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Source / Izvornik: **American Journal of Obstetrics & Gynecology MFM, 2023, 5**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1016/j.ajogmf.2023.101049>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:251380>

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Download date / Datum preuzimanja: **2024-09-27**



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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



Huzaifa Ahmad Cheema, MBBS; Aamna Badar Ahmad, MBBS; Muhammad Ehsan, MBBS; Abia Shahid, MBBS; Muhammad Ayyan, MBBS; Saleha Azeem, MBBS; Ayesha Hussain, MBBS; Aden Shahid, MBBS; Abdulqadir J. Nashwan, MSc; Mislav Mikuš, MD, PhD; Antonio Simone Laganà, MD, PhD

Introduction

Postpartum hemorrhage (PPH) is defined as a cumulative blood loss, including intrapartum loss, of >500 mL following vaginal delivery or >1000 mL following cesarean delivery, or blood loss accompanied by signs and

Cite this article as: Cheema HA, Ahmad AB, Ehsan M, et al. Tranexamic acid for the prevention of blood loss after cesarean section: an updated systematic review and meta-analysis of randomized controlled trials. *Am J Obstet Gynecol MFM* 2023;5:101049.

From the Department of Obstetrics and Gynaecology, King Edward Medical University, Lahore, Pakistan (Drs Cheema, Ahmad, Ehsan, Ab. Shahid, Ayyan, and Hussain); Department of Medicine, King Edward Medical University, Lahore, Pakistan (Drs Cheema, Ahmad, and Azeem); Department of Medicine, CMH Lahore Medical College and Institute of Dentistry, Lahore, Pakistan (Dr Ad. Shahid); Hamad Medical Corporation, Doha, Qatar (Mr Nashwan); Department of Obstetrics and Gynecology, Clinical Hospital Center Zagreb, Zagreb, Croatia (Dr Mikuš); Unit of Gynecologic Oncology, ARNAS "Civico – Di Cristina – Benfratelli," Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Palermo, Italy (Dr Laganà).

Received March 27, 2023; revised June 1, 2023; accepted June 6, 2023.

M.M. and A.S.L. are joint last authors.

The authors report no conflict of interest.

The publication of this article was funded by the Qatar National Library.

Corresponding author: Abdulqadir J. Nashwan, MSc. anashwan@hamad.qa

2589-9333/\$36.00

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<http://dx.doi.org/10.1016/j.ajogmf.2023.101049>

OBJECTIVE: Tranexamic acid is a cost-effective intervention for the prevention of postpartum hemorrhage among women who undergo cesarean delivery, but the evidence to support its use is conflicting. We conducted this meta-analysis to evaluate the efficacy and safety of tranexamic acid in low- and high-risk cesarean deliveries.

DATA SOURCES: We searched MEDLINE (via PubMed), Embase, the Cochrane Library, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform portal from inception to April 2022 (updated October 2022 and February 2023) with no language restrictions. In addition, grey literature sources were also explored.

STUDY ELIGIBILITY CRITERIA: All randomized controlled trials that investigated the prophylactic use of intravenous tranexamic acid in addition to standard uterotonic agents among women who underwent cesarean deliveries in comparison with a 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 the included randomized controlled trials. RevMan 5.4 was used to conduct all statistical analyses using a random-effects model.

RESULTS: We included 50 randomized controlled trials (6 in only high-risk patients and 2 with prostaglandins as the comparator) that evaluated tranexamic acid in our meta-analysis. Tranexamic acid reduced the risk for blood loss >1000 mL, the mean total blood loss, and the need for blood transfusion in both low- and high-risk patients. Tranexamic acid was associated with a beneficial effect in the secondary outcomes, including a decline in hemoglobin levels and the need for additional uterotonic agents. Tranexamic acid increased the risk for nonthromboembolic adverse events but, based on limited data, did not increase the incidence of thromboembolic events. The administration of tranexamic acid 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.

CONCLUSION: Tranexamic acid may reduce the risk for 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. The administration of tranexamic acid before skin incision, but not after cord clamping, was associated with a large benefit. Additional studies, especially in the high-risk population and focused on evaluating the timing of tranexamic acid administration, are needed to confirm or refute these findings.

Key words: antifibrinolytics, cesarean section, meta-analysis, postpartum hemorrhage, tranexamic acid

EDITOR'S CHOICE

symptoms of hypovolemia within 24 hours following the birthing 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

AJOG MFM at a Glance

Why was this study conducted?

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

Key findings

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

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.

including, but not limited to, a maternal age of <18 and >35 years, previous cesarean delivery, predelivery anemia, prolonged labor, placenta previa or abruption, fetal macrosomia, episiotomy, preeclampsia, 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 deliveries,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 pharmacologic 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 of action of TXA is the reversible blockage of lysine binding sites on plasminogen molecules.¹⁴ It has been used previously in reducing both traumatic bleeding as observed in head injuries¹⁵ and hyphemia and perioperative and postoperative surgical bleeding as observed 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 TXA may be useful in the prevention of blood loss after a cesarean delivery without serious adverse effects. However, only immediate administration is beneficial, which further suggests that it prevents coagulopathy instead of treating 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 that enrolled 11,000 patients, which is almost equal to the cumulative sample sizes of all previous randomized controlled trials (RCTs)²⁵—have not been incorporated yet into a meta-analysis. In addition, there is a lack of data from high-risk patients, and only 1 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 that needs 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 to provide updated evidence for clinical practice and further research.

