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Systematic review

Does tranexamic acid prevent postpartum haemorrhage? A systematic review of randomised controlled trials

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Background Postpartum haemorrhage is the leading cause of maternal mortality. Tranexamic acid (TXA) reduces surgical haemorrhage and the risk of death in bleeding trauma patients.

Objectives To assess the effects of TXA on risk of postpartum haemorrhage and other clinically relevant outcomes.

Search strategy We searched the MEDLINE, CENTRAL, EMBASE, PubMed, ClinicalTrials.gov and WHO ICTRP electronic databases to May 2015.

Selection criteria Randomised controlled trials comparing TXA with no TXA or placebo in women giving birth vaginally or by caesarean section.

Data collection and analysis Two authors extracted data and assessed the risk of bias for each trial. Because of data concerns we did not conduct a meta-analysis.

Main results We found 26 trials including a total of 4191 women. Examination of the trial reports raised concerns about the quality of the data. Eight trial reports contained identical or similar text and there were important data inconsistencies in several trials. Two trials did not have ethics committee approval. Meta-analysis of baseline variables suggested that randomisation was inadequate in many trials.

Conclusions There is no reliable evidence that TXA prevents postpartum haemorrhage during childbirth. Many of the trials conducted to date are small, low quality and contain serious flaws.

Keywords Postpartum haemorrhage, systematic review, tranexamic acid.

Tweetable abstract No evidence that TXA prevents postpartum haemorrhage. Existing trials are unreliable, with serious flaws.

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Introduction

Postpartum haemorrhage (PPH), one of the most common obstetric emergencies, occurs in about 10% of deliveries.[1] It is the leading cause of maternal mortality worldwide, responsible for about 50 000 deaths each year.[2] Because hysterectomy is sometimes carried out to control the bleeding, PPH deprives thousands of women of their ability to bear children. Anaemia is another important consequence that limits a mother's well-being and her ability to work and care for children.[3]

Tranexamic acid (TXA) reduces bleeding by inhibiting the breakdown of fibrin blood clots. The WOMAN trial is currently evaluating the effect of TXA on death and hysterectomy in women with established PPH.[4] However, for many women, treatment of PPH is too late. Over one-third of pregnant women in the world are anaemic and many are severely anaemic.[5] In these women, even moderate bleeding can be life-threatening and, by worsening their anaemia, can cause disabling fatigue that limits their ability to care for themselves and their baby.[6] TXA given at the time of delivery could prevent severe postpartum bleeding. Plasma t-PA (the main fibrinolytic activator) doubles within an hour of delivery, probably due to the trauma of childbirth.[7]

We conducted a systematic review of randomised controlled trials to assess the effects of TXA on the risk of postpartum haemorrhage and other clinically relevant outcomes.

Methods

We specified the methods in advanced and registered the review on PROSPERO (CRD42015020670).

Selection criteria and search strategy

We searched for randomised controlled trials comparing TXA with no TXA or a placebo in women delivering vaginally or by caesarean section. The primary outcome was the number of women with a clinical diagnosis of postpartum haemorrhage. Trials of TXA for the treatment of established postpartum haemorrhage were not eligible. Secondary outcomes were death, blood loss, blood transfusion, thromboembolic events (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism), surgical intervention, maternal well-being and quality of life, and adverse events in baby.

Eligible trials were identified from a register of randomised controlled trials of anti-fibrinolytic drugs maintained by the London School of Hygiene & Medicine Clinical Trials Unit (LSHTM CTU). The register contains records of trials identified through searches of MEDLINE, CENTRAL, EMBASE, PubMed, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. Each database was searched using a combination of subject headings and keywords (Appendix S1). In addition, we checked reference lists of relevant articles and searched the internet using the Google search engine for further potentially eligible trials. The searches were run to 13 May 2015 and were not restricted by date, language or publication status.

Procedures

One author screened the titles and abstracts of the search output to identify potentially eligible trials. The full text of these reports was then retrieved and assessed for eligibility. Data on the number of participants, type of delivery, dose and timing of TXA, type of comparator and outcome data were extracted by two authors using a form developed specifically for the review. We used the Cochrane Collaboration tool for assessing the risk of bias. The risk of bias assessments was based on the information presented in the trial report.[8] We assessed the sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting as being at low, high or unclear risk of bias for each trial.

