Systematic review

Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss

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Background: **Tranexamic acid (TXA) reduces blood transfusion in surgery but the extent of the reduction in blood loss and how it relates to the dose of TXA is unclear.**

Methods: **A systematic review of randomized trials was performed. Data were extracted on blood loss from trials comparing intravenous TXA with no TXA or placebo in surgical patients. A Bayesian linear regression was used to describe the relationship between the reduction in blood loss with TXA and the extent of bleeding as measured by the mean blood loss in the control group. A meta-analysis of the log-transformed data was conducted to quantify the effect of TXA on blood loss, stratified by type of surgery, timing of TXA administration and trial quality. Meta-regression was used to explore the effect of TXA dosage.**

Results: **Data from 104 trials were examined. Although the absolute reduction in blood loss with TXA increased as surgical bleeding increased, the percentage reduction was similar. TXA reduced blood loss by 34 per cent (pooled ratio 0·66, 95 per cent confidence interval 0·65 to 0·67; $P < 0·001$). The percentage reduction in blood loss with TXA differed by type of surgery, timing of TXA administration and trial quality, but the differences were small. The effect of TXA on blood loss did not vary over the range of doses assessed (5·5–300 mg/kg).**

Conclusion: **TXA reduces blood loss in surgical patients by about one-third. A total dose of 1 g appears to be sufficient for most adults. There is no evidence to support the use of high doses.**

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Introduction

Tranexamic acid (TXA) reduces the probability of receiving a blood transfusion in surgery. A systematic review of randomized clinical trials showed that TXA reduces the probability of blood transfusion by 38 per cent (pooled risk ratio 0·62, 95 per cent confidence interval (c.i.) 0·58 to 0·65; $P < 0·001$)[1]. However, the extent to which TXA reduces surgical bleeding and its relationship with the dose of TXA and type of surgery remains uncertain. Because the decision to transfuse depends on factors other than blood loss, the effect on blood transfusion may not be an accurate indicator of the effect of TXA on surgical bleeding.

Clinical trials of TXA in surgery usually report the mean blood loss in each group. Previous systematic reviews have combined these data to obtain the average difference in mean blood loss between TXA and control groups. However, the usefulness of such a measure is questionable. It would be surprising if TXA reduced blood loss by the same volume in surgical procedures that involved different amounts of bleeding. On the other hand, it may be reasonable to expect a similar percentage reduction in blood loss with TXA.

The objective of this study was to examine whether the effect of TXA on blood loss varies with the extent of surgical bleeding. The magnitude of the percentage reduction in blood loss with TXA was estimated, and how the effect varies by type of surgery, timing of TXA administration, trial quality and dosage was assessed.

Methods

A systematic review of randomized clinical trials of TXA in surgical patients was conducted. The methods used to identify trials for the review have been described in detail elsewhere[1]. In brief, a comprehensive search was undertaken for all randomized clinical trials comparing intravenous TXA with placebo or no intervention in elective or emergency surgery. Two authors screened

the search output and the full texts of all eligible trials were obtained. Information was extracted on patient characteristics, type of surgery, dose and timing of TXA administration and average blood loss (mean and standard deviation). The risk of bias associated with sequence generation, allocation concealment, blinding and the completeness of outcome data was assessed for each trial.

Statistical analysis

To explore the relationship between the reduction in blood loss with TXA and the extent of bleeding, for each trial the mean blood loss in the TXA group was plotted against the mean blood loss in the control group. This relationship was examined using linear regression estimated using a Bayesian model as proposed by Thompson *et al.*[2] to account for random sampling error in the estimates of the regression variables (in the sample means from each trial). Statistical details of the model are given in *Appendix S1* (supporting information).

To quantify the effect of TXA on the percentage reduction in blood loss, a meta-analysis using both fixed-effect and random-effects models was conducted. For the purpose of the meta-analysis, blood loss data were log-transformed and the analysis was conducted using the transformed values. The formulae used for the transformations are given in *Appendix S1* (supporting information). A meta-analysis (using arithmetic means) of the differences in means using the transformed blood loss data corresponds to a meta-analysis (using geometric means) of the ratio of means in the original scale. The pooled estimates were back-transformed to give the blood loss ratios and 95 per cent c.i. on the original scale. Statistical heterogeneity was examined by visual inspection of forest plots, the I^2 statistic and the χ^2 test.

