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# Tranexamic acid for the prevention of blood loss after cesarean section: an updated systematic review and meta-analysis of randomized controlled trials

***Running title:*** Antifibrinolytics for blood loss in cesarean section

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## Statements and Declarations

### Declarations of interest

The authors report no conflict of interest.

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No ethical approval was required for this study.

### Consent

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**Condensation:** Tranexamic acid may reduce the risk of blood loss in cesarean deliveries but the lack of high-quality evidence precludes any strong conclusions.

***Running title:*** Tranexamic acid for blood loss in cesarean section

## AJOG MFM at a Glance

**A. Why was this study conducted?**

This meta-analysis aimed to update evidence regarding the efficacy and safety of tranexamic acid (TXA) for the prevention of postpartum hemorrhage (PPH) in low- and high-risk cesarean deliveries.

**B. Key findings**

TXA may reduce the risk of blood loss in cesarean deliveries with a higher benefit observed in high-risk patients. However, the lack of high-quality evidence precludes any strong conclusions.

**C. What does this add to what is known?**

This study provides updated data on the use of TXA in cesarean deliveries by incorporating the results from the largest trial on this topic (11,000 patients) and highlights the lack of high-quality evidence to support its use.



**Word count:** 350 (Abstract); 5251 (Manuscript)

**Declarations of interest**

The authors report no conflict of interest.

**Keywords:** antifibrinolytics; tranexamic acid; cesarean section; postpartum hemorrhage; meta-analysis

## Abstract

**Objective:** Tranexamic acid (TXA) is a cost-effective intervention for the prevention of postpartum hemorrhage (PPH) in women undergoing cesarean section but the evidence to support its use is conflicting. We conducted this meta-analysis to evaluate the efficacy and safety of TXA in low- and high-risk cesarean deliveries.

**Data sources:** We searched MEDLINE (via PubMed), Embase, the Cochrane Library, ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform (ICTRP) portal from inception to April 2022 (updated October 2022 and February 2023) with no language restrictions. Additionally, grey literature sources were also explored.

**Study eligibility criteria:** All randomized controlled trials (RCTs) investigating the prophylactic use of intravenous TXA in addition to standard uterotonic agents in women undergoing cesarean deliveries as compared to placebo, standard treatment, or prostaglandins were included in this meta-analysis.

**Methods:** We used the revised Cochrane “Risk of Bias" tool (RoB 2.0) to assess the quality of included RCTs. RevMan 5.4 was used to conduct all statistical analyses under a random-effects model.

**Results:** We included 50 RCTs (6 in only high-risk patients and 2 with prostaglandins as the comparator) evaluating TXA in our meta-analysis. TXA reduced the risk of blood loss >1000 mL, mean total blood loss, and the need for blood transfusion in both low- and high-risk patients. TXA was associated with a beneficial effect in our secondary outcomes including decline in hemoglobin levels and the need for additional uterotonic agents. TXA increased the risk of non-thromboembolic adverse events but, based on limited data, did not increase the incidence of thromboembolic events. The administration of TXA before skin incision, but not after cord clamping, was associated with a large benefit. The quality of evidence was rated as low to very low for outcomes in the low-risk population and moderate for most outcomes in the high-risk subgroup.

**Conclusions:** TXA may reduce the risk of blood loss in cesarean deliveries with a higher benefit observed in high-risk patients but the lack of high-quality evidence precludes any strong conclusions. Additional studies, especially in the high-risk population and evaluating the timing of TXA administration, are needed to confirm or refute these findings.



## Introduction

Postpartum hemorrhage (PPH) is defined as cumulative blood loss, including intrapartum loss, more than 500 mL following vaginal delivery or more than 1000 mL following cesarean delivery, or blood loss accompanied by signs and symptoms of hypovolemia within 24 hours following the birth process.[1] It is responsible for approximately 27% of maternal deaths worldwide [2] and this number may be up to 60% in some countries,[3] making it the single most important leading cause of pregnancy-related deaths. Several maternal, gestational, and labor-

related risk factors have been identified for PPH including but not limited to a maternal age of <18 and >35 years, previous cesarean section, pre-delivery anemia, prolonged labor, placenta previa or abruption, fetal macrosomia, episiotomy, pre-eclampsia, fibroids, amnionitis, uterine rupture, and instrumental vaginal delivery.[4–7] Despite the identification of these risk factors, the probability of predicting PPH is very low.[8] For this reason, early identification and prompt initiation of treatment are clinically important to reduce adverse maternal outcomes.[9]

With the continued global rise in cesarean sections,[10] the risk for PPH also increases. This is because the rapid breakdown of fibrin and activation of plasminogen is triggered by an incision in the uterine body and the discharge of the placenta.[11] Currently, prophylactic administration of a uterotonic immediately after delivery is the only pharmacological intervention that has been shown to reduce PPH.[12] Antifibrinolytics, such as tranexamic acid (TXA), inhibit fibrinolysis and the stabilization of existing blood clots by preventing the activation of the proenzyme plasminogen to plasmin thereby preventing the proteolytic action of plasmin on fibrin threads.[13] The mechanism utilized by TXA is the reversible blockage of lysine binding sites on plasminogen molecules.[14] It has previously been used in reducing both traumatic bleeding as in head injuries [15] and hyphemia and perioperative and postoperative surgical bleeding as in cardiac, gastrointestinal, prostate and orthopedic surgery, and liver transplants, reducing the need for blood transfusions.[14,16] Clinical trials [17,18] have also suggested that the use of TXA may be useful in the prevention of blood loss after a cesarean section without serious adverse effects. However, only immediate administration is beneficial which further suggests that it prevents coagulopathy rather than treat established PPH.[19,20]

Although there have been systematic reviews published on the use of TXA in comparison with standard uterotonic agents alone in PPH,[9,21] recently published clinical trials[22–25] - including the

largest trial to date enrolling 11000 patients which is almost equal to the cumulative sample sizes of all previous randomized controlled trials (RCTs)[25] - have not yet been incorporated into a meta-analysis. In addition, there is a lack of data from high-risk patients, and only one previous meta-analysis based on a limited number of RCTs has been conducted in this vulnerable population.[26] Furthermore, no systematic review has evaluated the use of TXA in comparison with prostaglandin analogs. The use of TXA for the prevention of PPH has been identified as a research priority needing large RCTs and meta-analyses of available RCTs to reliably ascertain its role for this indication.[27] Hence, we undertook this comprehensive meta-analysis to address these knowledge gaps and provide updated evidence for clinical practice and further research.

## Methods

This systematic review was conducted according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Supplementary Table 1).[28,29] This review has been registered with the International Prospective Register of Systematic Reviews, PROSPERO (CRD42021282268). Our study did not require ethical approval.

### Eligibility criteria

The inclusion criteria were as follows: (1) study design: RCTs; (2) population: women undergoing cesarean delivery who received TXA irrespective of age or ethnicity; (3) intervention: prophylactic intravenous TXA at cesarean delivery irrespective of type or dosage or timing of administration; (4) comparator: placebo, no treatment, standard treatment or

prostaglandin analogs; and (5) outcome: reporting at least one outcome of interest. Studies that combined TXA with another agent provided that the same agent is also administered to the control arm were included in our review. We sought to include all RCTs regardless of their publication status.

The exclusion criteria were as follows: (1) all study designs other than RCTs, such as quasi-randomized trials and observational studies; (2) studies that administered TXA after a diagnosis of PPH was made instead of prophylactically; (3) studies conducted on animals; and (4) studies evaluating outcomes in women undergoing vaginal delivery.

**Information sources**

We searched the following electronic databases and international trial registers from inception to April 2022 (updated October 2022 and February 2023) with no language restrictions: Cochrane Central Register of Controlled Trials (CENTRAL, via The Cochrane Library), MEDLINE (via PubMed), Embase (via Ovid), ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform (ICTRP) portal. We also explored grey literature sources such as ProQuest Dissertations and Theses Global (PQDT) and OpenGrey to identify additional relevant data. The reference lists of included articles and relevant systematic reviews were screened to find other potentially eligible studies. We also performed forward citation tracking using the Web of Science to retrieve any other potential studies.

We used a search strategy using keywords and Medical Subject Headings (MeSH) subject headings pertaining to “antifibrinolytics”, “tranexamic acid”, “prostaglandin”, and “cesarean delivery”. The detailed search strategy is given in Supplementary Table 2.

**Selection process**

Mendeley Desktop 1.19.8 (Mendeley Ltd., Amsterdam, The Netherlands) was used for the deduplication and screening of all the articles retrieved through our online search. After deduplication, two authors independently carried out the initial phase of screening according to the titles and abstracts. The remaining articles were then subjected to comprehensive full-text screening by the same authors. Any disagreements between them were resolved by a third reviewer.