Statistical analysis

For dichotomous outcomes, we calculated risk ratios and 95% confidence intervals. For continuous outcomes, we calculated the mean difference and 95% confidence interval. However, for blood loss, we estimated the proportional change in blood loss with TXA. Full details of the method used are described elsewhere.[9] In brief, we expressed the change in blood loss with TXA as a proportion of the blood loss in the control group. As estimates of average blood loss are not normally distributed, we transformed blood loss data into a logarithmic scale and conducted the analysis using the transformed values. A meta-analysis of the differences in means using the transformed data on blood loss corresponds to a meta-analysis of the ratio of the geometric means on the original scale. The estimates were back-transformed to give the blood loss ratios and 95% confidence intervals on the original scale. If sufficiently homogeneous in terms of patients, intervention and outcome measurement, we planned to pool the trial data using the fixed effect model.

We planned to conduct subgroup analyses to examine whether the effect of TXA on the risk of PPH varied according to whether the women were anaemic at baseline (anaemic = Hb <11 g/dl and non-anaemic = Hb ≥11 g/dl). We also planned a sensitivity analysis restricted to trials at low risk of bias for allocation concealment. Analyses were carried out using STATA version 13 and REVMAN version 5.3.5. We reported the review in accordance with the PRISMA Statement (Table S1).

Results

Trial characteristics

We identified 31 reports[10–40] describing 26 trials involving a total of 4191 women (Figure S1). The trial reports were published between 2001 and 2015. Five trials were Master's degree projects that were later published in medical journals. Two trials were reported as conference abstracts only.

The characteristics of the included trials are shown in Table S2. The median sample size was 120 (min–max = 74–740). They were conducted in China (n = 3), Egypt (n = 2), India (n = 9), Iran (n = 5), Malaysia (n = 1), Pakistan (n = 2), Turkey (n = 3) and Ukraine (n = 1). All but one were single-centre trials. Twenty-two trials assessed the effect of TXA in women giving birth by caesarean section and four in women giving birth vaginally. One trial was restricted to anaemic women (Hb 7–10 g/dl).

TXA was given within 30 minutes prior to incision in all of the caesarean delivery trials except for one in which TXA was administered at delivery of anterior shoulder. Of the four trials involving vaginal delivery, TXA was given at delivery of anterior shoulder in three and at delivery of the placenta in one. The TXA dose ranged from 0.5 to 1 g. TXA was compared with placebo in 13 trials and with a no-TXA group in 13 trials.

The number of patients allocated to each group was not reported in one trial and so the data could not be used. The frequency of PPH was reported in 13 (50%) trials, blood loss in 24 (92%), thromboembolic events in 16 (62%), death in six (23%), surgical intervention in five (19%), and blood transfusion in 10 (38%). None of the trials collected data on maternal well-being or quality of life.

Risk of bias

A summary of the risk of judgements is shown in Figure S2. The method used to generate the allocation sequence was

adequate in eight trials and inadequate in four. The remaining 14 trials did not describe the method used and so the risk was unclear. Allocation concealment was adequate in four, inadequate in seven, and unclear in 15 trials. Blinding was adequate in 11 trials, inadequate in 13, and unclear in two trials. There were no missing outcome data in four trials (low risk of bias). However, there were post-randomisation exclusions in three trials (high risk of bias). For the remaining 19 trials, insufficient information was reported to judge the risk of bias from missing outcome data. In the one trial that was prospectively registered, comparison of prespecified and reported outcomes suggested selective outcome reporting. We could not determine the risk of bias from selective outcome reporting for the remaining trials, which were either retrospectively registered ($n = 5$) or not registered ($n = 20$).

Data reliability

Several reports raised concerns about the data and prompted further investigations. Eight reports contained sections of identical or very similar text despite purporting to be different trials (Table S3), in addition, many of the results sections contained discrepancies and other errors. We therefore sought further information from the authors of all trial reports to reassure ourselves about the reliability of the data. We identified contact information for as many authors as possible. Each author was contacted and asked to provide the dates when the first and last patients were randomised; a copy of the ethics committee approval; and the anonymised individual patient data. Where possible we also contacted the ethics committee for confirmation of their approval.

We received responses for 13 (50%) trials (Table S4). One author declined to provide the information requested. Authors of nine trials confirmed recruitment dates, one did not have a record of the dates, and one did not include this information in the response. We received a copy of the ethics approval for 10 trials, one of which was granted after the start of recruitment. Two trials did not receive ethics approval. In one case, an author explained that the trial was undertaken for a student thesis and formal approval from the ethics committee was not required (this was confirmed in a separate response from the ethics committee). In the other, although the trial report stated that ethics approval had been obtained, the author stated this was not in fact the case. This was confirmed by the ethics committee, who said that they had no record of the trial. No explanation was offered as to why approval was not obtained.