Subgroup analyses were undertaken to assess the effect of TXA by the type of surgery, timing of TXA administration (preincision, postincision), allocation concealment (adequate, unclear, inadequate) and type of comparator (placebo or no intervention). Heterogeneity between subgroups was assessed using the χ^2 test (fixed-effect analysis only). Finally, a random-effects meta-regression was carried out to investigate the association between the effect of TXA on blood loss and the total dose of TXA (mg/kg) as a continuous variable. If a fixed dose was used in the trials (for example 1000 mg), it was converted to milligrams per kilogram by dividing by 70 kg. A funnel plot was inspected for the presence of small study effects. STATA® version 12 (StataCorp, College Station, Texas, USA) statistical software[3] was used for all analyses.

Results

The trial selection process is shown in *Fig. 1*. One hundred and twenty-nine randomized clinical trials were identified. The characteristics of the included trials are summarized in *Table S1* (supporting information). Nine reports described multiarm trials involving a total of 23 eligible pair wise comparisons; each of these was included in the analysis as a separate trial. One hundred and four randomized comparisons, described in 90 articles[4–93], reported data on blood loss in a format suitable for this analysis. These trials involved a total of 8030 patients; 4224 received TXA and 3806 received a placebo or no intervention.

The trials involved cardiac (54 trials), orthopaedic (33), obstetric and gynaecological (7), head and neck (7), breast cancer (1), hepatic (1) and urological (1) surgery. Eighty trials gave TXA before surgical incision and 24 trials gave TXA after incision. Thirty-three trials were assessed as being adequately concealed (low risk of bias), and five trials as inadequately concealed (high risk of bias). The remaining 66 trials presented insufficient information on allocation concealment to allow judgement and were rated as unclear. Seventy-five trials were placebo-controlled, whereas a no-intervention group was used as the control in the remaining 29 trials.

Effect of tranexamic acid on blood loss

The relationship between mean blood loss in the TXA group and in the control group is shown in *Fig. 2*. Mean blood loss in the TXA group increased as that in the control group increased, but to a lesser extent. The intercept of the regression line (dotted line) estimated by the Bayesian model was 4 (95 per cent c.i. −8 to 18) ml, a negligible value in the context of the observed blood loss estimates. The Bayesian model corresponded closely with the regression line predicted, assuming a constant percentage reduction in blood loss (dashed line) and an intercept of zero.

The summary results of a fixed-effect meta-analysis of the percentage reduction in blood loss with TXA are shown in *Fig. 3*. A forest plot showing the estimates from each trial is shown in *Fig. S1* (supporting information). The back-transformed pooled ratio of blood loss with TXA was 0·66 (95 per cent c.i. 0·65 to 0·67; $P < 0·001$), indicating that TXA reduced blood loss by 34 per cent. There was substantial statistical heterogeneity between trials ($I^2 = 83$ per cent). There was heterogeneity in the magnitude of effect by type of surgery, although the extent of the variation was small. All of the subgroup estimates were consistent with a reduction in blood loss, and all but one was statistically significant at the 5 per cent level. TXA had a greater effect on blood loss when

