Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis
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CRD summary
The authors' conclusion that tranexamic acid was safe and effective in reducing blood loss for patients undergoing total knee arthroplasty should not be considered as reliable given the strong likelihood that relevant studies were excluded and because the analysis failed to take into account considerable variation between the trials.

Authors' objectives
To investigate the effectiveness and safety of tranexamic acid in reducing postoperative blood loss in total knee arthroplasty.

Searching
PubMed and EMBASE were searched for studies in English that were published before May 2011. Bibliographies of relevant articles were checked. Search terms were not reported.

Study selection
Randomised controlled trials (RCT) that compared tranexamic acid with placebo were included if they met a quality threshold (see Assessment of Study Quality). Patients underwent total knee arthroplasty with an intraoperative pneumatic tourniquet and without anticoagulant drugs. Studies were required to report one of seven blood-loss related outcomes (details reported).

The included studies were published between 1995 and 2011. More than two thirds of the patients were female. Mean ages ranged from 62 to 76 years. Use of non-steroidal anti-inflammatory drugs (NSAID) varied across the included studies; some required patients to stop two weeks before surgery and others allowed NSAID up to 12 hours prior to surgery. Fourteen of the 15 studies used a low dose of tranexamic acid of 10 to 50mg/kg and one study used 150mg/kg. Duration of surgery varied across included studies (range not reported).

It was not clear how many reviewers selected studies for inclusion.

Assessment of study quality
Studies were assessed using the five-point Jadad quality assessment scale of randomisation, blinding and drop-outs/withdrawals. Studies that scored 3 or more were considered to be of high quality and were included in the meta-analysis.

It was unclear how many reviewers performed the quality assessment.

Data extraction
Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for occurrence of deep-vein thrombosis and pulmonary embolism and the number of patients who needed transfusion for each study. Mean differences and standard deviations (SD) were calculated for amount of blood lost, number of blood transfusion units needed per patient, prothrombin time and activated partial thromboplastin time for each study.

Two reviewers extracted data independently and resolved disagreements through discussion.

Methods of synthesis
Random-effects and fixed-effect models (details not reported) were used to calculate odds ratios and weighted mean differences (WMD) for binary and continuous outcomes.

Results of the review
Fifteen trials were included in the review (837 patients, range 20 to 102). Quality assessment results were reported in a
supplement to the paper which was unobtainable despite contacting the authors. Although the trials clearly met a minimum standard (3 points on Jadad), details of the quality of the trials remained unclear.

Blood loss per patient was significantly lower in the tranexamic acid group compared with placebo across 14 trials (WMD -504.9mL, 95% CI -620.89 to -388.92; $I^2=93\%$). Significantly fewer blood transfusions were carried out for patients who received tranexamic acid versus placebo across six trials (WMD -1.43 units, 95% CI -1.69 to -1.17; $I^2=51\%$). Analysis of 14 trials that reported odds of receiving a transfusion found a significantly lower risk in the tranexamic acid group compared with placebo (OR 0.16, 95% CI 0.10 to 0.25; $I^2=3\%$).

There was no significant difference between tranexamic acid and placebo groups in the risk of developing a deep vein thrombosis (13 trials), a pulmonary embolism (six trials), prothrombin time (four trials) or activated partial thromboplastin time (five trials).

**Authors' conclusions**

Tranexamic acid was safe and effective in reducing blood loss for patients undergoing total knee arthroplasty.

**CRD commentary**

The review addressed a clear question. Only considering placebo-controlled studies may have limited the clinical applicability of the results. The authors searched two key databases. The lack of attention to the grey and non-English literature and exclusion of studies that fell below a crude quality threshold suggested that relevant trials may have been missed. The quality assessment used a summary score as part of the inclusion criteria but this did not ensure all included trials were reliable and details of the results could not be obtained. Partial reporting of the review processes made it difficult to rule out reviewer error and bias during study selection and quality assessment.

The limited study details presented indicated that there were substantial differences in how some of the key outcomes (such as blood loss) were measured and reported, publication dates were widely spread and there may have been important changes in the management of patients. It was unclear whether it was appropriate to pool these trials. Substantial heterogeneity for two analyses was neither commented on nor explored. The adverse event conclusions appeared to broadly reflect the data presented but the main efficacy outcomes may not be reliable due to substantial inter-study variation.

It seemed highly likely that this review did not include all of the relevant studies, use of a blunt quality threshold may have resulted in a biased sample and the analysis failed to take inter-study variations into account. The authors' strong conclusions are not supported by the evidence presented.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors recommended that more high quality randomised controlled trials were needed to strengthen their conclusion that tranexamic acid did not increase the risk of complications when used in total knee arthroplasty.

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