Seven of the 13 trials for which we received a response sent individual patient data. The authors of two trials did not respond to this part of our request and one author of two trials explained that he was unable to send us the data due to the theft of the laptop on which the data for both trials were stored.

We then explored the success of the randomisation process by conducting meta-analyses of selected baseline variables. As recommended by Clark et al.[41] we meta-analysed age as well as baseline haemoglobin (Hb), which we identified as another relevant prognostic covariate. The premise of this analysis is that if the trials are properly randomised, there will be no heterogeneity, i.e. $I^2 = 0\%$ and any difference in baseline variables will be minimal and the result of random error.[41] Figures S3 and S4 show the results of the meta-analyses of age and baseline Hb. There was no heterogeneity ($I^2 = 0\%$) observed for age. However, there was a statistically significant difference between groups suggesting that women allocated to the TXA group were younger than those in the control ($P = 0.01$), although this difference was not observed when the analysis was restricted to adequately concealed trials ($P = 0.59$). There was substantial heterogeneity between trials for baseline Hb ($I^2 = 67\%$) and a statistically significant difference between groups indicating that women allocated to the TXA group had a lower Hb at baseline than those in the control ($P = 0.02$). Substantial heterogeneity remained when the analysis was restricted to adequately concealed trials ($I^2 = 62\%$), although the difference in Hb between groups was no longer statistically significant ($P = 0.79$).

Data analysis

Although the patients, interventions and outcomes were sufficiently homogeneous to pool the data, because of our concerns about trial quality and data reliability we did not conduct a meta-analysis. However, effect estimates and 95% CIs were calculated and presented as Forest plots (Figures 1–3). We stratified the trials according to whether the final report contained similar text. Thirteen trials presented data on the number of women who developed postpartum haemorrhage. There was variation in the threshold used to diagnose PPH. Four trials applied the usual definition of blood loss ≥1000 ml after caesarean delivery or ≥500 ml after vaginal delivery. The remaining trials used other, lower thresholds, including ≥500 ml after caesarean delivery or ≥400 ml after vaginal delivery. Because none of the trials were prospectively registered, we cannot discount the possibility that the selection of these thresholds was *post hoc* and data-driven. In all trials, fewer women in the TXA group developed PPH than in the control group.

Twenty-four trials presented data on average blood loss in both groups. All of the effect estimates are consistent with less blood loss in the TXA group; the difference is statistically significant in all but one trial. There is notable variation in the magnitude of the effect estimates.

Nine trials reported blood transfusion data. There were no events in two trials. In all of the remaining seven trials,

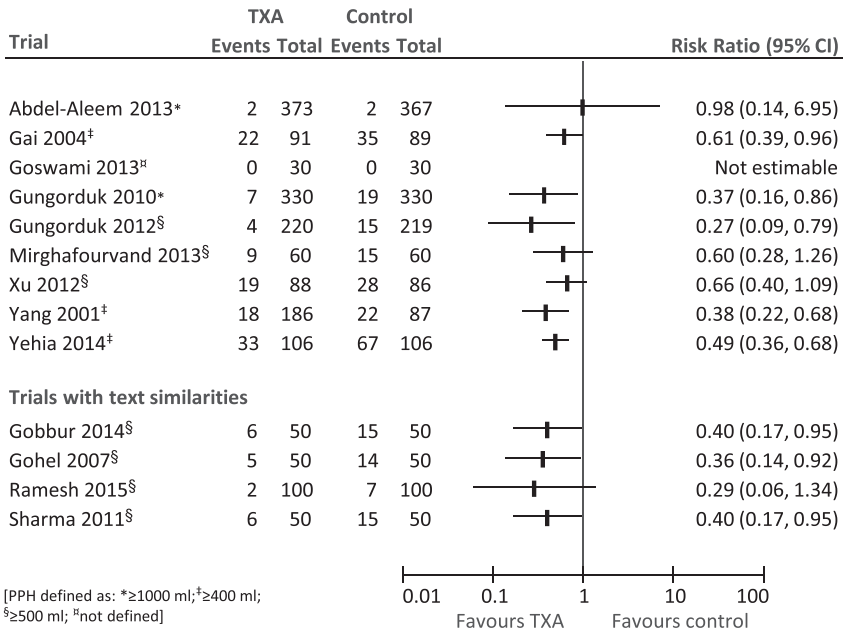

Figure 1. Results of trials assessing the effect of TXA on postpartum haemorrhage.