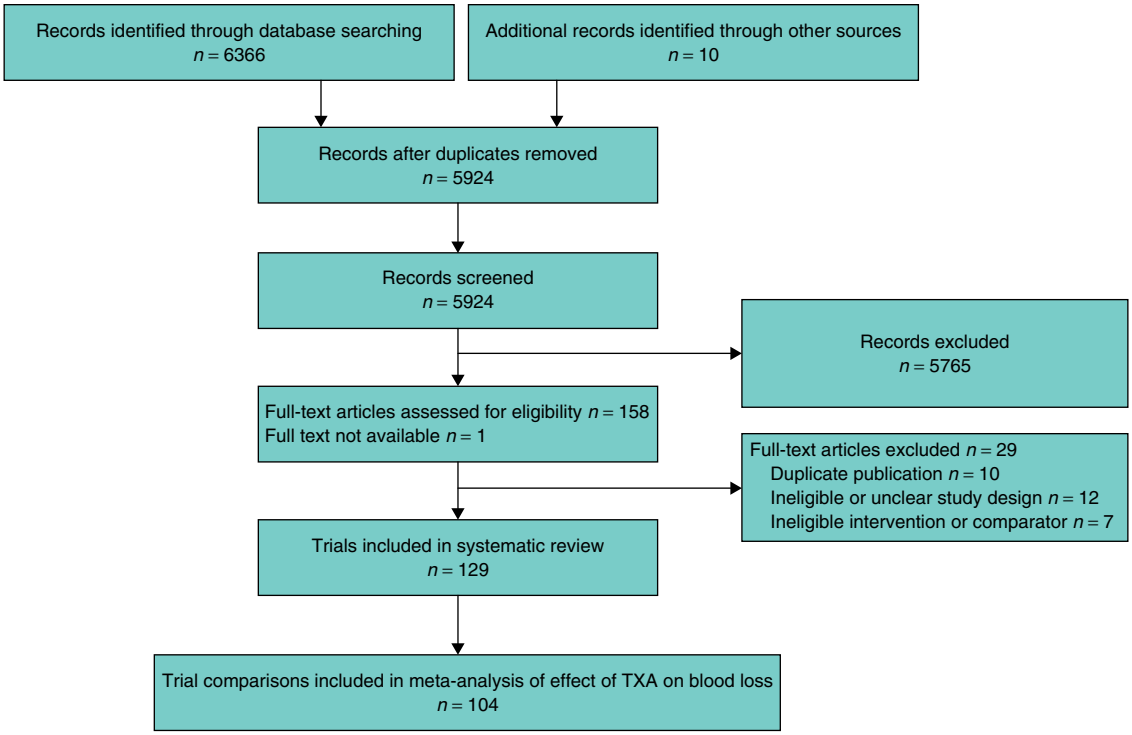

Fig. 1 PRISMA flow diagram for selection of trials. TXA, tranexamic acid

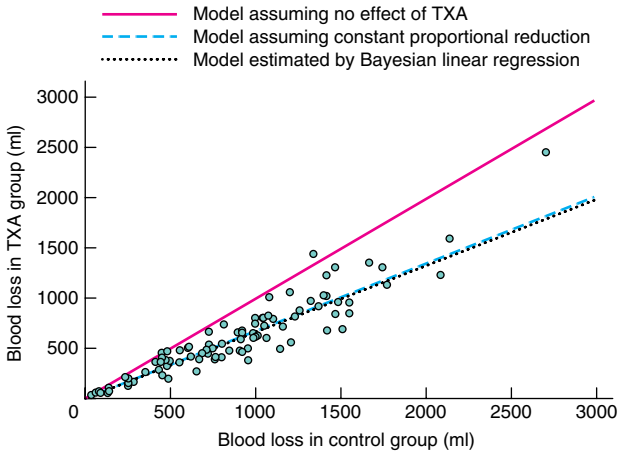

Fig. 2 Mean blood loss in tranexamic acid (TXA) group *versus* control group, with regression lines from models assuming no effect of TXA, a constant proportional reduction, and estimated by Bayesian linear regression

given after incision, although the difference between the preincision and postincision estimates was small. There was heterogeneity in the magnitude of effect by adequacy of allocation concealment. When the analysis was restricted to the 33 adequately concealed trials, TXA reduced blood loss by 30 per cent (effect estimate 0·70, 95 per cent c.i. 0·68 to 0·72; $P < 0·001$). There was no evidence for heterogeneity in the estimated effects of TXA compared with either placebo or a no-intervention control group. The results from random-effects meta-analyses were similar to those of the fixed-effect analyses, and are shown in *Table S2* (supporting information).