Materials and 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) under identifier 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 1 outcome of interest. Studies that combined TXA with another agent provided that the same agent was 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 (via The Cochrane Library), MEDLINE (via PubMed), Embase (via Ovid), ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform portal. We also explored grey literature sources such as

ProQuest Dissertations and Theses Global 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 with key words and Medical Subject Headings terms 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, 2 authors independently carried out the initial phase of screening 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 2 reviewers into a pre-piloted Excel spreadsheet to ensure consistency of data extraction. Relevant data items were extracted including patient characteristics (age, gestational age, history of cesarean delivery, 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 (eg, 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 were the incidence of PPH or blood loss >1000 mL, mean total blood loss (mL), and the need for blood transfusion. The secondary outcomes were blood loss >400 mL or 500 mL, the mean reduction in hemoglobin levels, the need for additional uterotonic agents,

nonthromboembolic 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 intensive care unit (NICU) 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 the following 5 domains: (1) bias arising from the randomization process; (2) bias caused by deviations from intended interventions; (3) bias caused by 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) with 95% confidence intervals (CIs). We converted medians and interquartile ranges (IQRs) to means and standard deviations (SDs) for uniform analyses using the methods described by Wan and colleagues.³¹ We reported continuous outcomes as mean difference (MD) with 95% CIs. The DerSimonian and Laird random-effects model was used to perform meta-analyses. We stratified our primary analyses for all efficacy outcomes, provided that there were enough data, into the following 2 groups: high-risk vs low-risk patients as defined by the included trials. Various risk factors were considered by

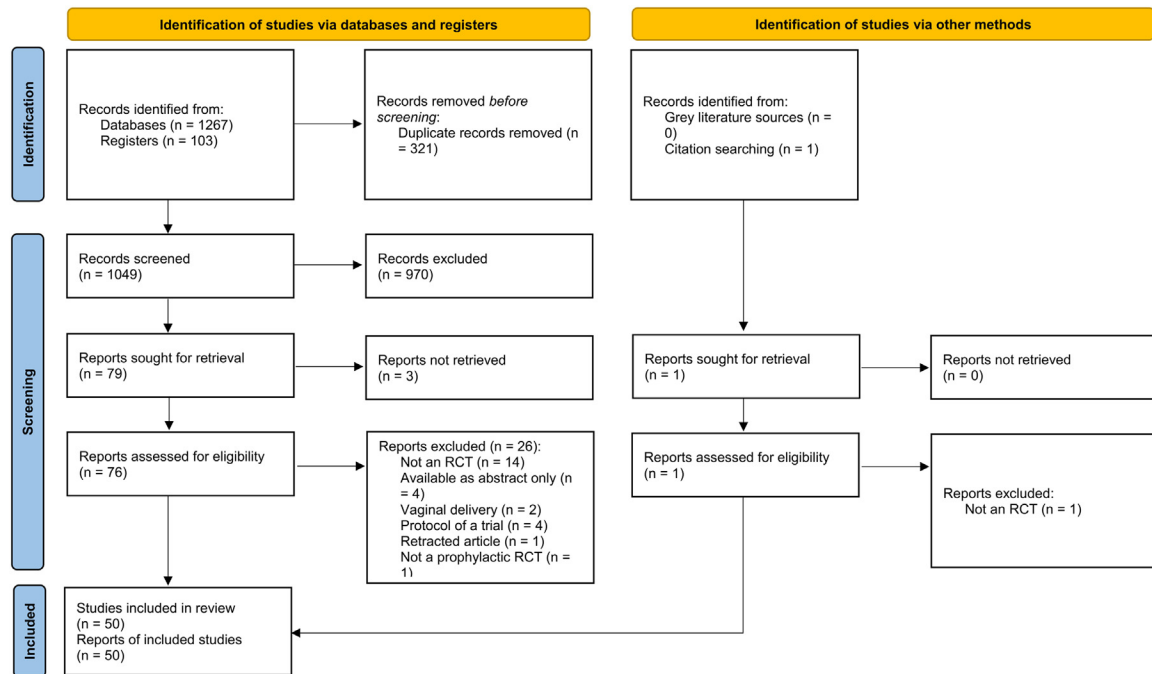
studies that enrolled patients with a high risk for PPH such as placenta previa, placenta accreta or percreta, history of PPH, polyhydramnios, chorioamnionitis, and uterine fibroids.

For each synthesis, the I^2 index and the chi-square test were used for the assessment of heterogeneity, and a P value of .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 the Jamovi (version 1.8) MAJOR module, which is based on the metafor package of R.³² Publication bias was indicated for P values <.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, Queensland, 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 nonsignificant 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 vs 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 vs estimation method). We conducted further post hoc subgroup

FIGURE 1
PRISMA 2020 flowchart

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial.

Cheema. Antifibrinolytics for blood loss in cesarean deliveries. *Am J Obstet Gynecol MFM* 2023.

analyses based on whether the trials were placebo-controlled or not and whether TXA was given before skin incision or after birth or cord clamping. A *P* value of <.1 was considered significant for the test for interaction.³⁶

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

Certainty of evidence assessment

For evaluation of the certainty of the evidence, we used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, and the quality of evidence of the 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} 1 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 al²⁵ 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 used oxytocin as a prophylactic uterotonic agent in all patients. Most of the studies included women who underwent an elective cesarean delivery. In most of the studies, the dose of TXA administered was 1 g intravenously. One study compared TXA with misoprostol,⁶⁰ whereas 1 study was a 3-armed trial evaluating TXA, misoprostol, and placebo.⁷² All the remaining studies used a placebo or standard treatment as the comparator.