**Data collection process and data items**

After the process of study selection, data were extracted by two reviewers into a pre-piloted Excel spreadsheet, in order to ensure consistency of data extraction. Relevant data items were extracted which included patient characteristics (age, gestational age, history of previous cesarean section, duration of surgery, bleeding risk, and use of routine uterotonic agents), intervention details (type, dose, and duration), comparator details (placebo, no treatment, or any other treatment), study characteristics (e.g., study design, first author, duration of the study, number of patients and name of the country of recruited patients) and the outcome variables. Our primary outcomes are the incidence of PPH or blood loss >1000 mL, mean total blood loss (mL), and the need for blood transfusion. The secondary outcomes are blood loss >400 mL or 500 mL, the mean reduction in hemoglobin levels, the need for additional uterotonic agents, non-thromboembolic adverse events, thromboembolic events, maternal morbidity and mortality, and neonatal morbidity or mortality. Maternal morbidity was defined as the need for any additional surgical or radiological interventions, the incidence of seizures, and postpartum infectious complications. Neonatal morbidity was defined as adverse neonatal outcomes such as low Apgar scores, neonatal ICU admission, thromboembolic events, seizures, infectious complications, and the need for mechanical ventilation.

**Risk of bias assessment**

We assessed the risk of bias in the included studies using the revised Cochrane "Risk of Bias" tool for randomized trials (RoB 2.0),[30] which assesses bias in five domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome and (5) bias in the selection of the reported result. Two authors independently rated the risk of bias for each included study as low, high, or some concerns. Any disagreement between them was resolved by a third reviewer.

**Data synthesis**

We used Review Manager (RevMan, Version 5.4; The Cochrane Collaboration, Copenhagen, Denmark) for statistical analysis. Dichotomous outcomes were reported as relative risk (RR) along with 95% confidence intervals (CIs). We converted medians and IQRs to means and SDs for uniform analyses using the methods described by Wan and colleagues.[31] We reported continuous outcomes as mean difference (MD) along with 95% CIs. DerSimonian and Laird random-effects model was used to perform meta-analyses. We stratified our primary analyses for all efficacy outcomes, provided that there was enough data, into two groups: high-risk versus low-risk patients as defined by the included trials. Various risk factors were considered by studies that enrolled patients at a high risk of PPH such as placenta previa, placenta accreta or percreta, history of previous PPH, polyhydramnios, chorioamnionitis, and uterine fibroids.

For each synthesis, the $I^2$ index and the $Chi^2$ test were used for the assessment of heterogeneity, and a *P*-value of 0.1 was considered critical for the heterogeneity of the included studies. Publication bias was checked using a funnel plot if there were at least 10 studies present in a synthesis. Egger's test was employed to check funnel plot asymmetry using Jamovi (version 1.8) MAJOR module which is based on the metafor package for R.[32] Publication bias was indicated

for *p*-values below 0.10. For outcomes with less than 10 studies, we constructed Doi plots and used the Luis Furuya-Kanamori (LFK) index to assess publication bias using MetaXL version 5.3 (EpiGear International Pty, Sunrise Beach, QLD, Australia). The LFK index has greater sensitivity and power than the Egger test and hence, is suitable for a lower number of studies.[33,34]

For each of our dichotomous primary outcomes (blood loss >1000 mL and need for blood transfusion, we calculated the Fragility Index which is a measure of the robustness of results. The Fragility Index is defined as the number of events that would be required in the intervention group to convert statistically significant estimates to non-significant ones.[35] A higher Fragility Index indicates more robust results, however, no standardized cutoff is available. Furthermore, it was developed primarily for use in RCTs and its application to systematic reviews might not be appropriate. Hence, it should be interpreted with due caution.

**Subgroup and sensitivity analyses**

We performed subgroup analyses on our primary outcomes according to the type of cesarean delivery (elective only versus emergent or both). In addition, we conducted a *post hoc* subgroup analysis for the outcome of mean total blood loss according to the method used for measuring blood loss (gravimetric method versus estimation method). We conducted further *post hoc* subgroup analyses based on whether the trials were placebo-controlled or not, and whether TXA was given before skin incision or after birth/cord clamping. A *P*-value of less than 0.1 was considered significant for the test for interaction.[36]

We also conducted sensitivity analyses for all outcomes by excluding studies at high risk of bias or some concerns of bias in multiple domains.

**Certainty of evidence assessment**

For the evaluation of the certainty of the evidence, we used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach, and the quality of evidence of pooled estimates was judged as high, moderate, low, or very low according to the GRADE Working Group.[37,38]

## Results

### Study selection and characteristics of included studies

After screening, a total of 50 RCTs were included in this systematic review.[17,22–25,39–83] The detailed selection process is presented in a PRISMA flowchart (Figure 1). The study characteristics of the individual studies are shown in Table 1 and the detailed data on our outcomes of interest are given in Supplementary Table 3. No study evaluated any antifibrinolytic other than TXA. Only 6 studies solely included patients at high risk for PPH,[23,47,48,67,71,79] one study enrolled both high- and low-risk patients,[25] and the rest of the studies enrolled only low-risk patients. The trial by Pacheco et al.[25] enrolled only a small proportion of high-risk patients (Table 1), hence, it was included in the low-risk subgroup in our analyses. Most of the studies utilized oxytocin as a prophylactic uterotonic agent in all patients. Most of the studies included women undergoing elective cesarean section. In most of the studies, the dose of TXA administered was 1g intravenously. One study compared TXA with misoprostol[60] while one study was a three-armed trial evaluating TXA, misoprostol, and placebo.[72] All the remaining studies used a placebo or standard treatment as the comparator.

### Risk of bias in included studies

The quality assessment of included studies is presented in Supplementary Figure 1. Out of 50 studies, seven studies were judged to be at low risk of bias,[23–25,44,45,64,71] and 9 studies were found to be at high risk of bias due to lack of allocation concealment, missing outcome data, and selective outcome reporting.[41,43,50,58,61,63,66,74,83] The remaining studies were rated to be at some concerns of bias. Most of the concerns arising in these studies were due to no information given about any pre-specified analysis plans and inadequate information about allocation concealment of randomization sequence.

**Synthesis of results**

**Comparison 1: Tranexamic acid versus placebo or no treatment**

**Primary outcomes**

*Blood loss >1000 mL*

A total of 18 trials reported blood loss >1000 mL, of which 3 trials included patients at a high risk of PPH. A meta-analysis of these 3 studies found the risk of blood loss >1000 mL to be significantly less in the TXA group compared to the control (RR 0.26; 95% CI: 0.17-0.42; Figure 2). Statistical heterogeneity was found to be minimal ($I^2$= 0%). The Doi plot showed evidence of major asymmetry (LFK index= -3.03). The certainty of evidence was assessed as moderate due to suspected publication bias (Table 2). The Fragility Index was calculated to be 36.

The remaining 15 trials evaluated TXA in low-risk patients. The summary RR was 0.64 (95% CI: 0.51-0.81; Figure 2) with moderate statistical heterogeneity ($I^2$ = 53%). Asymmetry was noted in the funnel plot (Egger's *P*-value of <0.001). The certainty of evidence was assessed to be low due to concerns about the risk of bias in included studies and publication bias (Table 2). The test for interaction between low-risk and high-risk patients was significant (*P*<0.001). The Fragility Index is equal to 135.

Sensitivity analysis by excluding low-quality studies did not change the results substantially (low-risk patients: RR 0.72; 95% CI: 0.59-0.88; $I^2$=46%; Supplementary Figure 2). Subgroup analysis based on indication for cesarean delivery (elective only vs emergent/both) found no significant differences between the two groups ($P_{interaction}$=0.32; Supplementary Figure 3). The data from placebo-controlled trials only showed a reduction in the risk of blood loss >1000 mL in the TXA group (RR 0.49; 95% CI: 0.37-0.65; $I^2$=74%; Supplementary Figure 4). Trials in which TXA was administered before skin incision showed a greater benefit (RR 0.33; 95% CI: 0.25-0.44; $I^2$=0%) as compared to those in which TXA was administered after birth/cord clamping (RR 0.86; 95% CI: 0.79-0.93; $I^2$=0%) ($P_{interaction}$<0.001; Supplementary Figure 5).

*Mean total blood loss (mL)*

Mean total blood loss was reported by 47 trials included in our review. The analysis of high-risk patients yielded a pooled mean difference of -377.89 mL (95% CI: -449.44 to -306.33; six trials; Figure 3) favoring TXA with a moderate degree of statistical heterogeneity ($I^2$ =46%). There was significant Doi plot asymmetry according to the LFK index (-4.03). The certainty of the evidence was graded as moderate due to concerns regarding publication bias (Table 2).

In the trials evaluating the low-risk population, patients in the TXA group experienced a significant reduction in mean total blood loss as compared to the control group (MD -179.97; 95% CI: -203.67 to -156.26; Figure 3). There was considerable interstudy heterogeneity ($I^2$= 96%) which along with concerns about the internal validity of included studies downgraded the certainty of the evidence to low (Table 2). No asymmetry was detected in the funnel plot ($P$=0.755). The test for interaction between low-risk and high-risk patients was significant ($P$<0.001).