A fixed dose was converted to the equivalent milligram per kilogram dose in 21 trials. The total dose of TXA used in the trials ranged from 5·5 to 300 mg/kg. The median dose was 22 mg/kg, with the majority of trials (70 per cent) using a total dose of 30 mg/kg or less. Results from the meta-regression suggested that the effect of TXA on blood loss did not vary over the dose range assessed (coefficient 0·889, 95 per cent c.i. 0·787 to 1·004; $P = 0·059$).

There was no clear asymmetry in the funnel plot (*Fig. 4*).

Discussion

The results of this meta-analysis suggest that TXA reduces surgical blood loss by about one-third. Although the magnitude of the reduction differs by type of surgery and timing of TXA administration, the differences are small and unlikely to be clinically important. A total dose of 1 g is likely to be sufficient for most adults, and there is no evidence to support the use of higher doses.

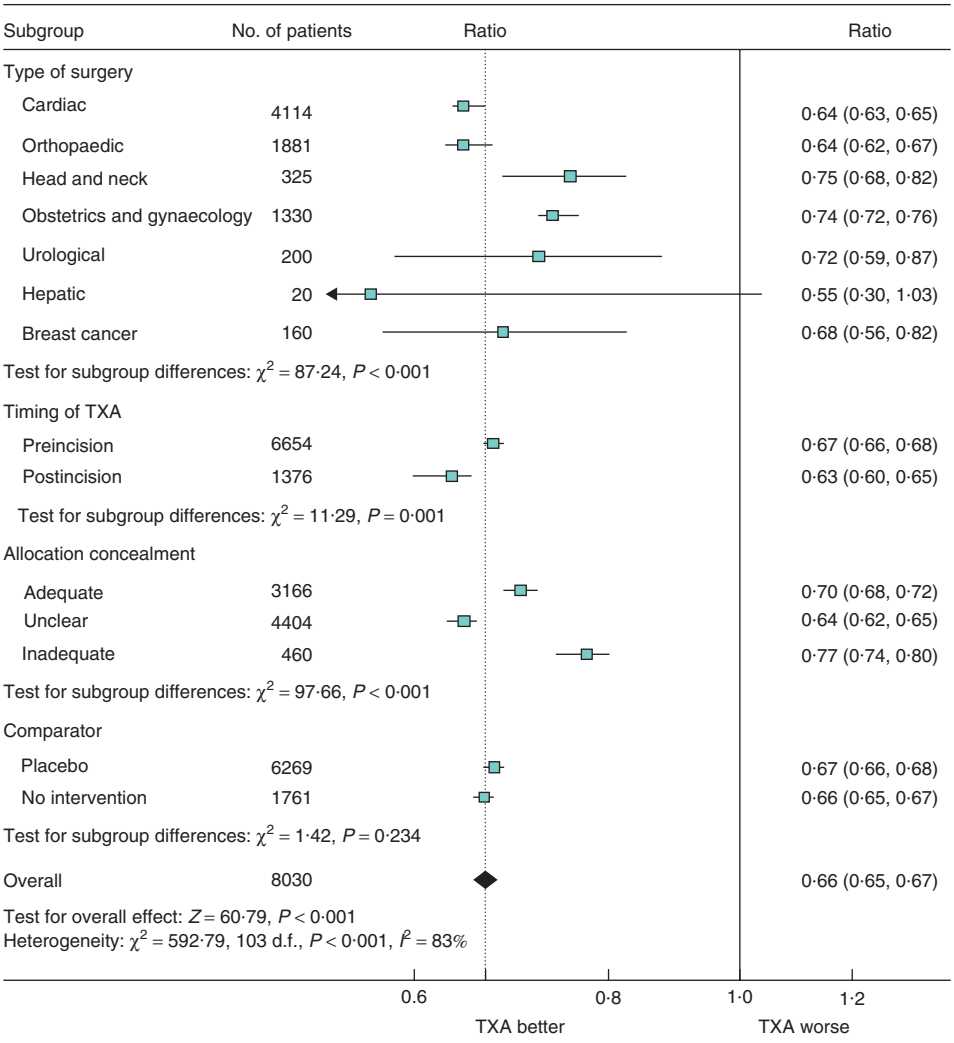

Fig. 3 Forest plot of the effect of tranexamic acid (TXA) on blood loss stratified by type of surgery, timing of TXA administration, adequacy of allocation concealment and type of comparator. A fixed-effect model was used for meta-analysis. Effect estimates are back-transformed ratios of geometric means with 95 per cent confidence intervals. The overall pooled estimate is marked by the diamond and dotted line

