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Tranexamic acid for preventing postpartum blood loss after cesarean delivery: a systematic review and meta-analysis of randomized controlled trials

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Key words
Tranexamic acid, cesarean delivery, postpartum hemorrhage

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Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Abstract

Introduction. There are several published clinical trials of the use of tranexamic acid (TXA) in an obstetric setting, but no consensus on its use or guidelines for management. *Material and methods.* The aim of this meta-analysis was to evaluate the effectiveness of TXA in reducing blood loss when given prior to cesarean delivery. We performed a systematic search in electronic databases. We included all randomized controlled trials comparing the use of TXA prior to cesarean delivery with controls (either placebo or no treatment). *Results.* Nine trials with 2365 women were included in the analysis. Women who received TXA had significantly less postpartum blood loss, a lower drop in hemoglobin and a lower incidence of postpartum hemorrhage and severe postpartum hemorrhage compared with controls. Moreover, the number of women who needed additional uterotonic agents was significantly lower in the TXA group than in controls. The percentage of women who required blood transfusions at, or immediately after, cesareans was significantly lower in the intervention group than in the controls. There was no difference in the incidence of thromboembolic events in the two groups. *Conclusions.* Prophylactic TXA given before cesarean skin incision in women undergoing cesarean delivery, under spinal or epidural anesthesia, significantly decreases blood loss, including postpartum hemorrhage and severe postpartum hemorrhage, in addition to the standard prophylactic oxytocin given after delivery of the neonate. The effect of TXA on thromboembolic events and mortality as well as its use in high-risk women should be investigated further.

Abbreviations: CD, cesarean delivery; CI, confidence interval; PPH, postpartum hemorrhage; RCT, randomized controlled trials; RR, relative risk; TXA, tranexamic acid.

Introduction

The World Health Organization defines postpartum hemorrhage (PPH) as "blood loss from the birth canal in excess of 500 mL during the first 24 h after delivery" (1),

Key Message

Prophylactic tranexamic acid given before cesarean skin incision significantly decreases blood loss.

although currently there is a debate about what definition to use (2).

Postpartum hemorrhage is responsible for about 25% of maternal deaths worldwide (1), and 12% of survivors will have severe anemia (1). Clinically, it is associated with weakness, sweating, and tachycardia, and with hemodynamic collapse occurring at losses of between 35 and 45% of blood volume (3). One of the most common complications of cesarean delivery (CD) is PPH, which can be life-threatening. Recently, CD rates have increased to as high as 25–35% in many areas of the developed world (4).

Antifibrinolytic agents, mainly tranexamic acid (TXA), have been demonstrated to reduce blood loss and the need for transfusion requirements in various non-obstetric surgeries (5–8). There are several published clinical trials for the use of TXA in the obstetric setting as well (9–16), but no consensus on its use or guidelines for management. Moreover, no meta-analysis evaluated specifically the efficacy of TXA given prophylactically at the time of CD to reduce blood loss.

The aim of this meta-analysis of randomized controlled trials (RCTs) was to evaluate the effectiveness of TXA given prior to CD to reduce blood loss in women undergoing CD.

Material and methods

The research protocol was designed a priori, defining methods for searching the literature, including and examining articles, and extracting and analyzing data. Searches were performed in MEDLINE, OVID, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE and the Cochrane Central Register of Controlled Trials with the use of a combination of the following text words: "cesarean", "postpartum hemorrhage", "caesarean", "randomized" and "tranexamic acid", from the inception of each database to August 2015. No restrictions in language or geographic location were applied. The articles, including their references, were initially scanned by two authors (G.S., M.B.) based on titles and abstracts.

We included all RCTs comparing the use of TXA prior to CD with controls (either placebo or no treatment). Quasi-randomized trials (trials in which allocation was done on the basis of a pseudo-random sequence, e.g. odd/even hospital number or date of birth, alternation) were excluded. Eligibility criteria were limited to intravenous TXA given prior to CD. Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No. CRD42014014826). The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement (17).

Database searching and data abstraction was completed by two independent investigators (G.S., M.B.). Each investigator independently abstracted data from each study separately onto custom-made data collection forms. Differences were reviewed and further resolved by common review of the entire data. All authors were contacted for missing data.