Risk of bias of included studies

The quality assessment of the included studies is presented in Supplementary Figure 1. Of 50 studies, 7 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 because of a 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 have some concerns of bias. Most of the concerns arising in these studies were because no information was given about any prespecified analysis plans and inadequate information about allocation concealment of randomization sequence.

Synthesis of results

Comparison 1: Tranexamic acid vs placebo or no treatment. Primary outcomes. Blood loss >1000 mL

A total of 18 trials reported blood loss >1000 mL, 3 of which included patients at a high risk for PPH. A meta-analysis of these 3 studies found that the risk for

TABLE 1
Characteristics of included studies

Study ID	Country	Study design	Sample size	Age (y)	Gestational age (wk) ^a	Previous cesarean delivery (mean ± SD or %)	Elective or emergent	Bleeding risk	Routine uterotonic agents	Experimental intervention	Comparator intervention	Duration of surgery (min) ^a	Blood loss quantification	Follow-up duration
Gai et al, ⁴¹ 2004	China	Open-label, multicentric	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	1 g TXA 10 min before incision	Standard treatment	—	Gravimetric	2 h postpartum
Gungorduk et al, ⁴⁴ 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	1 g TXA 10 min before incision	5% glucose	—	Estimated	6 wk after surgery
Movafegh et al, ⁵⁵ 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 h after surgery
Sharma et al, ⁷⁸ 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	1 g TXA 5 min before incision	Standard treatment	—	Gravimetric	3 d after surgery
Abdel-Aleem et al, ⁸¹ 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	1 g TXA 10 min before incision	Standard treatment	23.19±5.7 vs 24.29±4.09	Gravimetric	24 h after surgery
Goswami et al, ⁴³ 2013	India	Double-blinded, single-centric, placebo-controlled	90 (30 vs 30 vs 30) ^b	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 h postoperation
Sentürk et al, ⁶⁵ 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	1 g TXA 10 min before incision	5% dextrose solution	11.99±4.28 vs 12.57±3.38	Gravimetric	8 h after surgery
Shahid and Khan, ⁶⁸ 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	1 g TXA 10 min before incision	Distilled water	45–50 minutes in 50% of the cases	Gravimetric	3 d after the operation
Xu et al, ⁷⁶ 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 h after surgery
Ghosh et al, ⁴² 2014	India	Double-blinded, multi-centric, placebo-controlled	140 (70 vs 70)	25.94±3.78 vs 26.04±3.39	38.62±0.78 vs 38.72±0.67	—	Elective	Low	Oxytocin	1 g TXA before skin incision	10 mL sterile water	41.54±7.30 vs 42.7±7.15	Gravimetric	24 h postoperatively
Ramani and Nayak, ⁶¹ 2014	India	Open-label, single-centric	120 (60 vs 60)	24.9±3.9 vs 24.4±3.7	—	—	Emergent	Low	Oxytocin and misoprostol	1 g TXA 10 min before incision	Standard treatment	41±10 vs 43±10	Gravimetric	7 d postsurgery
Taj et al, ⁷³ 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	—	1 g TXA 20 min before incision	Placebo	—	—	2 h postoperation
Yehia et al, ⁷⁷ 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	1 g TXA with anesthesia	Placebo	—	Gravimetric	24 h postoperation
Ahmed et al, ⁸² 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 wk after the operation
Maged et al, ⁵² 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	1 g TXA 15 min before incision	Placebo	—	Estimated	4 wk after delivery
Bhavana et al, ⁸³ 2016	India	Single-centric, placebo-controlled	200 (100 vs 100)	—	—	—	Elective	Low	Oxytocin	1 g TXA before anesthesia	20 mL of normal saline	—	Gravimetric	48 h after surgery

(continued)

TABLE 1
Characteristics of included studies (continued)