The validity of these results depends on the quality of the included trials, and many were of low quality. Less than a third of trials were judged to be at low risk of bias on the basis of allocation concealment. Nevertheless, even when the analysis was restricted to adequately concealed trials, the effect of TXA on blood loss remained large and highly statistically significant. Statistical heterogeneity between trials was substantial and was not explained by type of surgery, trial quality, timing of TXA administration or dose. Differences in the methods used to estimate blood loss, the duration over which blood loss was measured and other aspects of trial quality may explain some of the heterogeneity. The subgroup analyses showed that the effect of TXA on blood loss varied by type of surgery, trial quality and timing of TXA. However, the extent of the variation was small and the clinical importance of such small variations is questionable.

There was no obvious asymmetry in the funnel plot, but reporting bias remains a concern, particularly as about one-fifth of trials were not included in the analysis owing to unsuitable data or inadequate reporting. If many of these or other unpublished trials showed little or no effect of TXA on blood loss, the analysis would have overestimated the treatment effect. However, in consideration of the magnitude and precision of the effect, it is unlikely that any such bias would account for all of the observed effect.

The reduction in bleeding with TXA is almost identical to the reduction in the risk of receiving a blood transfusion

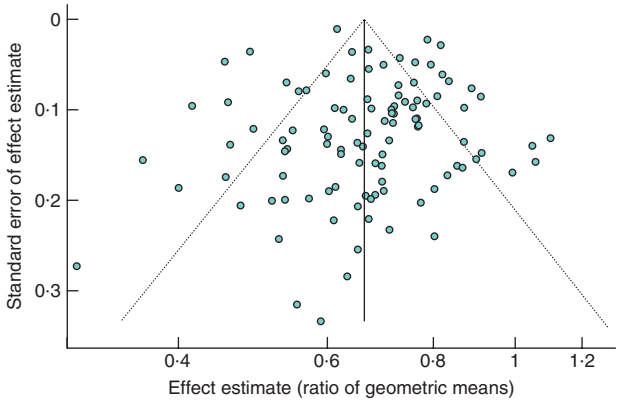

Fig. 4 Funnel plot with pseudo 95 per cent confidence intervals for meta-analysis of the effect of tranexamic acid on blood loss

with TXA, suggesting that, in surgery, transfusion may be closely titrated to blood loss. This may not be the case in injured patients. The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial found that early administration of TXA reduced the risk of death from bleeding by about one-third, but there was no clear reduction in the risk of receiving a blood transfusion[94,95].

Although there is reliable evidence that TXA reduces bleeding and blood transfusion in surgery, its effect on other important outcomes including death and thromboembolic events remains uncertain[1]. There is no evidence that it increases the risk of thromboembolic events, but this is a theoretical concern that may deter some surgeons from using TXA. These uncertainties need to be resolved before TXA can be recommended for routine use in surgery.

The apparent lack of a dose–response relationship across the range of doses examined (5·5–300 mg/kg) has important implications for the use of TXA in surgery. TXA crosses the blood–brain barrier and there is some evidence from observational studies of patients undergoing cardiac surgery that high-dose TXA (100 mg/kg or more) may cause seizures[96,97]. The present results imply that the clinical benefit of TXA on bleeding can be achieved at doses much lower than those associated with such adverse effects. Indeed, a total dose of about 14 mg/kg (or about 1 g in adults) appears to be sufficient for most patients.

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Further details of statistical methods (Word document)

Fig. S1 Fixed-effect meta-analysis of the effect of tranexamic acid on surgical blood loss (all trials) (Word document)

Table S1 Characteristics of included trials (Word document)

Table S2 Results of random-effects meta-analysis of the effect of tranexamic acid on blood loss stratified by type of surgery, timing of administration, adequacy of allocation concealment and type of comparator (Word document)