Upon exclusion of low-quality studies, the results did not change (high-risk patients: MD -369.32, 95% CI: -404.23 to -334.42; $I^2$=2%; and low-risk patients: MD -177.50, 95% CI: -209.93 to -145.08; $I^2$=93%; Supplementary Figure 6). There were no significant differences between the subgroups according to indication for cesarean delivery (elective only vs emergent/both) and method of measuring blood loss (gravimetric vs estimated) ($P_{interaction}$ =0.71 and $P_{interaction}$ =0.28, respectively) (Supplementary Figures 7 and 8). There was a greater benefit observed in placebo-controlled trials (MD -212.00, 95% CI: -238.10 to -185.90; $I^2$=94%) as compared to trials without placebo (MD -159.02, 95% CI: -203.50 to -114.53; $I^2$=97%) ($P_{interaction}$=0.04; Supplementary Figure 9). There was no significant difference between the subgroups according to the timing of TXA administration (before skin incision vs. after birth/cord clamping) ($P_{interaction}$=0.42; Supplementary Figure 10).

*Need for blood transfusion*

Twenty-nine clinical trials reported the need for blood transfusion. In the analysis of high-risk patients, the TXA group was found to be associated with a significantly less frequent need for blood transfusion as compared to the control group (RR 0.28; 95% CI: 0.17-0.44; five trials; Figure 4). The statistical heterogeneity between studies was minimal ($I^2$=0%). We found no asymmetry in the Doi plot (LFK index= -0.86). The quality of evidence was found to be high (Table 2). The Fragility Index was calculated to be 28.

In low-risk patients, TXA administration was also found to be associated with a less frequent need for blood transfusion as compared to the control group (RR 0.49; 95% CI: 0.35-0.68; Figure 4). The statistical heterogeneity was moderate ($I^2$=34%) and we found significant asymmetry in the funnel plot according to Egger's test ($P$<0.001). The certainty of the evidence was downgraded to low due to concerns about the risk of bias and publication bias (Table 2). The test

for interaction between low-risk and high-risk patients was significant (*P*=0.06). The Fragility Index was calculated as 57.

Sensitivity analysis, by excluding studies with a high risk of bias or some concerns in multiple domains, was consistent with the primary analysis (low-risk patients: RR 0.60; 95% CI: 0.44-0.83; $I^2$=30%; Supplementary Figure 11). We found no significant difference between the subgroups based on indication for cesarean delivery ($P_{interaction}$ =0.15; Supplementary Figure 12) and use of placebo ($P_{interaction}$=0.39; Supplementary Figure 13). TXA reduced the need for blood transfusion when given before skin incision (RR 0.30; 95% CI: 0.22-0.41; $I^2$=0%) but not when given after birth or cord clamping (RR 0.87; 95% CI: 0.74-1.04; $I^2$=1%) ($P_{interaction}$<0.001; Supplementary Figure 14).

**Secondary outcomes**

*Blood loss >400 mL or 500 mL*

Blood loss >400 mL or 500 mL was significantly less common in the TXA group when compared with the control group (RR 0.30; 95% CI: 0.17-0.53; Supplementary Figure 15). All the studies included in this analysis recruited patients at low risk of bleeding. There was considerable heterogeneity between the 10 studies ($I^2$ =96%). Egger's test indicated potential funnel plot asymmetry (*P*=0.006). Owing to concerns of risk of bias, inconsistency, and publication bias, the quality of evidence was judged to be very low (Table 2). Sensitivity analysis did not change the results significantly (Supplementary Figure 16).

*Mean reduction in hemoglobin levels*

Six trials of high-risk patients found that the hemoglobin drop was lower in the TXA group (MD 1.07 g/dl; 95% CI: 0.12-2.02; Supplementary Figure 17). The statistical heterogeneity was

substantial ($I^2$=96%) and there was minor asymmetry in the Doi plot (LFK index=1.73). The certainty of the evidence was assessed to be low due to downgrading in the domains of inconsistency and publication bias (Table 2).

TXA treatment was associated with significantly lower hemoglobin reduction (MD 0.63 g/dl; 95% CI: 0.53-0.74; Supplementary Figure 17) in low-risk patients. The estimated heterogeneity was considerable ($I^2$=95%). Funnel plot asymmetry was noted (Egger's *P*-value of <0.001). The quality of evidence was assessed to be very low due to downgrading in the domains of risk of bias, inconsistency, and publication bias (Table 2). There was no significant difference between low-risk and high-risk patients, however (*P* for interaction=0.38).

Sensitivity analysis by excluding low-quality studies did not change the results significantly (Supplementary Figure 18).

*Need for additional uterotonic agents*

In our pooled analysis of high-risk cases, the need for additional uterotonic agents was significantly less frequent in the TXA group (RR 0.26; 95% CI: 0.19-0.37; five trials; Supplementary Figure 19). Heterogeneity was estimated to be minimal ($I^2$=0%). Major asymmetry of the Doi plot was observed (LFK index= -3.35). The quality of evidence was moderate due to suspected publication bias (Table 2).

In our meta-analysis of low-risk cases, we found that the TXA group is associated with a decreased need for additional uterotonic agents as compared to the control group (RR 0.56; 95% CI: 0.46-0.69; Supplementary Figure 19). We found substantial statistical heterogeneity ($I^2$=74%) and significant funnel plot asymmetry according to Egger's test (*P*=0.001). The certainty of evidence was rated as very low due to concerns of risk of bias, inconsistency, and

publication bias (Table 2). The test for interaction between low-risk and high-risk patients was significant ($P$<0.001). Sensitivity analysis did not change the results substantially (Supplementary Figure 20).

*Non-thromboembolic adverse events*

A total of 18 studies reported non-thromboembolic adverse effects. The TXA group was at a significantly higher risk of non-thromboembolic adverse effects (RR 1.38; 95% CI: 1.15-1.65; Supplementary Figure 21). Heterogeneity was estimated to be substantial ($I^2$=75%). On inspection of the funnel plot, asymmetry was noted (Egger's $P$-value of <0.001). The credibility of evidence was judged to be low due to potential concerns about the risk of bias, inconsistency, and publication bias (Table 2). In sensitivity analysis by excluding low-quality studies, the results remained the same (Supplementary Figure 22).

*Thromboembolic events*

A total of 28 studies assessed thromboembolic events but since the trials were largely underpowered to detect this rare outcome, only three observed any events (Supplementary Table 3). Hence, we synthesized this outcome qualitatively. Xu et al. reported a similar incidence of deep vein thrombosis in the TXA arm (2/88) and the placebo arm (2/86; $P$=0.38).[76] Sentilhes et al. reported that the risk of thromboembolic events did not differ significantly between the two groups (RR 4.01; 95% CI: 0.85-18.88).[84] Pacheco et al. reported that the proportion of patients with a thromboembolic event was comparable between the two groups (8/5069 vs 13/4996).[25]

*Maternal morbidity*

Eighteen trials assessed maternal morbidity but most reported no events (Supplementary Table 3). Shady and Sallam reported that fewer women in the TXA group needed additional surgical interventions (17.5% vs 52.5% [uterine and internal iliac artery ligation]).[67] Abbas et al. and El-

Sttar et al. reported that a numerically higher number of women needed a hysterectomy and uterine artery ligation in the placebo group, although the difference was minimal (Supplementary Table 3). Sentilhes et al. reported that more women in the TXA group needed a uterus-sparing surgical procedure (vessel ligation or uterine compression suture; 7 vs 3) and hysterectomy (2 vs 1).[84] Pacheco et al. reported that the number of patients who required surgical or radiological interventions, such as laparotomy, hysterectomy, or intrauterine balloon tamponade, to control bleeding was similar between the two groups (233/5525 [4.2%) vs 231/5470 [4.2%]).[25]

*Maternal mortality*

Six trials assessed maternal mortality but only one trial reported any events (Supplementary Table 3). Pacheco et al. reported that the risk of maternal deaths was similar between the two groups (2/5069 vs 2/4996; RR 0.99, 95% CI: 0.07–13.6).[25]

*Neonatal mortality or morbidity*

Eighteen trials evaluated this outcome but the infant follow-up of women enrolled in the trials was largely insufficient. In general, trials reported no adverse neonatal outcomes and similar Apgar scores in both groups (Supplementary Table 3). Sujata et al. reported that there was one case of intrauterine fetal death in the placebo group while one neonate in the TXA group developed seizures within the first 24 h due to maternal chorioamnionitis and was diagnosed with early neonatal sepsis.[71] El-Gaber et al. reported no difference either in the rate of neonatal ICU admission (2.4% vs 2%) or neonatal respiratory distress syndrome (5.6% vs 5.2%) between the two groups.[80]

**Comparison 2: Tranexamic acid versus prostaglandin analogs**

Only 2 studies (360 patients) used prostaglandin analogs such as misoprostol as the comparator (Supplementary Table 3).[60,72] Tabatabaie et al. reported mean total blood loss through

gravimetric method (500.90 ± 102.24 in the TXA group as compared to 390.08 ±164.09 in the misoprostol group; *P*<0.001). Pakniat et al. reported the need for blood transfusion (1 in the TXA group vs 5 in the misoprostol group), the need for additional uterotonics (4 in the TXA group vs 3 in the misoprostol group), and non-thromboembolic adverse events (43 in the TXA group vs 35 in the misoprostol group). Both studies reported a reduction in hemoglobin levels. Tabatabaie et al. found a smaller reduction in hemoglobin levels in the TXA group compared to the misoprostol group (-1.02 ± 0.35 vs -1.19 ± 0.52 g/dL; *P*<0.001). Pakniat et al. reported a greater reduction in hemoglobin levels in the TXA group as compared to the misoprostol group (-2.45 ± 0.84 vs -2.14 ± 1.38 g/dL; *P*<0.001).