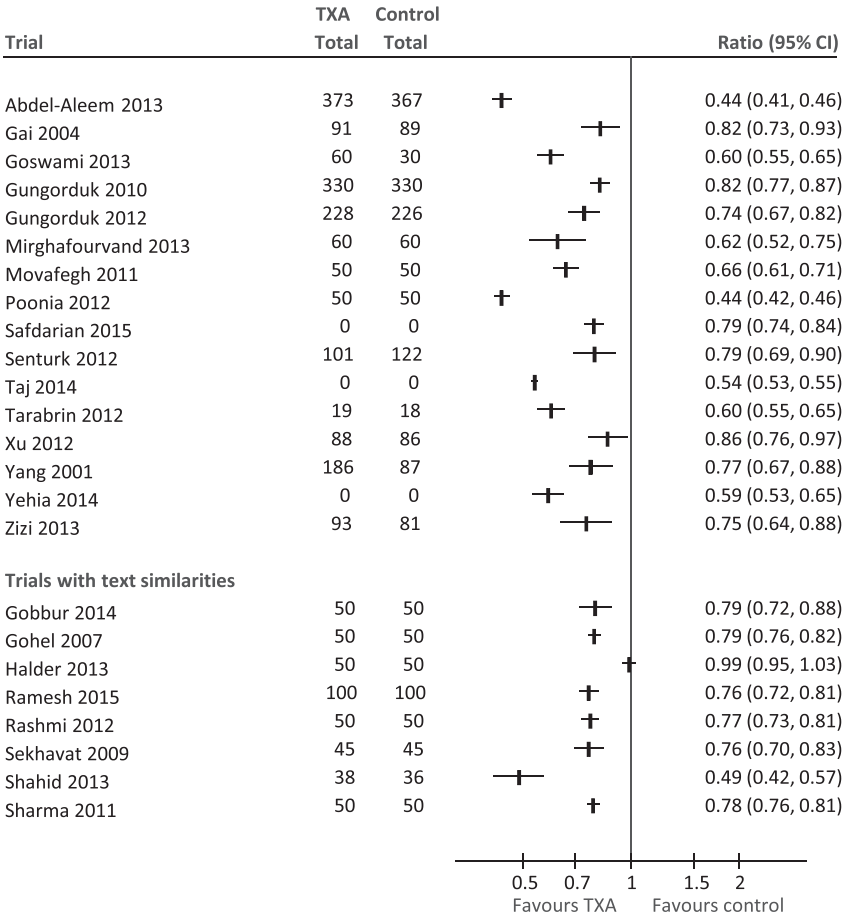

Figure 2. Results of trials assessing the effect of TXA on blood loss.

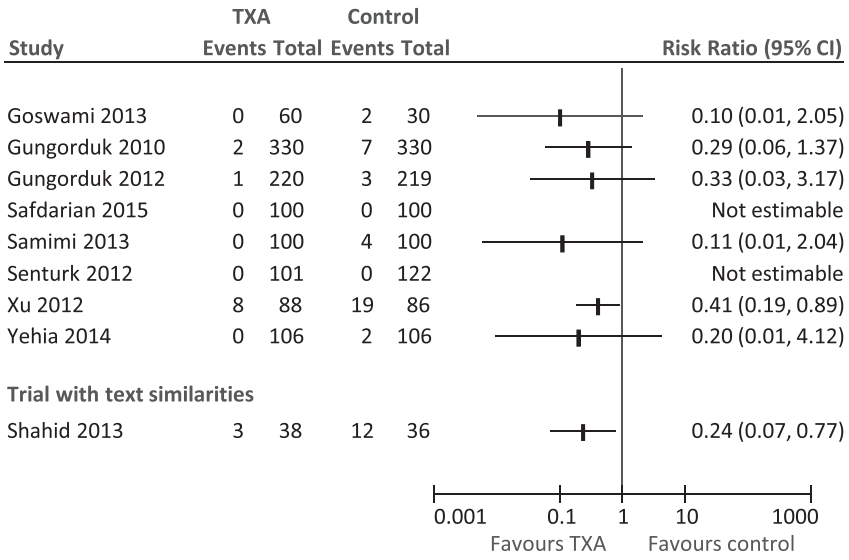

Figure 3. Results of trials assessing the effect of TXA on blood transfusion.

fewer women in the TXA group received a blood transfusion than those in the control group. There were no deaths, surgical interventions, or cases of myocardial infarction, stroke or pulmonary embolism in any of the trials reporting these outcomes. In one trial, four women suffered a deep vein thrombosis, there was no difference in risk between the groups (TXA 2/88 versus control 2/86; RR = 0.98, 95% CI 0.14–6.78).

