Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials
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CRD summary
The authors concluded that antifibrinolytic agents may reduce bleeding and transfusion risk in patients undergoing total knee arthroplasty or total hip replacement surgery who received concomitant antithrombotic prophylaxis, but further prospective trials are needed. Given the high level of heterogeneity between trials and the possibly inappropriate pooling of the trials, the reliability of the authors' conclusions is unclear.

Authors' objectives
To evaluate the impact of antifibrinolytic therapy on bleeding, transfusion and risk of venous thromboembolism in patients undergoing orthopaedic surgery.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane Database of Systematic Reviews were searched for articles published in English. The search dates varied across databases, spanning 1966 to May 2007. Manufacturers were contacted for further unpublished trials. The bibliography of included studies and relevant reviews were handsearched for further studies.

Study selection
Randomised controlled trials comparing the effect of tranexamic acid, epsilon aminocaproic acid or aprotinin with placebo or no treatment on bleeding, transfusion or incidence of venous thromboembolism, in adults undergoing total hip replacement or total knee arthroplasty, were eligible for inclusion. Trials were excluded if the surgery was a revision procedure or where there were multiple arms and the data specific to one antifibrinolytic agent could not be extracted.

The included trials were of tranexamic acid, epsilon aminocaproic acid or aprotinin alone or in combination, administered in varying doses at before, after or during surgery compared to saline, placebo or normal saline. The majority of trials were of tranexamic acid alone. In the majority of included trials, participants also received a mechanical and/or pharmacological prophylaxis for deep vein thrombosis. The mean age of participants in the intervention arms ranged from 55.5 to 76 years.

Outcomes included for review were total bleeding (measured intra-operatively by weighing surgical sponges, post-operatively through drainage or peri-operatively through haemoglobin balance method), the number of patients transfused, and number of units transfused and venous thromboembolism (investigated through a variety of methods). In the majority of trials venous thromboembolism was investigated only following clinical suspicion of venous thromboembolism. In eight trials screening for venous thromboembolism was routine. The follow-up ranged from three days to three months.

Two reviewers independently selected the studies for review blinded to author and journal publication. Disagreements were resolved by consensus.

Assessment of study quality
The methodological quality of the included trials was assessed using the Jadad scale, which assesses randomisation, blinding and patient attrition, giving a maximum score of 5 points. A score of two or less was deemed to indicate a low quality trial and a score of three or more a high quality trial. The authors also assessed quality according to treatment concealment, method of blinding, use of intention to treat analysis and the objectivity of the outcomes measured.

Validity was independently assessed by two reviewers, who were blind to the author and journal of publication, with disagreements resolved by consensus.
Data extraction
The number of patients undergoing transfusion in each group was extracted and used to calculate relative risks with 95% confidence intervals for each trial. The number of patients undergoing allogeneic transfusion was extracted and used to calculate odds ratio. The mean blood loss and standard deviations were extracted for each trial. The number of patients with venous thromboembolism in each group was extracted for each trial.

Two reviewers independently extracted the data for the review with disagreements resolved by consensus.

Methods of synthesis
Pooled relative risks with 95% confidence intervals were calculated for the number of patients transfused and pooled odds ratio was used to calculate the number of patients undergoing allogeneic transfusion. Weighted mean difference and standardised mean difference with corresponding 95% confidence intervals were calculated for the difference in blood loss between intervention and control groups. The authors stated that, given the high levels of no events for venous thromboembolism in individual trials, the relative risk of venous thromboembolism was calculated using a weighted mean difference, assuming an incidence of venous thromboembolism of 29.6% in the control group. However, it is unclear how this was calculated. The risk difference of venous thromboembolism was also calculated. Data were combined using a random-effects model. Heterogeneity was assessed using the $I^2$ statistic, with significant heterogeneity set at more than 40%. Subgroup analyses were carried out for type of surgery, type of antifibrinolytic agent and the number of doses administered.

Results of the review
Twenty nine randomised controlled trials (RCTs) were included for review (n=1,964 patients). Twenty one trials scored 3 or more on the Jadad scale. Twenty RCTs were double-blinded, 18 RCTs described the randomisation sequence, but no RCTs reported using intention-to-treat analyses.

