Use of intravenous tranexamic acid to reduce allogeneic blood transfusion in total hip and knee arthroplasty: a meta-analysis

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CRD summary
This review compared intravenous tranexamic acid with placebo for reducing blood loss in total hip and knee arthroplasty. The authors concluded that intravenous tranexamic acid reduces blood loss and the need for transfusion without increasing the risk of complications. Differences between the included studies may mean that the results of the review are not reliable.

Authors' objectives
To assess the effectiveness and safety of intravenous (IV) tranexamic acid for reducing blood loss and transfusion requirement in patients undergoing elective artificial total hip or knee joint replacement surgery.

Searching
MEDLINE and EMBASE (from January 1966 to December 2002), Current Contents (dates not stated) and the Cochrane Controlled Trials Register (Issue 4, 2002) were searched; the search terms were given. In addition, the reference lists of related reviews and identified articles were checked, and the manufacturers of IV tranexamic acid were contacted. Where possible, and if necessary, the authors of identified trials were contacted for additional information and unpublished data.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies of IV tranexamic acid compared with placebo were eligible for inclusion. Studies of tranexamic acid combined with another active intervention were included if the placebo group was also exposed to the other active intervention. The included studies used tranexamic acid at different time points during the operation; one also used it in the post-operative period. The dose ranged from 10 to 135 mg/kg and was administered in various regimens. Most of the studies gave low molecular weight heparin the night before surgery and daily after the surgery.

Participants included in the review
Studies of people undergoing elective or non-emergency hip or knee joint replacement surgery were eligible for inclusion. The mean age of the people in the included studies ranged from 65 to 75 years.

Outcomes assessed in the review
The inclusion criteria were not explicit. The outcomes measured in the included studies were the proportion of patients receiving allogeneic blood transfusion, the average number of units of blood transfused per patient, the total blood loss 24 hours after surgery or until removal of the surgical drain, and the proportion of patients with thromboembolic complications. Deep vein thrombosis was defined by venography or ultrasound; pulmonary embolism by computer tomography pulmonary angiography; myocardial infarction by elevated serum troponin; and cerebral accident by computed tomography head scan.

How were decisions on the relevance of primary studies made?
Two reviewers independently examined the titles and abstracts of all identified trials. Any disagreements were resolved by consensus.
Assessment of study quality
Allocation concealment, randomisation method, blinding of treatment, and inclusion and exclusion criteria were used to assess study quality. The grading of allocation concealment was based on the Cochrane approach (adequate, uncertain or clearly inadequate). Two independent reviewers extracted data on the validity criteria. If there was uncertainty, trial authors were contacted. Any disagreements between the two reviewers were resolved by consensus.

Data extraction
Two reviewers independently extracted the data using a pre-designed data extraction form. If there was uncertainty, trial authors were contacted. Any disagreements between the two reviewers were resolved by consensus. Duplicate publications were combined. If only the median and range were reported for continuous outcomes and the data were nearly normally distributed, the median was assigned as the mean and the standard deviation estimated (0.95 multiplied by the range, divided by 4).

Methods of synthesis
How were the studies combined?
The studies were combined using a meta-analysis. For binary outcomes, odds ratios (ORs) from individual studies were combined using a random-effects model. For continuous outcomes, mean differences were combined to produce a weighted mean difference (WMD) using a random-effects model. If continuous data were not normally distributed, the trial results were not included in the pooled analysis. The possibility of publication bias was assessed using funnel plots.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. The following sensitivity analyses were performed: trials with unknown or inadequate allocation concealment or blinding were excluded; hip and knee arthroplasty studies were analysed separately; trials using only regional anaesthesia were analysed separately.

Results of the review
Twelve RCTs were included in the analysis (the number of participants was not explicit, but the highest number included in the analyses shown was 619).

Patients treated with IV tranexamic acid were less likely to require allogenic blood transfusion than those treated with placebo (11 RCTs; pooled OR 0.16, 95% confidence interval, CI: 0.09, 0.26).

The number of units of blood transfused (11 RCTS) and the amount of blood loss peri-operatively (12 RCTs) was lower in the IV tranexamic group than the placebo group (WMD -0.85 units, 95% CI: -1.33, -0.36 and WMD -460.12 mL, 95% CI: -626.19, -274.06, respectively), but significant heterogeneity was seen in these results.

The occurrence of deep vein thrombosis was not significantly different in the IV tranexamic acid group than in the placebo group (12 RCTs; pooled OR 0.98, 95% CI: 0.45, 2.12).

Sensitivity analyses did not make a substantial difference to the results.

The funnel plot for the transfusion outcome suggested a small publication bias in favour of studies with positive results.

Seven of the 12 included RCTs had adequate allocation concealment.

Cost information
Two RCTs presented a cost comparison involving the cost of blood products (a unit of allogeneic blood, NZ$158) and drug cost (25 mg/kg, NZ$59); this favoured the use of IV tranexamic acid.

Authors' conclusions
IV tranexamic acid is safe and effective in reducing allogeneic blood transfusion in patients undergoing total hip or
knee arthroplasty.

**CRD commentary**
The question and inclusion criteria were clearly stated for this review, with the exception of inclusion criteria for the outcomes measured. Several sources were searched for relevant studies and the manufacturers of the drug were contacted. Two reviewers independently assessed studies for relevance and validity and extracted the data, which reduces the potential for error and bias in the review process. In addition, the trial authors were contacted for missing data. Despite this, there was still some evidence of publication bias in the results of the review, and this might have favoured positive findings. A validity assessment was carried out, but was only reported in terms of allocation concealment.

Characteristics of the included studies were not presented in any detail, which made it difficult to assess their similarity. It was not possible to assess whether the decision to pool the studies was appropriate (owing to missing study details), but sensitivity analyses were carried out. The analysis of safety seems to have been restricted to the occurrence of deep vein thrombosis, although it was stated that other outcomes were measured. The authors' conclusions seem too emphatic given the clinical heterogeneity they mention in the included studies.

**Implications of the review for practice and research**
Practice: The authors stated that the clinical effectiveness of tranexamic acid is likely to be more significant in settings where a high rate of blood transfusion commonly occurs.

Research: The authors stated that tranexamic acid and other blood conservation techniques in revision hip or knee arthroplasty surgery when blood loss is more significant should be compared in RCTs. Future trials should incorporate a full pharmacoeconomic analysis.

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