Discussion

Main findings

Worldwide, over 10 million women experience a postpartum haemorrhage each year. About 50 000 women die, many more lose their ability to bear children, and hundreds of thousands suffer debilitating fatigue from anaemia. TXA is an inexpensive, widely available medicine that has been shown to reduce bleeding in surgery and reduce the risk of death in bleeding trauma patients.[42,43] It is therefore unsurprising that there is interest in its role in the prevention of postpartum haemorrhage. However, our review shows that most trials of TXA are small, low quality, single-centre studies. We found that many trial reports shared similar or identical text, and contained important errors or inconsistencies. Two trials were conducted without ethics committee approval and only one was prospectively registered.

Strengths and limitations

Due to concerns about data quality and reliability we did not conduct a meta-analysis. When examined separately, the results of the individual trials were largely consistent with evidence from surgical bleeding, with most reporting less bleeding with TXA. However, the criteria used to diagnose PPH varied between trials and the absence of blinded outcome assessment in many trials may have introduced bias. Also, because the trials are too small to assess the effect of TXA on maternal health outcomes and none measured maternal well-being, the clinical importance of any reduction in bleeding is uncertain.

Most systematic reviews assume that trial reports provide an accurate description of the methods and results. However, after finding that eight trials contained identical text and that some of the trial results were also similar, we were obliged to question this assumption. We therefore asked the authors of all trials to provide dates of recruitment, a copy of the ethics committee approval, and the anonymised individual patient data in an attempt to assess their reliability. We received a response for only half of the included trials and less than half of these provided all the information requested. Moreover, the meta-analysis of baseline variables suggests that the randomisation process was inadequate in many trials. Although our review aimed to include only randomised controlled trials, many of the included trials were not properly randomised and were imbalanced for key prognostic variables.

Interpretation (in the light of other evidence)

Other systematic reviews have assessed the effect of TXA on obstetric bleeding.[44–46] However, ours is the first to describe the scale and nature of deficiencies in the evidence that go beyond the standard risk of bias assessment. Unless these deficiencies are brought to the attention of the maternal health community, treatment decisions could be based on unsound evidence, putting women at risk. Indeed, some of the trials have already informed the WHO

recommendations on the use of TXA for the treatment of postpartum haemorrhage.

As well as highlighting the poor quality of trial research in this area, the process of conducting this review has brought to our attention the lack of guidance on how systematic reviewers should deal with trial quality concerns that go beyond those assessed by the standard risk of bias approach.

Furthermore, because we were unwilling to ignore these concerns, we devised our own approach to investigating them. We do not claim that our approach is the best and we welcome ideas on more effective ways to deal with similar situations in the future.

Conclusions

Although reducing maternal mortality has been a development goal for 15 years, this review suggests that in some areas the quantity and quality of the research needed to support this humanitarian aspiration is inadequate and is not commensurate with the level of political ambition. We do not doubt that most of the included trials were conducted in good faith with the patients' interests in mind. However, a problem of such global health importance requires a strategic response from professional research teams rather than the efforts of concerned clinicians at a single hospital. Large, high quality, multi-centre trials with endpoints that matter to women are urgently needed.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

KK, IR and HS designed the study. KK screened the search output and extracted data with assistance from HS. KK carried out the analyses. KK wrote the manuscript with contributions from IR and HS. The final version was approved by all authors.

Details of ethics approval

Not required.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow diagram of the selection of trials.

Figure S2. Summary of the risk of bias judgements for each methodological quality domain ('L' = Low, 'U' = unclear, 'H' = High).

Figure S3. Forest plots showing the difference in age between women allocated to the TXA group and those allocated to the control group.

Figure S4. Forest plots showing the difference in haemoglobin between women allocated to the TXA group and those allocated to the control group.

Table S1. PRISMA Checklist.

Table S2. Characteristics of included trials.

Table S3. Selected extracts from eight included trials containing identical or similar text.

Table S4. Summary of response to review authors' requests for additional trial information.

Appendix S1. MEDLINE (Ovid) search strategy. ■

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