Data extraction
Two independent reviewers performed the data extraction, but the authors did not state how any disagreements were resolved. Data were extracted on the outcomes of interest; the authors did not provide details of the format in which these data were extracted.

Methods of synthesis
How were the studies combined?
The data were presented narratively, with additional data tabulated for the comparative studies.

**How were differences between studies investigated?**
Differences in intervention, study design, populations and outcomes were discussed in the text.

**Results of the review**
Forty-six studies (501 patients) were included: 2 randomised controlled trials (RCTs), 4 prospective comparative cohort studies, 3 prospective non-comparative studies, 13 retrospective chart/database reviews and 24 case report/series.

rFVII in refractory haemorrhage (44 studies including 4 comparative studies using historical controls).

Two studies (one of which was comparative) used rFVII before any blood product replacement, whereas in all other cases rFVIIa was given when all previous treatments seemed to have failed. Three of the comparative studies reported a reduction in blood loss or blood product requirements in the rFVIIa group compared with historical untreated controls; the fourth reported no difference between treatment groups in terms of blood loss, transfusion requirements or survival. The majority of non-comparative studies also reported reductions in blood loss. Thromboembolic events occurred in 5.3% of cases treated with rFVIIa.

rFVII as prophylactic agent (2 RCTs, n=101).

One RCT found a significant reduction in units of blood products required in patients treated with rFVIIa compared with placebo (13 versus 105 units, relative risk of any transfusion 0.26, p=0.037). The rate of thromboembolic adverse events was comparable between the groups. The other RCT in paediatric patients, which used a smaller dose of rFVIIa, found no difference in blood loss or blood transfusion requirements, or adverse events including thromboembolic events.

**Cost information**
The authors stated that while the costs of rFVII may be offset against the costs of transfusions, length of hospital stay and even death, this treatment remains an expensive option not affordable by many units.

**Authors' conclusions**
The use of rFVIIa appeared to reduce refractory post-operative bleeding, but there were insufficient data to support its use as a prophylactic agent. It appears to be a relatively safe treatment.

**CRD commentary**
This review addressed a well-defined question in terms of the participants, interventions and outcomes, while a broad definition of study design was used. Two databases and a trial register were searched and efforts were made to find further information by reviewing reference lists. Attempts were not made to identify unpublished studies and the potential influence of publication bias was not considered in the report. No language restrictions were applied, thereby limiting the potential for language bias. The authors attempted to minimise bias and errors during the review process by carrying out the data extraction in duplicate. It is unclear if study selection was also performed in duplicate, therefore reviewer error and bias might have been introduced at this stage. A formal quality assessment was not carried out although the authors did consider study design in their synthesis of the results.

The authors’ decision not to pool the studies in a meta-analysis was justified given the apparent clinical differences between the studies and the variety of study designs included. The authors’ conclusions should be interpreted with extreme caution given the methodological weaknesses of the review and that they are based on a few poor-quality studies with few participants. In particular, they made stronger recommendations for the use of rFVIIa for the reduction of refractory post-operative bleeding when only poor-quality studies were included in comparison with those included for its use as a prophylactic agent.

**Implications of the review for practice and research**
Practice: The authors did not state any implication for practice.
Research: The authors stated that further large studies are needed to establish the efficacy and safety, optimal dosage and cost-effectiveness of rFVIIa in cardiac surgery.

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