## Comment

### Main findings

In this meta-analysis, including 50 RCTs, we evaluated the efficacy of prophylactic administration of TXA to reduce PPH in groups of low- and high-risk women undergoing cesarean delivery. We found that administration of TXA probably reduced the risk of blood loss > 1000 mL in low-risk patients, with the reduction likely being greater in high-risk patients. We also found that TXA might slightly reduce mean total blood loss in low-risk patients and likely reduced it more in high-risk patients. In addition, blood transfusions and uterotonic agents were required less frequently in the TXA group, with a greater benefit observed in the high-risk population. Notably, TXA administered after cord clamping was associated with a slight reduction in blood loss >1000 mL, and had no effect on the need for blood transfusion as

compared to administration before skin incision which resulted in large reductions in blood loss >1000 mL and need for blood transfusion.

The TXA safety data suggest that there was a high risk of nonthromboembolic adverse events in the TXA group, whereas the incidence of thromboembolic events was similar in the 3 RCTs that provided data on this outcome. The certainty of evidence levels generated from the GRADE approach demonstrated that the quality of evidence in the low-risk group was low to very low for all outcomes while for the high-risk group, it was found to be moderate for most outcomes.

**Comparison with existing literature**

Our meta-analysis is consistent with the results of previous meta-analyses that reported similar benefits of TXA in controlling PPH in women who underwent cesarean section.[9,26,85] However, in contrast to the previous meta-analysis by Bellos and Pergialiotis[9] in low-risk patients which reported a higher level of certainty of evidence based on their assessment of the RCTs as being of high quality and at low risk of bias, our review and other previous reviews on this topic [85,86] highlight that the quality of the data is generally low because of various biases in the RCTs included. Of note, the quality of evidence was higher in the high-risk population, but the results were mostly based on a few small RCTs, underscoring the need for a large confirmatory study RCT in this subpopulation.

The two of the largest trials on this topic,[84] with a total of 4431 and 11000 participants, reported no substantial benefits of TXA in reducing the risk of PPH in a largely low-risk population, directly contrasting with the numerous smaller trials that report significant decreases in blood loss. It should be noted, however, that small trials are prone to biases, especially publication bias; positive findings in small trials are often not substantiated by subsequent large, randomized

trials.[87] Moreover, the criteria, thresholds, and methods used to define and assess PPH varied widely among the included trials in this review. Other issues in these smaller trials were lack of power, poor randomization procedures, and allocation concealment which may have contributed to the beneficial results.[88] It is well known that meta-analyses of smaller trials also markedly overestimate the treatment effects of interventions.[21,89,90] In light of this and the low certainty of evidence we found in our meta-analysis, our results should be interpreted with due caution.

On the other hand, the neutral findings of the large RCTs might be due to the timing of TXA administration which was after cord clamping in both. Accordingly, our subgroup analyses suggest that TXA might only be beneficial when administered earlier before skin incision. The use of TXA just before skin incision for reducing surgical bleeding is well established,[27] and the same may be applicable for the prevention of PPH. However, since subgroup analyses are observational in nature, these findings should be viewed as hypothesis-generating and require confirmation through large-scale RCTs either directly comparing different timings of administration or focusing on early administration of TXA before skin incision.

We also extend the findings of a previous meta-analysis that included 3 small RCTs of high-risk patients.[26] However, our meta-analysis is the first to use subgroup analyses to compare outcomes between high-risk and low-risk patients and to suggest that TXA is of greater benefit in the high-risk population. Our review also sought to compare the use of TXA vs. misoprostol; however, due to only 2 trials addressing this comparison and conflicting results in them,[60,72] no conclusion can be drawn about the comparative effectiveness of TXA vs. misoprostol.

Overall, TXA can be considered a cost-effective drug, relatively inexpensive, which makes it an attractive therapeutic option,[91] but the optimal pharmacokinetics need further investigation. In addition, most studies reported nonthromboembolic adverse events with TXA use but provided

little data on maternal and neonatal morbidity and major adverse events such as venous thromboembolism; therefore, the safety profile for mother and neonate remains unclear.[87]

**Strengths and limitations**

Our review includes studies conducted in a variety of resource settings and different populations, thus increasing the generalizability of our findings. The study population included both low- and high-risk patients, such as women with placenta previa, placental abruption, and prolonged labor, as well as women in whom blood loss must be minimized, such as women with anemia or hemodynamically unstable women. We also point out the shortcomings in the evidence supporting the use of TXA for the prevention of PPH through our GRADE assessment. Our meta-analysis is the first to examine high-risk patients, who have mostly been excluded in previous reviews, and it is also the first to examine TXA compared with misoprostol.

The major limitation of our study is that the included RCTs were mostly small and had flaws in the process of randomization, blinding, and balance of prognostic factors. Furthermore, data regarding long-term safety for the mother and neonate was also not reported in most trials due to a lack of post-discharge follow-up and small sample sizes. There were only 6 studies that exclusively included high-risk patients thus, limiting our confidence in the positive results in this population.

**Conclusion and implications**

PPH is a major contributor to maternal morbidity and mortality,[4] and drugs that are beneficial in reducing the risk of PPH are very much required. TXA can be a promising drug for reducing PPH as it shows a statistically significant reduction in the need for blood transfusion and risk of

bleeding >1000 mL. Combined with the fact that TXA has a low cost and easy administration further promises positive impacts in healthcare. Nevertheless, due to the low quality of the evidence that supports these findings, additional high-quality data is required before it can be administered prophylactically in all women undergoing cesarean section. Although most trials, including the two largest trials, report statistically significant reductions in mean total blood loss and a lower hemoglobin decline, the magnitude of these reductions was small (180 mL and 0.63 g/dl in the low-risk population, respectively) calling into question their clinical significance. Additionally, more studies in high-risk patients are required and the ongoing TRAAPrevia (NCT04304625) and WOMAN-2 trials[92] will provide valuable evidence in this regard. Further research is also needed to shed light on the pharmacokinetics and timing of administration of TXA, and to compare the efficacy of TXA with other uterotonic agents, especially misoprostol. The ongoing WOMAN-PharmacoTXA trial,[93] will help provide more evidence in this regard.