Study ID	Country	Study design	Sample size	Age (y)	Gestational age (wk) ^a	Previous cesarean delivery (mean $\pm$ SD or %)	Elective or emergent	Bleeding risk	Routine uterotonic agents	Experimental intervention	Comparator intervention	Duration of surgery (min) ^b	Blood loss quantification	Follow-up duration
Lakshmi and Abraham, ⁵¹ 2016	India	Open-label, single-centric	120 (60 vs 60)	26.77 $\pm$ 2.807 vs 26.82 $\pm$ 2.801	—	—	Elective	Low	Oxytocin	1 g TXA 20 min before incision	Standard treatment	50 $\pm$ 10.36 vs 70.33 $\pm$ 11.93	Gravimetric	24 h after the surgery
Malathi et al, ⁵³ 2016	India	Open-label, single-centric	200 (100 vs 100)	23.40 $\pm$ 3.06 vs 23.59 $\pm$ 3.56	—	1.24 $\pm$ 0.45 vs 1.20 $\pm$ 0.44	Elective	Low	Oxytocin	10 mg/kg TXA 15–20 min before incision	Standard treatment	—	Gravimetric	24 h after surgery
Ray et al, ⁶² 2016	India	Single-centric, placebo-controlled	100 (50 vs 50)	25.00 $\pm$ 4.71 vs 25.88 $\pm$ 5.39	38.92 $\pm$ 1.38 vs 39.02 $\pm$ 1.42	—	Elective	Low	Oxytocin	1 g TXA 20 min before anesthesia	5% dextrose solution	—	Gravimetric	24 h postoperation
Sujata et al, ⁷¹ 2016	India	Double-blinded, single-centric, placebo-controlled	60 (30 vs 30)	29.40 $\pm$ 4.16 vs 30.27 $\pm$ 4.31	—	13% vs 7%	Both	High	Oxytocin	10 mg/kg TXA 10 min before incision	Normal saline	—	Estimated	48 h postoperation
Shady and Sallam, ⁶⁷ 2017	Egypt	Double-blinded, single-centric, placebo-controlled	120 (40 vs 40 vs 40) ^c	29.6 $\pm$ 2.68 vs 29.5 $\pm$ 2.42	36.45 $\pm$ 0.9 vs 36.38 $\pm$ 0.87	85% vs 82.5%	Both	High	Oxytocin	1 g TXA IV just before incision	Placebo	48.05 $\pm$ 5.49 vs 48.13 $\pm$ 5.88	Gravimetric	24 h postoperation
El-Gaber et al, ⁸⁰ 2018	Egypt	Double-blinded, single-centric, placebo-controlled	500 (250 vs 250)	27.14 $\pm$ 4.986 vs 26.77 $\pm$ 4.942	38.32 $\pm$ 1.124 vs 38.24 $\pm$ 1.518	—	Elective	Low	Oxytocin	1 g TXA after birth	Normal saline 0.9%	—	Gravimetric	24 h postoperation
Kafayat et al, ⁴⁹ 2018	Pakistan	Open-label, single-centric	62 (31 vs 31)	28.13 $\pm$ 4.79 vs 27.38 $\pm$ 4.80	39.07 $\pm$ 1.07 vs 39.24 $\pm$ 1.26	—	Elective	Low	Oxytocin	1 g TXA over 5 min at the time of skin incision	Standard treatment	—	Estimated	2 h after birth
Kamel et al, ⁵⁰ 2018	Egypt	Open-label, single-centric	300 (150 vs 150)	29.39 $\pm$ 3.84 vs 29.82 $\pm$ 3.94	39.49 $\pm$ 1.01 vs 39.29 $\pm$ 1.01	—	Elective	Low	Oxytocin	1 g TXA 20 min before incision	Standard treatment	—	Gravimetric	Postsurgery
Abbas et al, ⁷⁹ 2019	Egypt	Double-blinded, single-centric, placebo-controlled	62 (31 vs 31)	30.6 $\pm$ 2.5 vs 30.7 $\pm$ 2.8	36.5 $\pm$ 0.8 vs 36.6 $\pm$ 0.6	2.8 $\pm$ 0.8 vs 2.9 $\pm$ 0.8	Elective	High	Oxytocin	1 g TXA just before skin incision	IV saline just before skin incision	98.2 $\pm$ 9.8 vs 101.9 $\pm$ 11.6	Gravimetric	24 h postoperative
El-Sittar et al, ³⁹ 2019	Egypt	Open-label, multi-centric	150 (75 vs 75)	27.81 $\pm$ 5.07 vs 28.32 $\pm$ 4.65	38.19 $\pm$ 0.70 vs 38.22 $\pm$ 1.10	—	Elective	Low	Misoprostol	1 g TXA 10 mins before incision	Standard treatment	42.65 $\pm$ 8.57 vs 43.28 $\pm$ 21.87	Gravimetric	24 h postoperation
Ibrahim, ⁴⁷ 2019	Saudi Arabia	Double-blinded, single-centric, placebo-controlled	46 (23 vs 23)	32.3 $\pm$ 5.2 vs 30.6 $\pm$ 5.7	—	—	Elective	High	—	10 mg/kg TXA over 10 min after cord clamping and 10 mg/kg/h continued until skin closure	Normal saline	—	Estimated	24 h postoperative
Ifunanya et al, ⁴⁸ 2019	Nigeria	Double-blinded, single-centric, placebo-controlled	168 (84 vs 84)	28.2 $\pm$ 5.2 vs 28.6 $\pm$ 5.4	38 $\pm$ 1.5 vs 38 $\pm$ 1.3	—	Both	High	Oxytocin	1 g TXA 20 min before incision	20 mL of 0.9% normal saline	—	Estimated	6 wk after discharge
Milani et al, ⁵⁴ 2019	Iran	Double-blinded, single-centric, placebo-controlled	60 (30 vs 30)	29.33 $\pm$ 5.59 vs 29.53	31.2 $\pm$ 37.93 $\pm$ 0.69 vs 37.86 $\pm$ 0.80	—	Elective	Low	Oxytocin	1 g TXA 15 min before incision	5% dextrose in water	—	Gravimetric	Within 12–24 h after the operation
Obi et al, ⁵⁹ 2019	Nigeria	Double-blinded, multi-centric, placebo-controlled	115 (57 vs 58)	29.5 $\pm$ 4.8 vs 28.2 $\pm$ 3.7	39.6 $\pm$ 1.5 vs 39.3 $\pm$ 1.4	—	Elective	Low	Oxytocin	1 g TXA, 20 min before incision	Distilled water	42.4 $\pm$ 5.6 vs 40.6 $\pm$ 7.5	Estimated	48 h after the cesarean delivery

(continued)

TABLE 1

Characteristics of included studies (continued)