The risk of bias in each included study was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (18). Seven domains

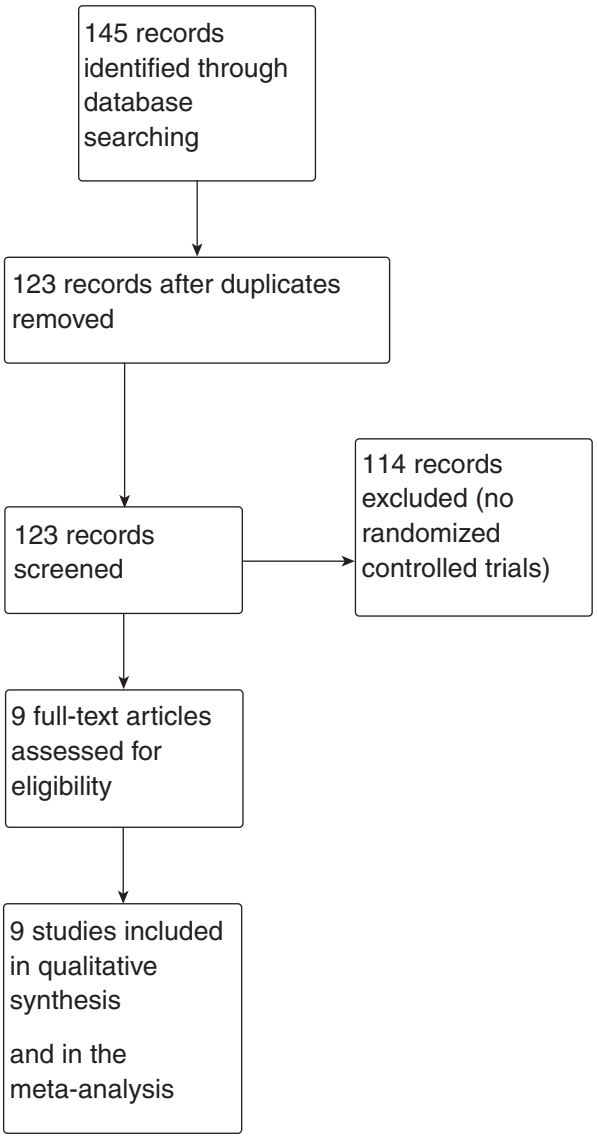

Figure 1. Flow diagram of studies identified in the systematic review. Prisma template (Preferred Reporting Item for Systematic Reviews and Meta-analyses).

related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: (i) random sequence generation; (ii) allocation concealment; (iii) blinding of participants and personnel; (iv) blinding of outcome assessment; (v) incomplete outcome data; (vi) selective reporting; and (vii) other bias. Review authors' judgments were categorized as "low risk", "high risk" or "unclear risk" of bias (18).

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated in the original trials. The primary outcome was postpartum blood loss, defined as the amount of blood loss (mL) in case of cesarean section, as defined in the trial. Secondary outcomes included incidence of PPH (i.e. blood loss more than 500 mL), severe PPH (i.e. blood loss more than 1000 mL), use of additional medical interventions to control PPH, thromboembolic events, hemoglobin and hematocrit drop 24 h after CD, blood transfusions at or immediately after cesarean, severe maternal morbidity (e.g. intensive care unit admission, hysterectomy, organ failure) and maternal adverse drug reactions. We planned a subgroup analysis using only placebo-controlled trials.

The data analysis was completed independently by authors (G.S., M.B.) using REVIEW MANAGER 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014). The completed analyses were then compared and any difference was resolved by review of the entire data and independent analysis. Statistical heterogeneity between studies was assessed using the Higgins I^2 statistic. In case of statistically significant heterogeneity (I^2 ≥50%) the random effect model of DerSimonian and Laird was used to obtain the pooled risk estimate, otherwise a fixed effect model was used. The summary measures were reported as relative risk (RR) or mean difference with 95% confidence interval (CI). Potential publication biases were assessed statistically using Begg's and Egger's tests. A p-value <0.05 was considered statistically significant.