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## Figure legends

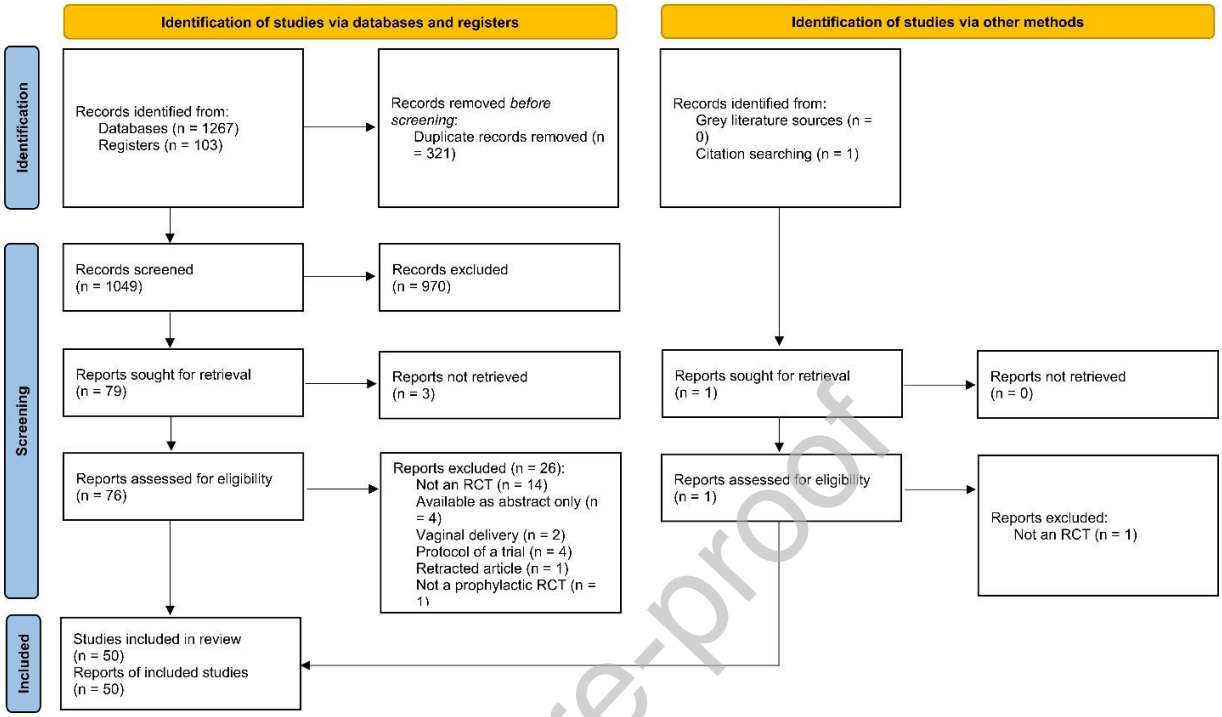


**Figure 1.** PRISMA 2020 flowchart.

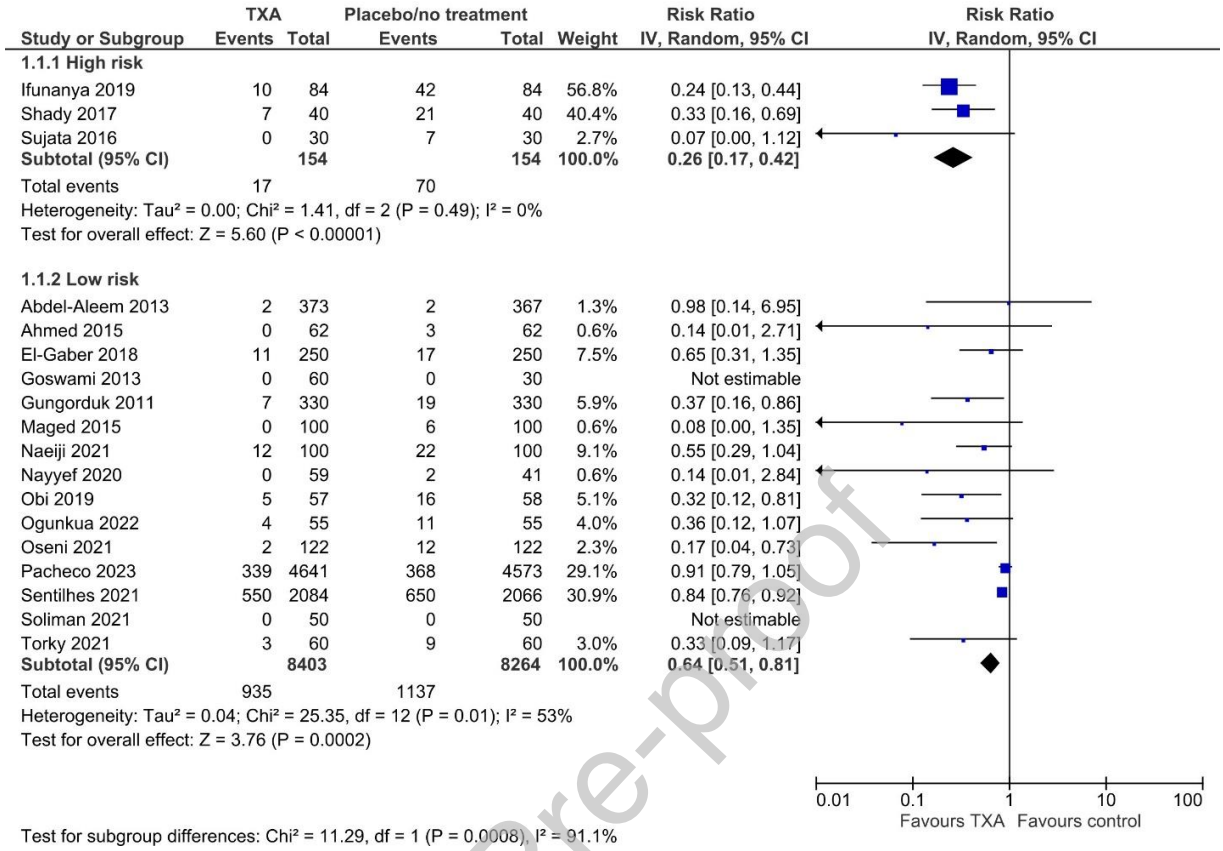


**Figure 2.** Effect of tranexamic acid on blood loss >1000mL in women undergoing cesarean section.

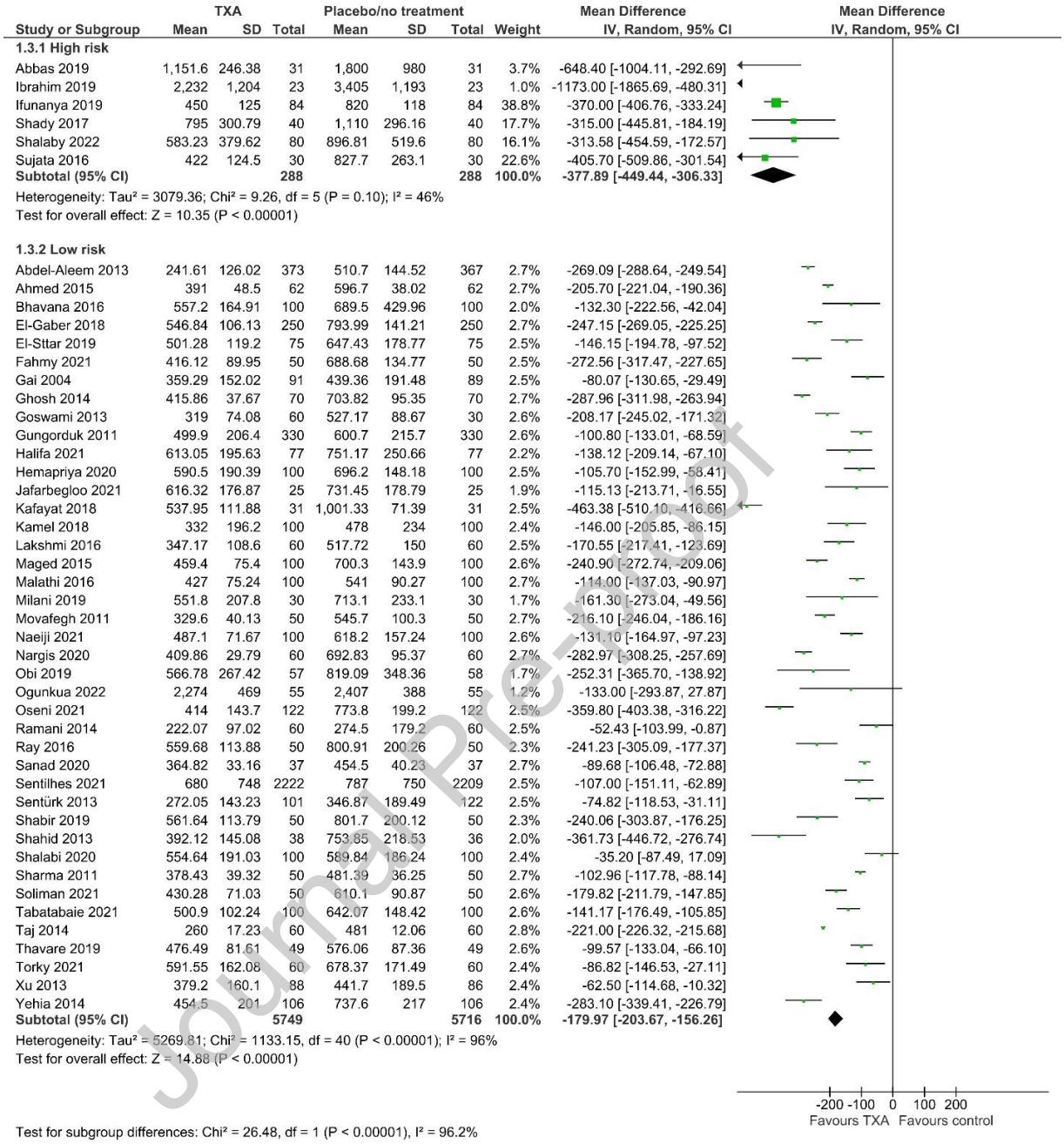


**Figure 3.** Effect of tranexamic acid on mean total blood loss in women undergoing cesarean section.

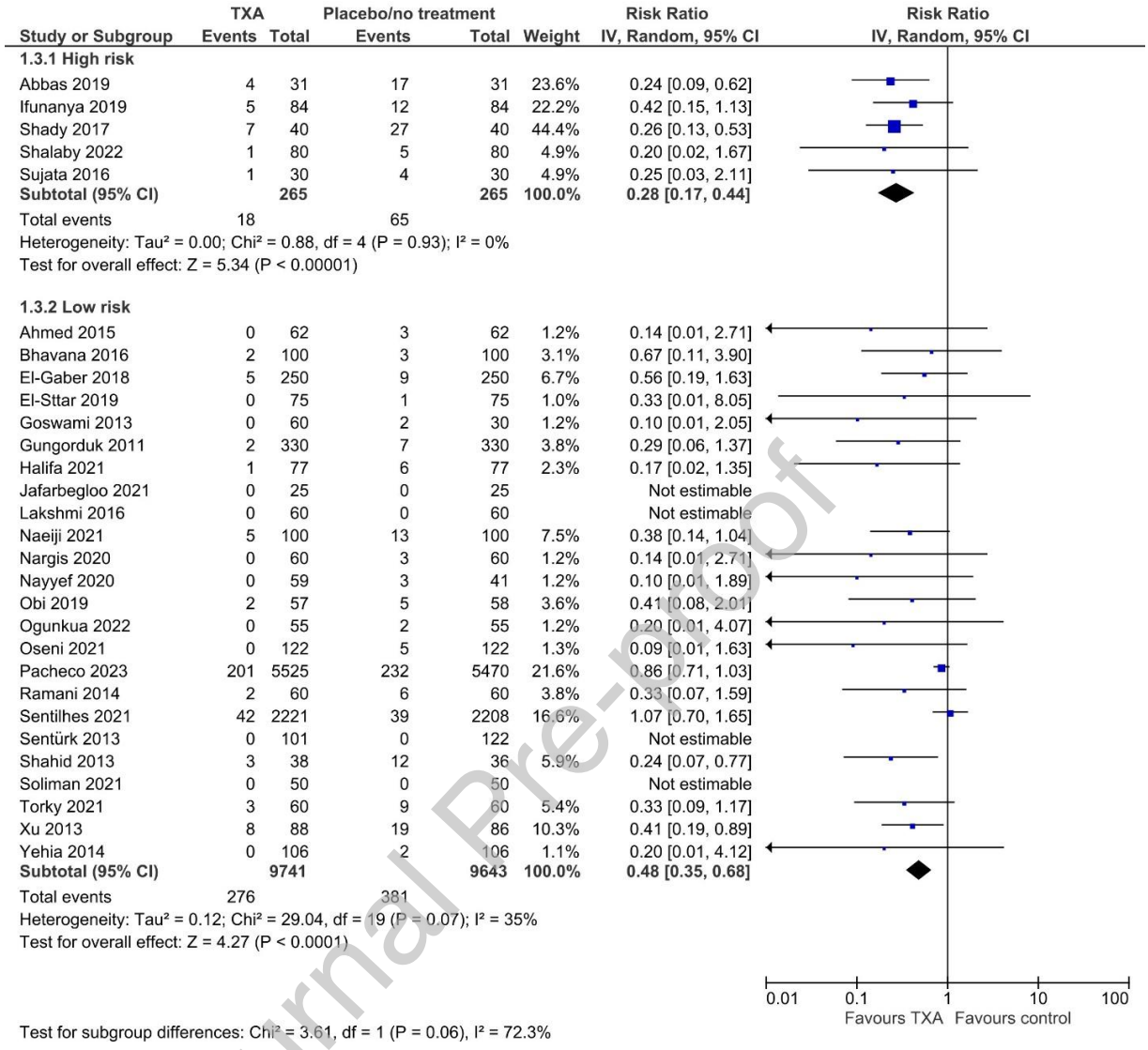


**Figure 4.** Effect of tranexamic acid on the need for blood transfusion in women undergoing cesarean section.

**Table 1.** Characteristics of included studies.

| Study ID | Country | Study Design | Sample size | Age (y) | Gestational age (wk)[1] | Previous cesarean delivery (mean ± SD or %) | Elective or emergent | Bleeding risk | Routine uterotonic agents | Experimental intervention | Comparator intervention | Duration of surgery (min)[1] | Blood loss quantification | Follow-up duration |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gai et al, 2004 | China | Open-label, multi-centric | 180 (91 vs 89) | 29.71 ± 4.18 vs 29.75 ± 4.01 | 38.80 ± 1.11 vs 38.67 ± 1.03 | - | Elective | Low | Oxytocin | 1g TXA 10 min before incision | Standard treatment | - | Gravimetric | 2 hours post-partum |
| Gungorduk et al, 2011 | Turkey | Double-blinded, single-centric, placebo-controlled | 660 (330 vs 330) | 26.3 ± 3.5 vs 26.6 ± 3.6 | 38.7 ± 0.6 vs 38.8 ± 0.6 | 97.6% vs 98.5% | Elective | Low | Oxytocin | 1g TXA 10 min before incision | 5% glucose | - | Estimated | 6 weeks after surgery |
| Movafegh et al, 2011 | Iran | Double-blinded, single-centric, placebo-controlled | 100 (50 vs 50) | 27.0 ± 3.4 vs 27.6 ± 4.1 | 38.9 ± 0.4 vs 39.0 ± 0.6 | - | Elective | Low | Oxytocin | 10 mg/kg TXA 20 min before anesthesia | 200 ml normal saline | 40.2 ± 1.0 vs 40.4 ± 2.8 | Gravimetric | 24 hours after surgery |
| Sharma et al, 2011 | India | Open-label, single-centric | 100 (50 vs 50) | 25.63 ± 3.72 vs 25.88 ± 3.8 | 39.25 ± 0.99 vs 39.06 ± 1.12 | - | Both | Low | Oxytocin | 1g TXA 5 min before incision | Standard treatment | - | Gravimetric | 3 days after surgery |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abdel-Aleem et al, 2013 | Egypt | Open-label, single-centric | 740 (373 vs 367) | 26.34 ± 5.16 vs 26.62 ± 5.05 | 39.32 ± 1.15 vs 39.31 ± 1.17 | 40.6% vs 61.1% | Elective | Low | Oxytocin | 1g TXA 10 min before incision | Standard treatment | 23.19 ± 5.7 vs 24.29 ± 4.09 | Gravimetric | 24 hours after surgery |
| Goswami et al, 2013 | India | Double-blinded, single-centric, placebo-controlled | 90 (30 vs 30 vs 30)[2] | 23.6 ± 2.5 vs 22.8 ± 2.2 vs 24.3 ± 2.6 | - | - | Elective | Low | Oxytocin | 10 mg/kg and 20 mg/kg TXA, 20 min before incision | Distilled water in 5% dextrose | - | Gravimetric | 24 hours post-operation |
| Sentürk et al, 2013 | Turkey | Single-centric, placebo-controlled | 223 (101 vs 122) | 30.20 ± 6.83 vs 29.22 ± 6.93 | - | 58.4% vs 59.8% | Both | Low | Oxytocin | 1g TXA 10 min before incision | 5% dextrose solution | 11.99 ± 4.28 vs 12.57 ± 3.38 | Gravimetric | 8 hours after surgery |
| Shahid and Khan, 2013 | Pakistan | Double-blinded-single-centric, placebo-controlled | 74 (38 vs 36) | 24.18 ± 3.93 vs 24.89 ± 4.16 | 38.32 ± 0.80 vs 38.47 ± 0.910 | - | Elective | Low | Oxytocin | 1g TXA 10 min before incision | Distilled water | 45-50 minutes in 50% of the cases | Gravimetric | 3 days after the operation |
| Xu et al, 2013 | China | Double-blinded, single-centric, placebo-controlled | 174 (88 vs 86) | 26.7 ± 3.7 vs 27.1 ± 4.1 | 38.7 ± 1.0 vs 38.8 ± 1.1 | - | Elective | Low | Oxytocin and methylergometrine | 10 mg/kg TXA 20 min before anesthesia | 200 ml normal saline | - | Gravimetric | 24 hours after surgery |