Total blood loss: Antifibrinolytic agents were associated with significantly less blood loss than placebo in both patients undergoing total knee arthroplasty (SMD -1.12, 95% confidence interval (CI): -1.31 to -0.93; eight RCTs, n=519 patients) and patients undergoing total hip replacement (standardised mean difference -0.89, 95% CI: -1.05 to -0.72; 13 RCTs, n=662 patients). There was evidence of significant heterogeneity (total knee arthroplasty group $I^2=74.5%$; total hip replacement group $I^2=83%$). Subgroup analyses revealed that tranexamic acid (weighted mean difference -393 mL, 95% CI:-442 to -345), epsilon aminocaproic acid (weighted mean difference -331 mL, 95% CI: -544 to -118,) and aprotinin (weighted mean difference -639 mL, 95% CI: -725 to -536,) were also associated with significantly less blood loss compared to placebo. P-values and levels of heterogeneity were not reported for these analyses.

Transfusion: Patients receiving antifibrinolytic therapy were significantly less likely to need a blood transfusion (relative risk 0.52, 95% CI: 0.42 to 0.64, p<0.00001; 25 RCTs, n=1,557 patients) and less likely to undergo an allogeneic blood transfusion (odds ratio 0.24, 95% CI: 0.17 to 0.32, p<0.00001; 19 RCTs, n=1,002 patients) compared to controls. There was evidence of heterogeneity for both these outcomes ($I^2=57.9%$ and 44.8% respectively). Subgroup analysis by type of surgery revealed a reduction in the risk of transfusion of 87% for patients undergoing total knee arthroplasty (relative risk 0.13, 95% CI: 0.08 to 0.20; number of RCTs and patients unclear) and 58% for patients undergoing total hip replacement (relative risk 0.42, 95% CI: 0.30 to 0.58; number of RCTs and patients not reported). P-values and heterogeneity for these analyses were not reported.

Venous thromboembolism complications: The analyses showed no significant difference of risk of venous thromboembolism between patients receiving antifibrinolytic therapy and those receiving placebo (relative risk 0.95, 95% CI: 0.80 to 1.10 and risk difference 0.00, 95% CI: -0.02 to 0.01; 27 RCTs, n=1,637 patients). Subgroup analyses according to type of therapy continued to show no significant difference in the risk of venous thromboembolism between intervention and control groups. For the majority of trials, there were no events in one or both arms.

Cost information
Cost-effectiveness was not formally evaluated in the review. However, the authors stated that there were potential cost benefits due to the reduced need for transfusion, a reduced risk of complications arising from bleeding or transfusion,
and a reduced need for post-operative erythropoietic stimulating agents.

**Authors' conclusions**
Antifibrinolytic agents may have reduced bleeding and the risk of transfusion in patients undergoing total knee arthroplasty or total hip replacement who received concomitant antithrombotic prophylaxis, but further adequately powered prospective trials are needed.

**CRD commentary**
The review addressed a clear question with well-defined inclusion criteria. Several relevant databases were searched, but the search was limited to published articles in English. The possibility of language and publication bias cannot be ruled out, even though manufacturers were contacted for unpublished data. Appropriate steps were taken throughout the review process in order to minimise reviewer error and bias. A suitable validity assessment was carried out and the majority of trials were of high quality. There was a high level of statistical and clinical heterogeneity between trials and the authors' description of the synthesis was unclear. The authors did attempt to investigate potential sources of heterogeneity, so the results may have been better treated through a narrative synthesis. Also, p values and levels of heterogeneity were not reported for some outcomes, making it difficult for the reader to ascertain the importance of these findings. The small size of included trials made the detection of venous thromboembolism difficult; it is unclear whether appropriate steps were taken in the analysis to account for the lack of events in included trials. Given the high level of heterogeneity between trials, the pooling of trials that may not have been appropriate, the reliability of the authors' conclusions is unclear.

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

**Research:** The authors stated that a large randomised placebo-controlled trial of antifibrinolytic therapy in orthopaedic patients is needed, with adequate power to assess bleeding, transfusion and risk of venous thromboembolism.

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