Study ID	Country	Study design	Sample size	Age (y)	Gestational age (wk) ^a	Previous cesarean delivery (mean ± SD or %)	Elective or emergent	Bleeding risk	Routine uterotonic agents	Experimental intervention	Comparator intervention	Duration of surgery (min) ^a	Blood loss quantification	Follow-up duration
Pakniat et al, ⁶⁰ 2019	Iran	Double-blinded, single-centric, placebo-controlled	158 (80 vs 78) ^d	27.12±5.28 vs 27.25±5.85	39.05±2.31 vs 39.25±1.3	—	Both	Low	Oxytocin	5 mL TXA, 10 min before incision	2 sublingual misoprostol tablets	38.64±2.1 vs 39.54±1.82	Gravimetric	24 h after surgery
Shabir et al, ⁶⁶ 2019	Pakistan	Single-centric, placebo-controlled	100 (50 vs 50)	26.01±4.69 vs 26.79±5.39	37.95±1.41 vs 38.97±1.44	0 vs 0	Elective	Low	Oxytocin	1 g TXA, 20 min before anesthesia	5% dextrose	—	Gravimetric	24 h after the operation
Thavare and Patil, ⁷⁴ 2019	India	Open-label, single-centric	100 (50 vs 50)	—	—	—	—	Low	Oxytocin	1 g TXA, 20 min before incision	Standard treatment	—	Gravimetric	2 h postpartum
Hemapriya et al, ⁴⁶ 2020	India	Open-label, single-centric	200 (100 vs 100)	—	—	—	Elective	Low	Oxytocin	10 mg/kg TXA 10 min before incision	Standard treatment	—	Gravimetric	24 h after surgery
Nargis and Dewan, ⁶⁷ 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	1 g TXA, immediately after delivery	Distilled water	41.35±6.285 vs 42.6±5.132	Gravimetric	24 h postoperatively
Nayyef et al, ⁵⁸ 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	1 g TXA, with induction of anesthesia	Normal saline	26.6±3.6 vs 25.9±2.4	Gravimetric	24 h after surgery
Sanad et al, ⁶³ 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	1 g TXA, 10 min before incision	Standard treatment	—	Estimated	4 h postoperation
Shalabi et al, ⁵⁹ 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	1 g TXA, 10 min before incision	5% glucose	—	Estimated	24 h postpartum
Fahmy et al, ⁴⁰ 2021	Egypt	Double-blinded, single-centric, placebo-controlled	100 (50 vs 50)	27.60±4.03 vs 26.88±4.55	—	—	Elective	Low	Oxytocin	2 g TXA with induction of anesthesia	Placebo	—	Estimated	24 h postoperation
Halifa et al, ⁴⁵ 2021	Nigeria	Double-blinded, single-centric, placebo-controlled	154 (77 vs 77)	31.10±4.28 vs 21.35±4.97	—	—	Both	Low	Oxytocin	1 g TXA, 10 min before incision	Normal saline	—	Gravimetric	24 h postoperation
Jafarbegloo et al, ¹⁷ 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	1 g TXA IV 10 min before incision	Distilled water	—	Gravimetric	48–72 h after delivery
Naeiji et al, ⁵⁶ 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	1 g TXA, before incision	5% dextrose	—	Gravimetric	6 h after surgery
Oseni et al, ²² 2021	Nigeria	Double-blinded, single-centric, placebo-controlled	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	1 g TXA IV 5 min before incision	Normal saline	52.6±5.3 vs 52.5±5.6	Gravimetric	5 d postoperation
Sentilhes et al, ⁶⁴ 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	1 g TXA 3 min after birth	Placebo	36 (30–45) vs 37 (29–46)	Estimated	3 mo after delivery
Soliman et al, ⁷⁰ 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	1 g TXA, 20 min before incision	Standard treatment	—	Gravimetric	24 h after the surgery

(continued)

TABLE 1
Characteristics of included studies (continued)

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) ^a	Blood loss quantification	Follow-up duration
Tabatabaie et al, ⁷² 2021	Iran	Multi-centric, placebo-controlled	300 (100 vs 100 vs 100) ^a	—	—	—	Elective	Low	Oxytocin	10 mg/kg TXA 20 min before incision	Normal saline	—	Gravimetric	24 h after the operation
Torky et al, ⁷⁵ 2021	Egypt	Double-blinded, multi-center, placebo-controlled	180 (60 vs 60 vs 60) ^f	30.7±4.66 vs 30.8±4.37	—	1.8±1.44 vs 1.85±1.49	Elective	Low	Oxytocin	1 g TXA, 20 min before incision	Normal saline	63.08±18.39 vs 65.67±19.95	Estimated	24 h after the procedure
Ogunkua et al, ²⁴ 2022	United States	Double-blind, single-centric, placebo-controlled	110 (55 vs 55)	29.8±5.2 vs 28.7±5.2	—	—	Elective	Low	Oxytocin	1 g TXA, 10 min before incision	Normal saline	—	Estimated	24 h after delivery
Shalaby et al, ²³ 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	1 g TXA, diluted in 20 mL glucose 5% 15 min before surgery	30 mL of glucose 5%	49.9±19.7 vs 47.8±19.1	Estimated	48 h, re-examination done at 1 and 4 wk after discharge
Pacheco et al, ²⁵ 2023	United States	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	1 g TXA IV immediately following umbilical cord clamping	50 mL normal saline	—	Estimated	7 d after delivery