| Ghosh et al, 2014 | India | Double-blinded, multi- | 140 (70 vs 70) | 25.94 ± 3.78 vs | 38.62 ± 0.78 vs | - | Elective | Low | Oxytocin | 1g TXA before skin incision | 10 ml sterile water | 41.54 ± 7.30 vs | Gravimetric | 24 hours post- |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | centric, placebo - controlled | | 26.04 ± 3.39 | 38.72 ± 0.67 | | | | | | | 42.7 ± 7.15 | | operatively |
| Ramani et al, 2014 | India | Open-label, single-centric | 120 (60 vs 60) | 24.9 ± 3.9 vs 24.4 ± 3.7 | - | - | Emergent | Low | Oxytocin and misoprostol | 1g TXA 10 min before incision | Standard treatment | 41 ± 10 vs 43 ± 10 | Gravimetric | 7 days post surgery |
| Taj et al, 2014 | Pakistan | Single-centric, placebo - controlled | 120 (60 vs 60) | 23.56 ± 3.82 vs 24.18 ± 3.47 | 39 ± 2 vs 39 ± 2 | - | Elective | Low | - | 1g TXA 20 min before incision | Placebo | - | - | 2 hours post-operation |
| Yehia et al, 2014 | Egypt | Double-blinded, single-centric, placebo - controlled | 212 (106 vs 106) | 28.4 ± 4.9 vs 28.6 ± 4.7 | 39.1 ± 1.1 vs 39.0 ± 1.2 | - | Elective | Low | Oxytocin | 1g TXA with anesthesia | Placebo | - | Gravimetric | 24 hours post-operation |
| Ahmed et al, 2015 | Egypt | Open-label, single-centric | 124 (62 vs 62) | 28.6 ± 5.9 vs 26.9 ± 5.2 | 38.5 ± 0.7 vs 38.5 ± 0.6 | 75.8% vs 85.5% | Elective | Low | Oxytocin and ergometrine | 10 mg/kg TXA 5 min before incision | Standard treatment | 44.9 ± 2.7 vs 44.8 ± 2.7 | Gravimetric | 1 week after the operation |
| Maged et al, 2015 | Egypt | Single-blinded, single-centric, placebo - controlled | 200 (100 vs 100) | 24.9 ± 4.6 vs 25.3 ± 4.7 | - | 1.7 ± 1.1 vs 1.6 ± 1.1 | Elective | Low | Oxytocin and ergometrine | 1g TXA 15 min before incision | Placebo | - | Estimated | 4 weeks after delivery |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bhavana et al, 2016 | India | Single-centric, placebo-controlled | 200 (100 vs 100) | - | - | - | Elective | Low | Oxytocin | 1g TXA before anesthesia | 20 ml of normal saline | - | Gravimetric | 48 hours after surgery |
| Lakshmi and Abraham, 2016 | India | Open-label, single-centric | 120 (60 vs 60) | 26.77±2.807 vs 26.82±2.801 | - | - | Elective | Low | Oxytocin | 1g TXA 20 min before incision | Standard treatment | 50 ± 10.36 vs 70.33 ± 11.93 | Gravimetric | 24 hours after the surgery |
| Malathi et al, 2016 | India | Open-label, single-centric | 200 (100 vs 100) | 23.40 ± 3.06 vs 23.59 ± 3.56 | - | 1.24 ± 0.45 vs 1.20 ± 0.44 | Elective | Low | Oxytocin | 10 mg/kg TXA 15-20 min before incision | Standard treatment | - | Gravimetric | 24 hours after surgery |
| Ray et al, 2016 | India | Single-centric, placebo-controlled | 100 (50 vs 50) | 25.00 ± 4.71 vs 25.88 ± 5.39 | 38.92 ± 1.38 vs 39.02 ± 1.42 | - | Elective | Low | Oxytocin | 1g TXA 20 min before anesthesia | 5% dextrose solution | - | Gravimetric | 24 hours post-operation |
| Sujata et al, 2016 | India | Double-blinded, single-centric, placebo-controlled | 60 (30 vs 30) | 29.40 ± 4.16 vs 30.27 ± 4.31 | - | 13% vs 7% | Both | High | Oxytocin | 10 mg/kg TXA 10 min before incision | Normal saline | - | Estimated | 48 hours post-operation |
| Shady and Sallam 2017 | Egypt | Double-blinded, single-centric, placebo-controlled | 120 (40 vs 40 vs 40)[3] | 29.6 ± 2.68 vs 29.5 ± 2.42 | 36.45 ± 0.9 vs 36.38 ± 0.87 | 85% vs 82.5% | Both | High | Oxytocin | 1g TXA IV, just before incision | Placebo | 48.05 ± 5.49 vs 48.13 ± 5.88 | Gravimetric | 24 hours post-operation |