Results

Nine RCTs which met inclusion criteria for this meta-analysis were analyzed (9–16,19). Figure 1 shows the flow

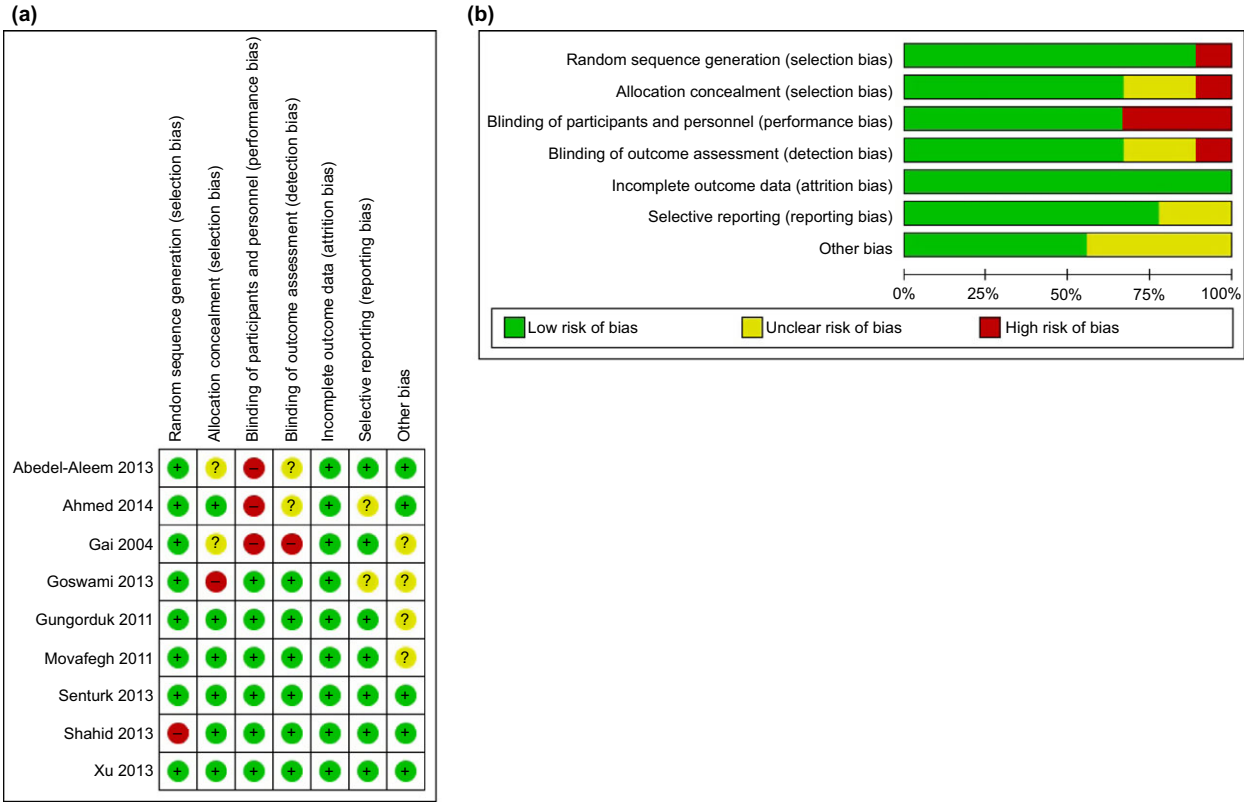

Figure 2. Assessment of risk of bias. (a) Summary of risk of bias for each trial; plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (b) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

Table 1. Descriptive data of included trials.