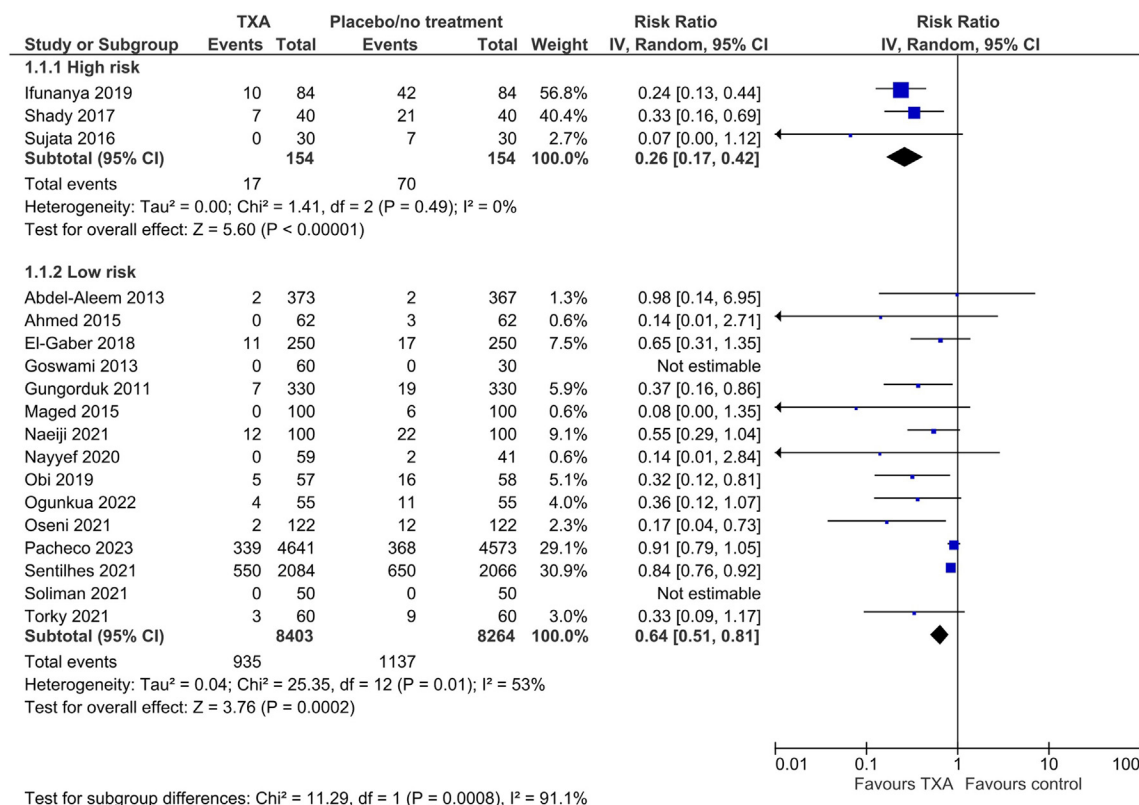
TXA, tranexamic acid; IV, intravenous.

^a Data reported as mean ± standard deviation or median (interquartile range); ^b Two arms receiving different doses of TXA vs control; ^c Two arms receiving IV or topical TXA. The topical TXA arm was excluded from our study; ^d TXA vs misoprostol; ^e TXA vs misoprostol vs placebo. For meta-analysis, the TXA and placebo arms were used (100 vs 100 patients), whereas the results of TXA vs misoprostol were reported qualitatively; ^f TXA vs placebo vs etamsylate. The etamsylate arm was excluded from our study.

Cheema. Antifibrinolytics for blood loss in cesarean deliveries. Am J Obstet Gynecol MFM 2023.

FIGURE 2

Effect of tranexamic acid on blood loss >1000 mL in women undergoing cesarean deliveries



CI, confidence interval; IV, intravenous; TXA, tranexamic acid.

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blood loss >1000 mL was significantly less in the TXA group than in 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 to be moderate because of 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 $< .001$). The certainty of evidence was assessed to be low because of concerns about the risk of bias in the included studies and publication bias (Table 2). The test for interaction between low-risk and high-risk patients was

significant ($P < .001$). The fragility index was 135.

A sensitivity analysis with exclusion of 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). A subgroup analysis based on the indication for cesarean delivery (elective only vs emergent or both) found no significant differences between the 2 groups (Pinteraction, 0.32) (Supplementary Figure 3). The data from placebo-controlled trials only showed a reduction in the risk for 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; $I^2 = 0\%$) than for those in which TXA was administered after birth or cord clamping (RR, 0.86; 95% CI, 0.79

–0.93; $I^2 = 0\%$; Pinteraction $< .001$) (Supplementary Figure 5).

Mean total blood loss (mL)

Mean total blood loss was reported in 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 for 6 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 because of concerns related to 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 when compared with the control group (MD, -179.97 ; 95% CI, -203.67 to -156.26) (Figure 3). There was considerable interstudy