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| El-Gaber et al, 2018 | Egypt | Double-blinded, single-centric, placebo-controlled | 500 (250 vs 250) | 27.14 ± 4.986 vs 26.77 ± 4.942 | 38.32 ± 1.124 vs 38.24 ± 1.518 | - | Elective | Low | Oxytocin | 1g TXA after birth | Normal saline 0.9% | - | Gravimetric | 24 hours post-operation |
| Kafayat et al, 2018 | Pakistan | Open-label, single-centric | 62 (31 vs 31) | 28.13 ± 4.79 vs 27.38 ± 4.80 | 39.07 ± 1.07 vs 39.24 ± 1.26 | - | Elective | Low | Oxytocin | 1g TXA over 5 min at the time of skin incision | Standard treatment | - | Estimated | 2 hours after birth |
| Kamel et al, 2018 | Egypt | Open-label, single-centric | 300 (150 vs 150) | 29.39 ± 3.84 vs 29.82 ± 3.94 | 39.49 ± 1.01 vs 39.29 ± 1.01 | - | Elective | Low | Oxytocin | 1g TXA 20 min before incision | Standard treatment | - | Gravimetric | Post-surgery |
| Abbas et al, 2019 | Egypt | Double-blinded, single-centric, placebo-controlled | 62 (31 vs 31) | 30.6 ±2.5 vs 30.7 ± 2.8 | 36.5 ± 0.8 vs 36.6 ± 0.6 | 2.8 ± 0.8 vs 2.9 ± 0.8 | Elective | High | Oxytocin | 1g TXA just before skin incision | IV saline just before skin incision | 98.2±9.8 vs101.9±11.6 | Gravimetric | 24 hours post-operative |
| El-Sttar et al, 2019 | Egypt | Open-label, multi-centric | 150 (75vs75) | 27.81 ± 5.07 vs 28.32 ± 4.65 | 38.19 ± 0.70 vs 38.22 ± 1.10 | - | Elective | Low | Misoprostol | 1g TXA 10 mins before incision | Standard treatment | 42.65 ± 8.57 vs 43.28 ± 21.87 | Gravimetric | 24 hours post-operation |
| Ibrahim, 2019 | Saudi Arabia | Double-blinded, single-centric, placebo-controlled | 46 (23 vs 23) | 32.3 ± 5.2 vs 30.6 ± 5.7 | - | - | Elective | High | - | 10mg/kg TXA over 10 minutes after cord clamping and 10mg/kg/h continued | Normal saline | - | Estimated | 24 hours post-operative |

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| | | | | | | | | | | till skin closure | | | | |
| Ifunanya et al, 2019 | Nigeria | Double-blinded, single-centric, placebo-controlled | 168 (84 vs 84) | 28.2 ±5.2 vs 28.6 ± 5.4 | 38 ± 1.5 vs 38 ±1.3 | - | Both | High | Oxytocin | 1g TXA 20 mins before incision | 20ml of 0.9% normal saline | - | Estimated | 6 weeks after discharge |
| Milani et al, 2019 | Iran | Double-blinded, single-centric, placebo-controlled | 60 (30 vs 30) | 29.33 ± 5.59 vs 31.2 ± 5.53 | 37.93 ± 0.69 vs 37.86 ± 0.80 | - | Elective | Low | Oxytocin | 1g TXA 15mins before incision | 5% dextrose in water | - | Gravimetric | Within 12-24 hours after the operation |
| Obi et al, 2019 | Nigeria | Double-blinded, multi-centric, placebo-controlled | 115 (57 vs 58) | 29.5 ± 4.8 vs 28.2 ± 3.7 | 39.6 ± 1.5 vs 39.3 ± 1.4 | - | Elective | Low | Oxytocin | 1g TXA, 20 min before incision | Distilled water | 42.4 ± 5.6 vs 40.6 ± 7.5 | Estimated | 48 hours after the cesarean section |
| Pakniat et al, 2019 | Iran | Double-blinded, single-centric, placebo-controlled | 158 (80 vs 78)[4] | 27.12 ± 5.28 vs 27.25 ± 5.85 | 39.05 ± 2.31 vs 39.25 ± 1.3 | - | Both | Low | Oxytocin | 5ml TXA, 10 min before incision | 2 sublingual misoprostol tablets | 38.64 ± 2.1 vs 39.54 ± 1.82 | Gravimetric | 24 hours after surgery |
| Shabir et al, 2019 | Pakistan | Single-centric, placebo | 100 (50 vs 50) | 26.01 ± 4.69 vs | 37.95 ± 1.41 vs | 0 vs 0 | Elective | Low | Oxytocin | 1g TXA, 20 min before anesthesia | 5% dextrose | - | Gravimetric | 24 hours after the operation |