	Study location	Number of patients at randomization[a]	Intervention TXA i.v.	Control	Uterotonic standard prophylaxis[b]	Primary outcome	Time period for blood loss collection	Method for estimation blood loss
Gai 2004[9]	China	180 (91/89)	1 g, 10 min before incision, over 5 min	No treatment	Oxytocin 10 IU bolus and 20 IU infusion after delivery of neonate	Postpartum blood loss	From placenta delivery to 2 h post partum	Via a suction container (the volume was measured) and soaked gauze, pads and a specially designed operation table sheet were weighed.
Gungorduk 2011 [10]	Turkey	660 (330/330)	1 g, 10 min before incision, over 5 min	Placebo	Oxytocin 5 IU bolus and 30 IU infusion after delivery of neonate	Postpartum blood loss	From the skin incision to 48 h after CD	N/R
Movafegh 2011 [11]	Iran	100 (50/50)	10 mg/kg, 20 min before spinal anesthesia, over 10 min	Placebo	Oxytocin 10 IU infusion after delivery of placenta	Postpartum blood loss	From placenta delivery to 2 h post partum	Via a suction container (the volume was measured) and soaked gauze, pads and a specially designed operation table sheet were weighed
Abdel-Aleem 2013[12]	Egypt	740 (373/367)	1 g over 10 min before planned CD	No treatment	Oxytocin 5 IU bolus and 20 IU infusion after delivery of neonate	Postpartum blood loss	During and for 2 hours after the operation	Blood escaped from the vagina was collected in the plastic drape. The weight of dry towels was subtracted from the weight of wet towels
Xu 2013[13]	Germany	174 (88/86)	10 mg/kg, 20 min before spinal anesthesia, over 10 min	Placebo	Oxytocin 10 IU bolus and methylergometrine 0.4 mg after delivery of neonate	Postpartum blood loss	From placenta delivery to 2 h post partum	Via a suction container (the volume was measured) and soaked gauze, pads and a specially designed operation table sheet were weighed
Shahid 2013[14]	Pakistan	74 (38/36)	10 mg/kg slow infusion at least 10 min, before incision	Placebo	Oxytocin 5 IU bolus, methylergometrine 0.4 mg bolus and oxytocin 30 IU infusion after delivery of neonate	Postpartum blood loss	From placenta delivery to 2 h post partum	Via a suction container (the volume was measured) and soaked gauze, pads and a specially designed operation table sheet were weighed

Table 1. Continued

	Study location	Number of patients at randomization[a]	Intervention TXA i.v.	Control	Uterotonic standard prophylaxis[b]	Primary outcome	Time period for blood loss collection	Method for estimation blood loss
Senturk 2013[15]	German	223 (101/122)	1 g, 10 min before the incision, over 5 min	Placebo	Oxytocin 20 IU bolus after delivery of placenta	Postpartum blood loss	From the skin incision before the entrance of the intrauterine cavity and from the delivery of the placenta until the patients was in service room	The bleeding that occurred from the incision was soaked up using compresses that had known weights. The dry end wet pad has been measured by surgeon pre and postoperative period.
Goswami 2013 [19]	India	90 (60/30)	10 mg/kg over 20 min before incision15 mg/kg over 20 min before incision[c]	Placebo	Oxytocin 20 IU infusion after delivery of neonate	Postpartum blood loss	From placenta delivery to 6 h post partum	Via a suction container (the volume was measured), while post-operative blood loos was measured by weighing and numbering the vaginal pads
Ahmed 2014[16]	Egypt	124 (62/62)	10 mg/kg over 5 min before planned CD	No treatment	Oxytocin 10 IU bolus and Ergometrine 1 amp after delivery of neonate	Postpartum blood loss	From placenta delivery to 2 h post partum	Blood escaped from the vagina was collected in the plastic drape. The weight of dry towels was subtracted from the weight of wet towels
Total	–	2365 (1193/1172)	–	–	–	–	–	

CD, cesarean delivery; N/R, not reported; PPH, postpartum hemorrhage; TXA, tranexamic acid.

[a]Total number (*n* intervention/control).

[b]In both groups.

[c]Goswami et al., two intervention groups (T1 and T2).

diagram (PRISMA template) of information through the different phases of the review. The quality of RCTs included in our meta-analysis was assessed by the Cochrane Collaboration's tool (Figure 2). Most of the included studies had low risk of bias in "random sequence generation" and all of them had low risk of bias in "incomplete outcome data". All trials were rated as low risk of bias for selective outcome reporting and the overall risk of bias was low. Publication bias, assessed using Begg's and Egger's tests, showed no significant bias ($p = 0.61$ and $p = 0.51$, respectively).

Table 1 shows the characteristics of the included RCTs. Six studies used placebo as control. Of the 2365 women undergoing CD under spinal or epidural anesthesia included in the analysis, 1193 (50%) were randomized to TXA groups and 1172 (50%) to control. Six studies included only singleton gestations (9,11–14,16). Two studies included only women who planned to have a scheduled CD at ≥37 weeks (12,16). All studies used I g TXA (or 10 or 15 mg/kg) i.v. 10–20 min before skin incision or spinal anesthesia as intervention. One study enrolled two random intervention groups (10 and 15 mg/kg) (19). All included studies used oxytocin standard prophylaxis, usually after delivery of the neonate or, in two studies (11,15), after delivery of the placenta, in both intervention and control groups. Blood loss was measured as described in Table 1 in the different studies. The Indian RCT enrolled 90 women with anemia defined by authors as hemoglobin between 7 and 10 g/dL (19), while the rest of the RCT participants were low-risk women undergoing CD under spinal or epidural anesthesia.

