Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia (Review)

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[Intervention Review]

Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

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ABSTRACT

Background

Recombinant factor VIIa (rFVIIa) is licensed for use in patients with haemophilia and inhibitory allo-antibodies and for prophylaxis and treatment of patients with congenital factor VII deficiency. It is also used for off-license indications to prevent bleeding in operations where blood loss is likely to be high, and/or to stop bleeding that is proving difficult to control by other means. This is the third version of the 2007 Cochrane review on the use of recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia, and has been updated to incorporate recent trial data.

Objectives

To assess the effectiveness of rFVIIa when used therapeutically to control active bleeding or prophylactically to prevent (excessive) bleeding in patients without haemophilia.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and other medical databases up to 23 March 2011.

Selection criteria

Randomised controlled trials (RCTs) comparing rFVIIa with placebo, or one dose of rFVIIa with another, in any patient population (except haemophilia). Outcomes were mortality, blood loss or control of bleeding, red cell transfusion requirements, number of patients transfused and thromboembolic adverse events.

Data collection and analysis

Two authors independently assessed potentially relevant studies for inclusion, extracted data and examined risk of bias. We considered prophylactic and therapeutic rFVIIa studies separately.

Main results

Twenty-nine RCTs were included: 28 were placebo-controlled, double-blind RCTs and one compared different doses of rFVIIa. In the 'Risk of bias' assessment, most studies were found to have some threats to validity although therapeutic RCTs were found to be less prone to bias than prophylactic RCTs.

Sixteen trials involving 1361 participants examined the prophylactic use of rFVIIa; 729 received rFVIIa. There was no evidence of mortality benefit (risk ratio (RR) 1.04; 95% confidence interval (CI) 0.55 to 1.97). There was decreased blood loss (mean difference (MD) -297 mL; 95% CI -416 to -178) and decreased red cell transfusion requirements (MD -261 mL; 95% CI -367 to -154) with rFVIIa treatment; however, these values were likely overestimated due to the inability to incorporate data from trials (four RCTs in the outcome of blood loss and three RCTs in the outcome of transfusion requirements) showing no difference of rFVIIa treatment compared to placebo. There was a trend in favour of rFVIIa in the number of participants transfused (RR 0.85; 95% CI 0.72 to 1.01). However, there was a trend against rFVIIa with respect to thromboembolic adverse events (RR 1.35; 95% CI 0.82 to 2.25).

Thirteen trials involving 2929 participants examined the therapeutic use of rFVIIa; 1878 received rFVIIa. There were no outcomes where any observed advantage or disadvantage of rFVIIa over placebo could not have been observed by chance alone. There was a trend in favour of rFVIIa for reducing mortality (RR 0.91; 95% CI 0.78 to 1.06). However, there was a trend against rFVIIa for increased thromboembolic adverse events (RR 1.14; 95% CI 0.89 to 1.47).

When all trials were pooled together to examine the risk of thromboembolic events, a significant increase in total arterial events was observed (RR 1.45; 95% CI 1.02 to 2.05).

Authors' conclusions

The effectiveness of rFVIIa as a more general haemostatic drug, either prophylactically or therapeutically, remains unproven. The results indicate increased risk of arterial events in patients receiving rFVIIa. The use of rFVIIa outside its current licensed indications should be restricted to clinical trials.

PLAIN LANGUAGE SUMMARY

Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

The purpose of this review was to evaluate the evidence of effectiveness and safety for the use of recombinant factor VIIa (rFVIIa). This drug has been used in patients who are either at risk of major bleeding (e.g. because of planned high-risk surgery), or who have uncontrolled bleeding (e.g. related to trauma). There have been many articles in the literature describing the off-license use of this drug, which often suggest benefit. However, most of the publications are based on small numbers of patients (in case reports or case series) and may be affected by bias. Randomised controlled trials provide higher-quality research findings and allow us to assess the evidence of drug effectiveness with more certainty.

This review included 29 randomised controlled trials with 4290 patients. The trials showed modest reductions in total blood loss or red cells transfused (equivalent to less than one unit of red cell transfusion) with the use of rFVIIa. However, the reductions were likely to be overestimated due to the limitations of the data. We also observed an increase in the risk of having a blood clot in the arteries (such as a heart attack or stroke) in those patients receiving rFVIIa. When taken together, the data supporting the off-license use of recombinant FVIIa are weak. The use of rFVIIa outside its current licensed indications should be restricted to clinical trials.