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| | | -controlled | | 26.79 ± 5.39 | 38.97 ± 1.44 | | | | | | | | | |
| Thavare et al, 2019 | India | Open-label, single-centric | 100 (50 vs 50) | - | - | - | - | Low | Oxytocin | 1g TXA, 20 min before incision | Standard treatment | - | Gravimetric | 2 hours post-partum |
| Hemapriya et al, 2020 | India | Open-label, single-centric | 200 (100 vs 100) | - | - | - | Elective | Low | Oxytocin | 10mg/kg TXA, 10 min before incision | Standard treatment | - | Gravimetric | 24 hours after surgery |
| Nargis and Dewan, 2020 | Bangladesh | Double-blinded, single-centric, placebo-controlled | 120 (60 vs 60) | 25.34 ± 3.8 vs 25.68 ± 3.3 | 38.84 ± 1.28 vs 38.6 ± 1.67 | - | Elective | Low | Oxytocin | 1g TXA, immediately after delivery | Distilled water | 41.35 ± 6.285 vs 42.6 ± 5.132 | Gravimetric | 24 hours post-operatively |
| Nayyef et al, 2020 | Iraq | Open-label, single-centric | 100 (59 vs 41) | 26.6 ± 4.3 vs 24 ± 4 | 37.9 ± 1.02 vs 38.4 ± 1.3 | - | Elective | Low | Oxytocin | 1g TXA, with induction of anesthesia | Normal saline | 26.6 ± 3.6 vs 25.9 ± 2.4 | Gravimetric | 24 hours after surgery |
| Sanad et al, 2020 | Egypt | Open-label, multi-centric | 74 (37 vs 37) | 26.08 ± 3.53 vs 26.68 ± 3.05 | 38.95 ± 1.03 vs 38.73 ± 1.19 | - | Elective | Low | Oxytocin | 1g TXA, 10 min before incision | Standard treatment | - | Estimated | 4 hours post-operation |
| Shalabi et al, 2020 | Egypt | Double-blinded, multi-centric, placebo-controlled | 200 (100 vs 100) | 28.41 ± 4.63 vs 29.12 ± 5.54 | 38.54 ± 0.64 vs 38.76 ± 1.00 | - | Elective | Low | Oxytocin | 1g TXA, 10 min before incision | 5% glucose | - | Estimated | 24 hours post partum |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fahmy et al, 2021 | Egypt | Double-blinded, single-centric, placebo-controlled | 100 (50 vs 50) | 27.60 ± 4.03 vs 26.88 ± 4.55 | - | - | Elective | Low | Oxytocin | 2g TXA, with induction of anesthesia | Placebo | - | Estimated | 24 hours post-operation |
| Halifa et al, 2021 | Nigeria | Double-blinded, single-centric, placebo-controlled | 154 (77 vs 77) | 31.10 ± 4.28 vs 21.35 ± 4.97 | - | - | Both | Low | Oxytocin | 1g TXA, 10 min before incision | Normal saline | - | Gravimetric | 24 hours post-operation |
| Jafarbegloo et al, 2021 | Iran | Double-blinded, single-centric, placebo-controlled | 50 (25 vs 25) | 30.48 ± 4.71 vs 31.46 ± 4.85 | 38.24 ± 0.44 vs 37.83 ± 1.76 | 1.21 ± 0.50 vs 1.04 ± 0.62 | Elective | Low | Oxytocin | 1g TXA IV, 10 min before incision | Distilled water | - | Gravimetric | 48-72 hours after delivery |
| Naeiji et al, 2021 | Iran | Double-blinded, single-centric, placebo-controlled | 200 (100 vs 100) | 27.2 vs 27.9 | 38.7 vs 38.5 | 52.0% vs 55.0% | Elective | Low | Oxytocin | 1g TXA, before incision | 5% dextrose | - | Gravimetric | 6 hours after surgery |
| Oseni et al, 2021 | Nigeria | Double-blinded, single-centric, placebo | 244 (122 vs 122) | 27.6 ± 4.6 vs 27.5 + 4.6 | 39.2 ± 1.1 vs 39.4 ± 1.1 | - | Emergent | Low | Oxytocin | 1g TXA IV, 5 min before incision | Normal saline | 52.6 ± 5.3 vs 52.5 ± 5.6 | Gravimetric | 5 days post-operation |

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| | | -controlled | | | | | | | | | | | | |
| Sentilhes et al, 2021 | France | Double-blinded, multi-centric, placebo-controlled | 4431 (2086 vs 2067) | 33.3 ± 5.3 vs 33.3 ± 5.3 | 39 (38–40) | 51.8% vs 52.4% | Both | Low | Oxytocin or carbetocin | 1g TXA, 3 min after birth | Placebo | 36 (30–45) vs 37 (29–46) | Estimated | 3 months after delivery |
| Soliman et al, 2021 | Egypt | Open-label, single-centric | 100 (50 vs 50) | 21.46 ± 2.71 vs 21.46 ± 2.71 | 39.34 ± 0.47 vs 39.28 ± 0.45 | - | Elective | Low | Oxytocin | 1g TXA, 20 min before incision | Standard treatment | - | Gravimetric | 24 hours after the surgery |
| Tabatabaie et al, 2021 | Iran | Multi-centric, placebo-controlled | 300 (100 vs 100 vs 100)[5] | - | - | - | Elective | Low | Oxytocin | 10mg/kg TXA, 20 min before incision | Normal saline | - | Gravimetric | 24 hours after the operation |
| Torky et al, 2021 | Egypt | Double-blinded, multi-center, placebo-controlled | 180 (60 vs 60 vs 60)[6] | 30.7 ± 4.66 vs 30.8 ± 4.37 | - | 1.8 ± 1.44 vs 1.85 ± 1.49 | Elective | Low | Oxytocin | 1g TXA, 20 min before incision | Normal saline | 63.08 ± 18.39 vs 65.67 ± 19.95 | Estimated | 24 hours after the procedure |
| Ogunkuya et al, 2022 | USA | Double-blind, single-centric, placebo-controlled | 110 (55 vs 55) | 29.8 ± 5.2 vs 28.7 ± 5.2 | - | - | Elective | Low | Oxytocin | 1g TXA, 10 min before incision | Normal saline | - | Estimated | 24 hours after delivery |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Shalaby et al, 2022 | Egypt | Double-blinded, single-centric, placebo-controlled | 160 (80 vs 80) | 28.9 ± 4.6 vs 28.5 ± 4.45 | 38.1 ± 1.1 vs 39.1 ± 1.1 | 67.5% vs 61.25% | Elective | High | Oxytocin and ergometrine | 1g TXA, diluted in 20ml of glucose 5% 15 mins before surgery | 30ml of glucose 5% | 49.9 ± 19.7 vs 47.8 ± 19.1 | Estimated | 48 hours, re-examination done at 1 and 4 weeks after discharge |
| Pacheco, 2023 | USA | Double-blinded, multi-centric, placebo-controlled | 11000 (5529 vs 5471) | 30.1 ± 5.8 vs 30.1 ± 5.8 | - | - | Both | Both: Placenta previa (1.7% vs 1.9%), placental abruption (0.8% vs 0.8%), placenta accreta, increta, or percreta (0.3% vs 0.3%), Chorioamnionitis (3.3% vs 3.3%) | Oxytocin | 1g TXA, IV immediately following umbilical cord clamping | 50cc normal saline | - | Estimated | 7 days after delivery |

TXA, tranexamic acid; IV, intravenous.

[1]Data reported as mean ± SD or median (IQR).
[2]Two arms receiving different doses of TXA vs control.
[3]Two arms receiving IV or topical TXA. The topical TXA arm was excluded from our study.
[4]TXA vs misoprostol.
[5]TXA vs misoprostol vs placebo. For meta-analysis, the TXA and placebo arms were used (100 vs 100 patients) while the results of TXA vs misoprostol were reported qualitatively.
[6]TXA vs placebo vs etamsylate. The etamsylate arm was excluded from our study.

**Table 2.** Grading of recommendations assessment, development, and evaluation (GRADE) summary of findings.

| **Outcome** | | **No. of participants (studies)** | **Effect estimate (95% CI)** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Quality of Evidence (GRADE)** |
|---|---|---|---|---|---|---|---|---|---|
| Blood loss >1000 mL | High-risk population | 308 (3) | RR 0.26 (0.17-0.42) | Not serious | Not serious | Not serious | Not serious | Suspected | ⊕⊕⊕⊖ MODERATE |
| | Low-risk population | 16667 (15) | RR 0.64 (0.51-0.81) | Serious | Not serious | Not serious | Not serious | Suspected | ⊕⊕⊖⊖ LOW |
| Mean total blood loss (mL) | High-risk population | 576 (6) | MD -377.89 (-449.44 to -306.33) | Not serious | Not serious | Not serious | Not serious | Suspected | ⊕⊕⊕⊖ MODERATE |
| | Low-risk population | 11465 (41) | MD -179.97 (-203.67 to -156.26) | Serious | Serious | Not serious | Not serious | Undetected | ⊕⊕⊖⊖ LOW |
| Need for blood transfusion | High-risk population | 530 (5) | RR 0.28 (0.17-0.44) | Not serious | Not serious | Not serious | Not serious | Undetected | ⊕⊕⊕⊕ HIGH |
| | Low-risk population | 19384 (24) | RR 0.48 (0.35-0.68) | Serious | Not serious | Not serious | Not serious | Suspected | ⊕⊕⊖⊖ LOW |
| Blood loss >400 or 500 mL | | 6176 (10) | RR 0.30 (0.17-0.53) | Serious | Serious | Not serious | Not serious | Suspected | ⊕⊖⊖⊖ VERY LOW |
| Hb levels | High-risk population | 576 (6) | MD 1.07 (0.12-2.02) | Not serious | Serious | Not serious | Not serious | Suspected | ⊕⊕⊖⊖ LOW |
| | Low-risk population | 21088 (34) | MD 0.63 (0.53-0.74) | Serious | Serious | Not serious | Not Serious | Suspected | ⊕⊖⊖⊖ VERY LOW |
| Need for additional uterotonic agents | High-risk population | 530 (5) | RR 0.26 (0.19-0.37) | Not serious | Not serious | Not serious | Not serious | Suspected | ⊕⊕⊕⊖ MODERATE |
| | Low-risk population | 19054 (17) | RR 0.56 (0.46-0.69) | Serious | Serious | Not serious | Not serious | Suspected | ⊕⊖⊖⊖ VERY LOW |
| Non-thromboembolic adverse events | | 18642 (18) | 1.38 (1.15-1.65) | Serious | Serious | Not serious | Not serious | Suspected | ⊕⊕⊖⊖ LOW |

Graphical abstract