Women who received TXA had a statistically significant lower postpartum blood loss (mean difference –160.27 mL, 95% CI −224.63 to −95.92) compared with women who did not receive it (Figure 3). The statistical heterogeneity within the studies was high ($I^2 = 97\%$) and therefore the random effect model of DerSimonian and Laird was utilized to obtain the pooled risk estimates for all outcomes.

Table 2 shows the pooled results for secondary outcomes. Women who were randomized to TXA had a significantly lower incidence of PPH, i.e. blood loss more than 500 mL (9.4 vs. 44.5%; RR 0.21, 95% CI 0.16–0.28), and of severe PPH, i.e. blood loss more than 1000 mL (1.2 vs. 2.9%; RR 0.42, 95% CI 0.19–0.92), compared with controls. The number of women who needed additional uterotonic agents was statistically significantly lower in the TXA than in the control group (4.2 vs. 7.3%; RR 0.54, 95%CI 0.36–0.81). Women who received TXA had a statistically significantly lower hemoglobin drop 24 h after CD compared with controls (mean difference −0.61 g/dL, 95% CI −1.04 to −0.18). The percentage of women who required blood transfusions at or immediately after cesarean was significantly lower in the intervention group than in the control group (1.9 vs. 5.7%; RR 0.33, 95% CI 0.19–0.58). No significant differences were found in the hematocrit drop (mean difference −0.66%, 95% CI −2.32 to 1.00). All studies specifically reported thromboembolic events. However, no cases of thromboembolic events in either group was found, except for one study (12) which reported four women who experienced thromboembolic events, two in the intervention and two in the placebo group [2/1133 (0.18%) vs. 2/1142 (0.17%); RR 0.98, 95% CI 0.13–7.09]. No maternal severe morbidity or adverse drug reactions were reported in either group (9–16).

In the sensitivity analysis of only placebo-controlled trials, women who received TXA had a statistically significantly lower postpartum blood loss (mean difference −136.75 mL, 95% CI −217.39 to −56.11; Figure 4), severe PPH (1.8 vs. 5.3%; RR 0.37, 95% CI 0.16–0.86), blood transfusion (2.1 vs. 6.3%; RR 0.33, 95% CI 0.19–0.58) and had a significantly lower hemoglobin drop (mean difference −0.19 g/dL, 95% CI −0.26 to −0.12) but a higher hematocrit drop 24 h after CD (mean difference 0.21%, 95% CI 0.15–0.28) compared with women who did not. Moreover, the number of women who

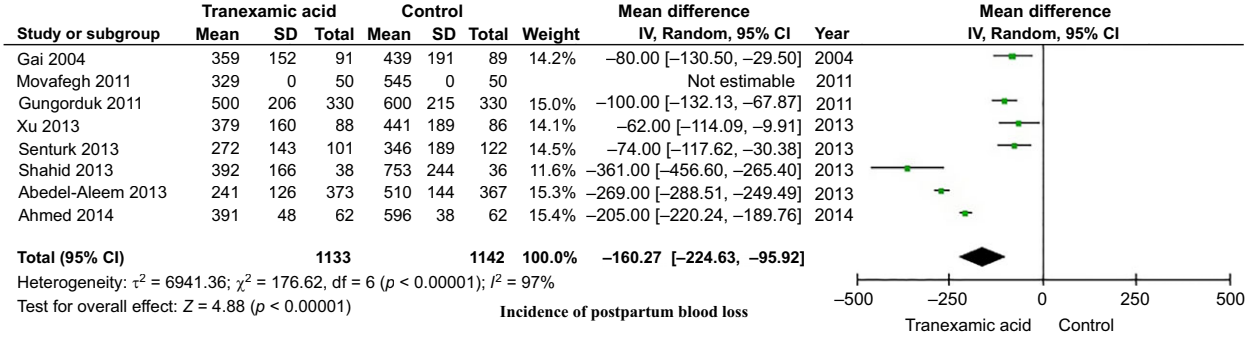

Figure 3. Forest plot for incidence of postpartum blood loss. CI, confidence interval; IV, independent variable; SD, standard deviation.

