Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications


CRD summary
The review concluded that limited evidence suggested off-label use of recombinant factor VIIa (rFVIIa) for five indications did not benefit mortality rates, but increased the risk of thromboembolism for some indications. This was a generally well-conducted review and the authors’ conclusions appear to reflect the evidence, but the limitations of the included studies should be borne in mind.

Authors' objectives
To assess the effectiveness of in-hospital off-label use of recombinant factor VIIa (rFVIIa) for the treatment of adults with intracranial haemorrhage, massive bleeding from trauma or those undergoing cardiac surgery, liver transplantation or prostatectomy.

Searching
Ten databases (including PubMed, EMBASE and The Cochrane Library) were searched from inception to December 2010 to identify English-language articles. Search terms were not reported. Regulatory sites, clinical trial registries, conference proceedings and grant-funded and federally funded research sites were searched for grey literature. Abstracts were excluded. Reference lists of relevant systematic reviews, files supplied by manufacturers and manufacturer’s website were searched manually. Experts in the field were contacted for further data.

Study selection
Randomised controlled trials (RCTs) and observational studies that compared the effectiveness of rFVIIa with alternative therapies, placebo or usual care in treatment of hospitalised patients with off-label indications (intracranial haemorrhage, bleeding from trauma, cardiac surgery, liver transplantation or prostatectomy) were eligible for inclusion. Non-comparative studies with at least 15 patients were eligible for inclusion in the harms analyses. The main outcomes of interest were rates of mortality and thromboembolism. Studies of human factor VIIa or modified recombinant forms under development were excluded.

Mean age of included patients ranged from 11 to 81.5 years. Patients with intracranial haemorrhage or brain trauma who were included in the RCTs did not receive oral anticoagulation; patients in the comparative observational studies received oral anticoagulation. Doses of rFVIIa ranged from 5µg/kg to 400µg/kg. Some studies reported surrogate outcomes (poor functional status measured using the modified Rankin scale, haematoma expansion, red blood cell transfusion units, days of intensive care unit stay, acute respiratory distress syndrome and minutes of operating room time).

Two reviewers independently screened studies for inclusion.

Assessment of study quality
Two reviewers independently assessed the quality of RCTs according to randomisation, allocation concealment, blinding and follow-up. Observational studies were assessed according to comparability of treatment groups, control for confounding, blinding and follow-up. Studies were rated as fair or good quality if they partially or fully achieved (or adequately reported) criteria. Studies were rated as poor quality if they did not achieve (or did not adequately report) criteria. Discrepancies were resolved by consensus and referral to a third reviewer if necessary.

Data extraction
Two reviewers independently extracted continuous outcome data to calculate mean differences and extracted dichotomous outcomes to calculate risk differences (RDs) and arcsine standardised mean differences (only RDs were reported in the review); 95% confidence intervals (CIs) were also calculated.

Discrepancies were resolved by consensus and referral to a third reviewer where necessary.
Methods of synthesis
Meta-analysis was performed only for good or fair quality RCTs or good quality observational studies, and only when there were at least two studies (one of which had to be good quality). A fixed-effect model (or random effects model where there was evidence of statistical heterogeneity) was used to combine standardised mean differences (SMDs) and risk differences, along with 95% CIs.

Statistical heterogeneity was assessed using the Q and I² statistics. Subgroup analyses were undertaken for low (≤40µg/kg), medium (>40 but <120µg/kg) and high doses (≥120µg/kg) for intracranial haemorrhage and for arterial versus venous thromboembolism.

It was not possible to assess publication bias due to the small number of studies for any given indication.

Results of the review
Sixty-two articles (64 studies) were included in the review: 16 RCTs, 26 comparative observational studies and 22 non-comparative observational studies. Two RCTs (13%) and 16 of 26 comparative observational studies (62%) were of poor quality. Results from fixed-effects analyses were reported due to the small number of studies included in each comparison.

Effectiveness: (16 RCTs, 10 comparative observational studies, n=3,965, range six to 573)

Intracranial haemorrhage: four RCTs, one comparative observational study

There were no statistically significant differences in mortality rates and poor functional status between rFVIIa (at any dose) and usual care (four RCTs). Medium and high dose rFVIIa increased rates of arterial thromboembolism (medium dose RD 0.03, 95% CI 0.01 to 0.06; four RCTs and high dose RD 0.06, 95% CI 0.01 to 0.11; two RCTs). rFVIIa significantly reduced relative haematoma expansion at all doses (low dose SMD -0.15, 95% CI -0.29 to 0.00, medium dose SMD -0.24, 95% CI -0.39 to -0.10 and high dose SMD -0.33, 95% CI -0.58 to -0.09).

Cardiac surgery: two RCTs, four comparative observational studies

rFVIIa did not significantly effect mortality rates compared with usual care, but increased risk of thromboembolism (RD 0.05, 95% CI 0.01 to 0.10; two RCTs and two observational studies). Results on red blood cell transfusion and length of stay in intensive care were inconsistent.

Body trauma: four RCTs, three comparative observational studies

rFVIIa did not significantly effect rates of morality or thromboembolism, but significantly reduced acute respiratory distress syndrome compared to usual care (RD -0.05, 95% CI -0.08 to -0.02; four RCTs). One of four RCTs reported a statistically significant reduction in transfusion requirements (but this analysis included previously censored patients).

Brain trauma: one RCT, one comparative observational study

rFVIIa did not significantly effect rates of mortality or thromboembolism.

Liver transplant: four RCTs, one comparative observational study

rFVIIa did not significantly effect mortality or thromboembolism, or indirect outcomes (red blood cell transfusion, operating room time, length of stay in intensive care).

Prostatectomy: one RCT

Mortality and thromboembolic events could not be evaluated due to the limited number of events. Red blood cell transfusion requirements and operating room time were significantly reduced with rFVIIa compared to usual care (p values were reported in the review).

Harms: 16 RCTs, 26 comparative observational studies, 22 non-comparative observational studies
Comparisons of results from RCTs versus observational studies were reported in the review.

Authors' conclusions
The limited evidence suggested that off-label use of rFVIIa for five indications did not benefit mortality rates, but increased the risk of thromboembolism for some indications.

CRD commentary
The review question and supporting inclusion criteria were clearly stated. A comprehensive review of the literature was undertaken and included a search for unpublished data. Language restrictions were applied, so language bias may have been introduced. Publication bias could not be assessed and the authors acknowledged the possibility for publication bias. The authors assessed study quality using appropriate criteria and only fair and good quality studies were included in the meta-analysis. The authors undertook each stage of the review in duplicate, which reduced potential for reviewer error and bias. There was evidence of clinical and methodological heterogeneity among studies and pooling of the results separately for different indications was appropriate. The authors acknowledged that only a small number of studies were included in the analyses for the different indications and highlighted potential for bias in studies that relied on surrogate outcomes. One author was supported by the US Department of Veterans Affairs.

This was a generally well-conducted review and the authors' conclusions appear to reflect the limited evidence, but the limitations of the included studies should be borne in mind when interpreting the findings.

Implications of the review for practice and research
The authors did not state any implications for practice and research.

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