TABLE 2

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

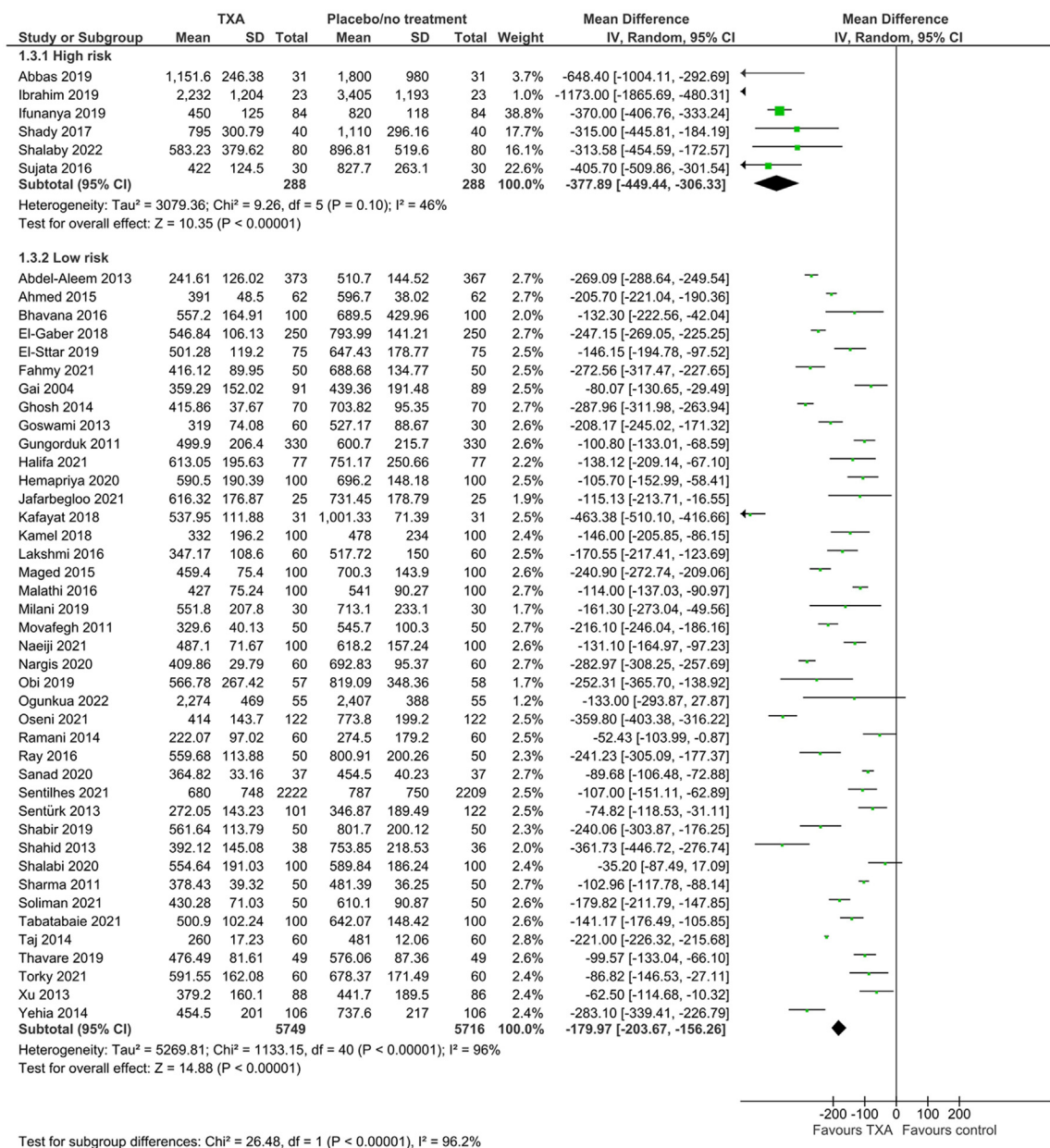
Outcome		No. of participants (studies)	Effect estimate (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of Evidence (GRADE)
Blood loss >1000 mL	High-risk population	308 (3)	RR, 0.26 (0.17–0.42)	Not serious	Not serious	Not serious	Not serious	Suspected	⊕⊕⊕⊕ MODERATE
	Low-risk population	16,667 (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	11,465 (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	19,384 (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	21,088 (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	19,054 (17)	RR, 0.56 (0.46–0.69)	Serious	Serious	Not serious	Not serious	Suspected	⊕⊕⊕⊕ VERY LOW
Nonthromboembolic adverse events		18,642 (18)	1.38 (1.15–1.65)	Serious	Serious	Not serious	Not serious	Suspected	⊕⊕⊕⊕ LOW

CI, confidence interval; Hb, hemoglobin; MD, mean difference; RR, relative risk.

Cheema. Antifibrinolytics for blood loss in cesarean deliveries. Am J Obstet Gynecol MFM 2023.

FIGURE 3

Effect of tranexamic acid on mean total blood loss in women undergoing cesarean deliveries



CI, confidence interval; IV, intravenous; SD, standard deviation; TXA, tranexamic acid.

Cheema. Antifibrinolytics for blood loss in cesarean deliveries. Am J Obstet Gynecol MFM 2023.

heterogeneity ($I^2 = 96\%$), which, along with concerns about the internal validity of the included studies, downgraded the certainty of the evidence to low (Table 2). No asymmetry was detected in the funnel plot ($P = .755$). The test for interaction between low-risk and high-risk patients was significant ($P < .001$).

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 based on

indication for cesarean delivery (elective only vs emergent or both) or method of measuring blood loss (gravimetric vs estimated) (Pinteraction, 0.71 and Pinteraction, 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; $I^2=94\%$) than in trials without a placebo (MD, −159.02; 95% CI, −203.50 to −114.53; $I^2=97\%$; Pinteraction, 0.04) (Supplementary Figure 9). There was no significant difference between the subgroups based on the timing of TXA administration (before skin incision vs after birth or cord clamping) (Pinteraction, 0.42) (Supplementary Figure 10).

Need for blood transfusion

A total of 29 clinical trials reported the need for a blood transfusion. In the analysis of high-risk patients, the TXA group was found to be associated with a

significant reduction in the frequency of need for blood transfusion when compared with the control group (RR, 0.28; 95% CI, 0.17–0.44 for 5 trials) (Figure 4). The statistical heterogeneity between the 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.