Table 2. Secondary blood loss-related outcomes.

	PPH	Severe PPH	Additional medications	Hb drop (g/dL)	HTC drop (%)	Thromboembolic events	Blood transfusion
Gai 2004[9]	22/91 (24.2%) vs. 35/89 (39.3%)	N/R	N/R	N/R	N/R	0/91 vs. 0/89	N/R
Gungorduk 2011[10]	N/R	7/330 (2.1%) vs. 19/330 (5.8%)	28/330 (8.5%) vs. 48/330 (14.5%)	N/R	2.7 ± 0.6 vs. 2.3 ± 0.2	0/330 vs. 0/330	2/330 (0.6%) vs. 7/330 (2.1%)
Movafegh 2011[11]	N/R	N/R	0/50 vs. 0/50	1 ± 0.4 vs. 1.8 ± 0.7	N/R	0/50 vs. 0/50	0/50 vs. 0/50
Abdel-Aleem 2013[12]	11/373 (2.9%) vs. 179/367 (48.8%)	2/373 (0.5%) vs. 2/367 (0.5%)	1/373 (0.3%) vs. 1/367 (0.3%)	0.5 ± 0.9 vs. 1.4 ± 1.2	1.8 ± 2.9 vs. 4.3 ± 3.6	0/373 vs. 0/367	N/R
Xu 2013[13]	19/88 (7.9%) vs. 28/86 (12.8%)	N/R	N/R	1.1 ± 0.3 vs. 1.6 ± 0.6	N/R	2/88 vs. 2/86	8/88 (9.1%) vs. 19/86 (22.1%)
Shahid 2013[14]	N/R	N/R	N/R	1.9 ± 0.1 vs. 1.8 ± 0.3	1.9 ± 0.6 vs. 4.3 ± 0.3	0/38 vs. 0/36	3/38 (7.9%) vs. 12/36 (33.3%)
Senturk 2013[15]	N/R	N/R	N/R	1.1 ± 0.6 vs. 1.3 ± 0.7	3.5 ± 2.1 vs. 0.5 ± 0.3	0/101 vs. 0/122	1/101 (1.0%) vs. 1/122 (0.8%)
Goswami 2013[19]	N/R	0/60 vs. 0/30	5/60 (8.3%) vs. 8/30 (26.7%)	N/R	N/R	0/60 vs. 0/30	0/60 vs. 2/30 (6.7%)
Ahmed 2014[16]	N/R	N/R	N/R	1 ± 0.9 vs. 2.4 ± 0.1	2 ± 1.1 vs. 3.8 ± 0.4	0/62 vs. 0/62	0/62 vs. 0/62
Total	52/552 (9.4%) vs. 242/542 (44.5%)	9/763 (1.2%) vs. 21/727 (2.9%)	34/813 (4.2%) vs. 57/777 (7.3%)	–	–	2/1,193 (0.2%) vs. 2/1172 (0.2%)	14/729 (1.9%) vs. 41/716 (5.7%)
RR (95%CI)	**0.21 (0.16–0.28)**	**0.42 (0.19–0.92)**	**0.54 (0.36–0.81)**	**Mean differences −0.61 g (−1.04 to −0.18)**	Mean differences: −0.66% (−2.32 to 1.00)	0.98 (CI 0.13–7.09)	**0.33 (0.19–0.58)**

RR, relative risk; CI, confidence interval; PPH, blood loss more than 500 mL; severe PPH, blood loss more than 1000 mL; Hb, hemoglobin; HTC, hematocrit; N/R, not reported.
Data are presented as number of intervention vs. number of control (percentage) or as mean ± standard deviation.
Boldface data: statistically significant.

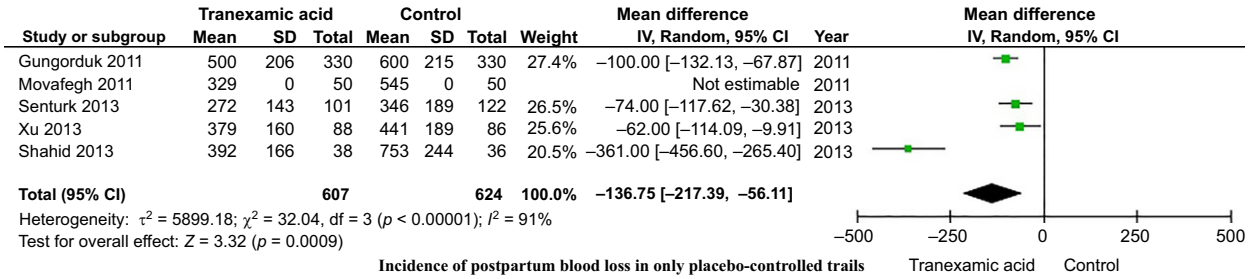

Figure 4. Forest plot for incidence of postpartum blood loss in only placebo-controlled trials. CI, confidence interval; IV, independent variable; SD, standard deviation.

needed additional uterotonic agents was statistically significantly lower in the TXA than the control group (8.5 vs. 15.6%; RR 0.53, 95% CI 0.36–0.80). No significant difference was found in the incidence of PPH comparing TXA with controls (7.9 vs. 12.8%; RR 0.62, 95% CI 0.25–1.53) (Table 3).

Discussion

This meta-analysis of the nine RCTs evaluating the efficacy of prophylactic TXA in reducing postpartum blood loss at CD shows that TXA is associated with a significant decrease in postpartum blood loss, a significantly lower incidence of PPH and severe PPH, a significantly lower hemoglobin drop, and significantly less need for additional uterotonic agents with two controls (either placebo or no treatment).

Another meta-analysis, published as a Cochrane Review, evaluated the efficacy of TXA in reducing postpartum blood loss (20). It showed that TXA decreases postpartum blood loss. However it included studies both on vaginal birth and on CD and did not include a recent RCT (16). Faraoni et al. and Heesen et al. published meta-analyses evaluating the prophylactic efficacy of TXA in women at low risk for post-partum haemorrhage (21,22). Both showed TXA reduces port-partum blood loss. Unfortunately, these two meta-analyses did not include all currently available RCTs on cesarean, had therefore smaller numbers, and included vaginal delivery trials, too (21,22). This is the first meta-analysis specifically evaluating the efficacy of TXA given prophylactically at time of CD to reduce blood loss.

TXA is a lysine analogue which acts as an antifibrinolytic via competitive inhibition of the binding of plasmin and plasminogen to fibrin (23). Peak plasma TXA concentration is obtained immediately after intravenous administration, then concentration decreases until the 6th h. Its half-life is about 2 h (23). It has been studied extensively in non-pregnant adults (5–8,24,25). A Cochrane review showed that TXA significantly reduces blood transfusion in patients undergoing emergency or urgent non-obstetrical surgery (24). TXA is safe in pregnancy, being FDA category B. One concern regarding use of TXA in pregnancy is the potential for thromboembolic events in a population at already high baseline risk of thrombosis (26). This should be kept in mind when considering use of TXA. However, our analysis showed no significant difference in incidence of thromboembolic events comparing TXA with the control groups.

Our study has several strengths. The included studies were of high quality and with a low risk of bias according to the Cochrane risk of bias tools. Other strengths are the inclusion of only randomized trials, of only patients with cesarean delivery, and of similar dosing used in the trials. To our knowledge, no prior meta-analysis on the issue of TXA in obstetrics is as large, up-to-date or comprehensive. Moreover, we studied a specific population, only women having a cesarean delivery, as incidences of blood loss complications are different in this population compared to women delivering vaginally. Additionally, while most of the included studies primarily reported on postpartum blood loss, we further analyzed PPH, severe PPH, and need for additional uterotonics. All trials reported results regarding safety data, i.e. risk for thrombotic events and no increased risk was noticed.

Limitations of our study are inherent to the limitations of the included RCTs. While blood transfusion was significantly less in the TXA group, the transfusion policy was specified only in two studies (11,13). Movafegh and colleagues transfused at a hemoglobin level below 7 g/dL, while Xu et al. below 8 g/dL. No cost-effectiveness analysis was assessed. In 5 studies (9–11,15,16), data were reported regarding neonate effects, and no increased risk was noticed. Nonetheless, TXA has not been reported to have effects on the neonate, and is FDA category B. In some of the included trials, the prevalence of reported complications in the placebo arm appeared excessively high. Movafegh et al. reported separately data regarding mean intraoperative blood loss (262 ± 39 mL vs. 404 ± 94 mL) and regarding mean postoperative blood

Table 3. Secondary blood-loss related outcomes in the subgroup analysis of only placebo-controlled trials.

	PPH	Severe PPH	Additional medications	Hb Drop (g/dL)	HTC drop (%)	Blood transfusion
Gungorduk 2011[10]	N/R	7/330 (2.1%) vs. 19/330 (5.8%)	28/330 (8.5%) vs. 48/330 (14.5%)	N/R	2.7 ± 0.6 vs. 2.3 ± 0.2	2/330 (0.6%) vs. 7/330 (2.1%)
Movafegh 2011[11]	N/R	N/R	0/50 vs. 0/50	1 ± 0.4 vs. 1.8 ± 0.7	N/R	0/50 vs. 0/50
Xu 2013[13]	7/88 (7.9%) vs. 11/86 (12.8%)	N/R	N/R	1.1 ± 0.3 vs. 1.6 ± 0.6	N/R	8/88 (9.1%) vs. 19/86 (22.1%)
Shahid 2013[14]	N/R	N/R	N/R	1.9 ± 0.1 vs. 1.8 ± 0.3	1.9 ± 0.6 vs. 4.3 ± 0.3	3/38 (7.9%) vs. 12/36 (33.3%)
Senturk 2013[15]	N/R	N/R	N/R	1.1 ± 0.6 vs. 1.3 ± 0.7	3.5 ± 2.1 vs. 0.5 ± 0.3	1/101 (1.0%) vs. 1/122 (0.8%)
Goswami 2013[19]	N/R	0/60 vs. 0/30	5/60 (8.3%) vs. 8/30 (26.7%)	N/R	N/R	0/60 vs. 2/30 (6.7%)
Total	7/88 (7.9%) vs. 11/86 (12.8%)	7/390 (1.8%) vs. 19/360 (5.3%)	33/390 (8.5%) vs. 56/360 (15.6%)	–	–	14/667 (2.1%) vs. 41/654 (6.3%)
RR (95%CI)	0.62 (0.25–1.53)	**0.37 (0.16–0.86)**	**0.53 (0.36–0.80)**	**Mean differences 0.19 g (−0.26 to −0.12)**	**Mean differences 0.21% (0.15–0.28)**	**0.33 (0.19–0.58)**

CI, confidence interval; Hb, hemoglobin; HTC, hematocrit; N/R, not reported; PPH, blood loss more than 500 mL; severe PPH, blood loss more than 1000 mL; RR, relative risk.
Data are presented as number of intervention vs. number of control (percentage) or as mean ± standard deviation.
Boldface data: statistically significant.

loss (67 ± 6.5 mL vs. 141 ± 34 mL); we reported the added means in the primary analysis but calculating the standard deviations was not feasible, and so this study was excluded from the primary analysis (Figures 3 and 4). Goswani et al. reported separately data regarding mean blood loss in the two intervention groups (256.83 ± 102.946 and 159.0 ± 68.143) and so calculating the primary outcome for the all women enrolled in the intervention arm was not feasible.

In summary, the addition of TXA to the standard oxytocin prophylaxis at CD is associated with significant decreases in all of the following: postpartum blood loss, PPH and severe PPH, need for additional uterotonic agents, hemoglobin drop, and need for blood transfusion. Therefore, given its benefit in preventing one of the most common and serious complications of pregnancy, as well as its safety and now proven effectiveness in pregnancy, we suggest consideration for adding tranexamic acid, 1 g (or 10 mg/kg) i.v. 10–20 min before skin incision or spinal anesthesia, to oxytocin prophylaxis given after delivery of the neonate, as prophylaxis to further reduce of blood loss at cesarean delivery. This should be in particular for cases at risk for complications from PPH, such as women with prior PPH, anemia, grandmultiparity, infection, Jehovah's witnesses, etc. However, given the lack of safety data, large and well-designed placebo-controlled trials are needed. Trials in selected women (e.g. women already anemic before cesarean delivery) are also required.

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