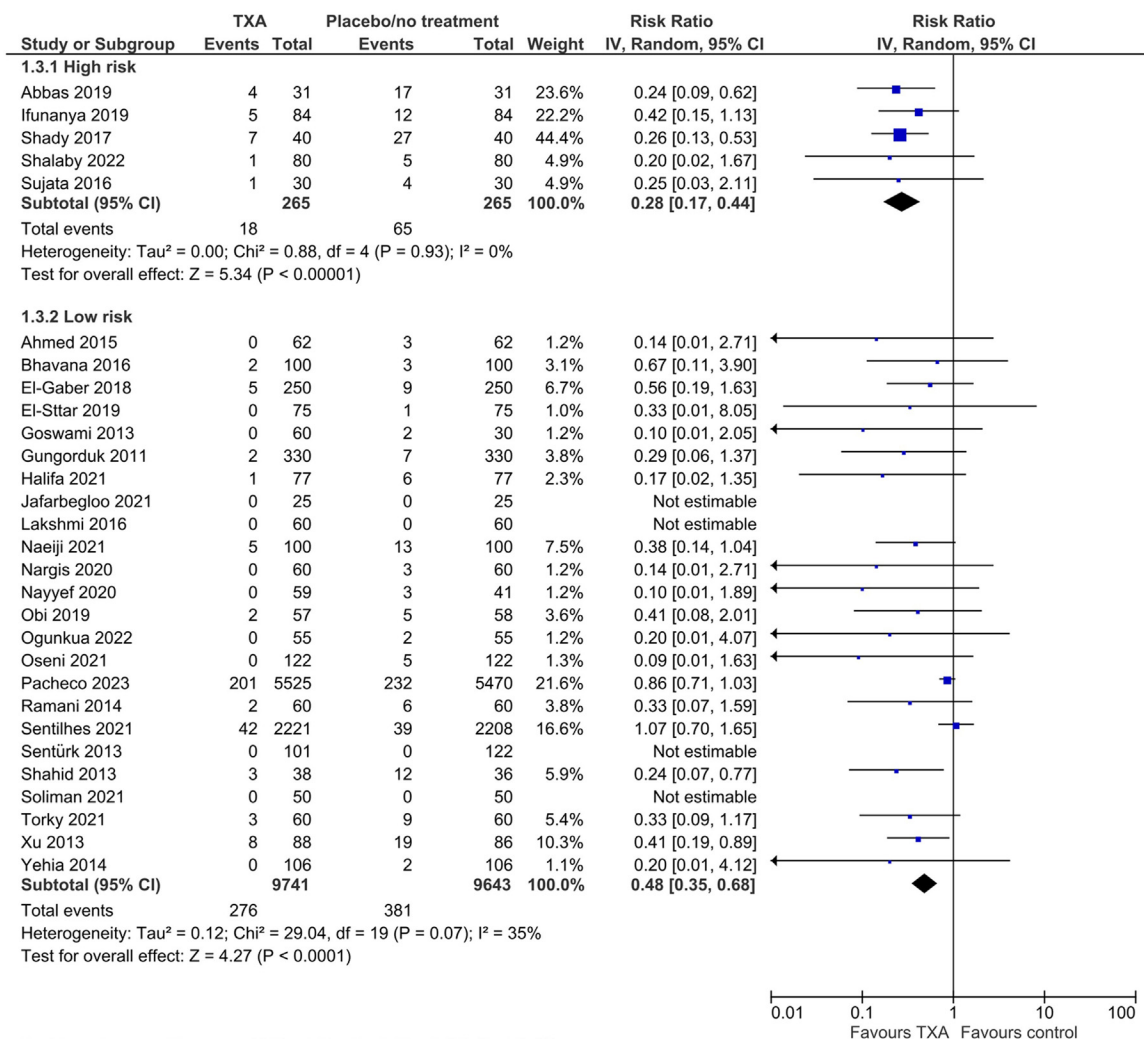
In low-risk patients, TXA administration was also found to be associated with a less frequent need for blood transfusion

when compared with 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 ($P<.001$). The certainty of the evidence was downgraded to low because of concerns related to the risk of bias and publication bias (Table 2). The test for interaction between low-risk and high-risk patients was significant ($P=.06$). The fragility index was calculated to be 57.

In a sensitivity analysis with exclusion of studies with a high risk of bias

FIGURE 4

Effect of tranexamic acid on the need for blood transfusion in women undergoing cesarean deliveries



or some concerns in multiple domains, the results were consistent with those of 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 (Pinteraction, 0.15) (Supplementary Figure 12) or use of placebo (P for interaction, .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; $I^2=1\%$; Pinteraction, <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 than in 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 ($P=.006$). Owing to concerns of risk of bias, inconsistency, and publication bias, the quality of evidence was judged to be very low (Table 2). A 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 because of downgrading in the domains of inconsistency and publication bias (Table 2).

TXA treatment was associated with a 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,

<.001). The quality of evidence was assessed to be very low because of downgrading in the domains of risk of bias, inconsistency, and publication bias (Table 2). There was, however, no significant difference between low-risk and high-risk patients (P for interaction, .38).

A sensitivity analysis with exclusion of 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 reduced in the TXA group (RR, 0.26; 95% CI, 0.19–0.37 for 5 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 because of suspected publication bias (Table 2).

In our meta-analysis of low-risk cases, we found that the TXA group had a decreased need for additional uterotonic agents when compared with 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 based on Egger's test ($P=.001$). The certainty of evidence was rated as very low because of concerns of risk of bias, inconsistency, and publication bias (Table 2). The test for interaction between low-risk and high-risk patients was significant ($P<.001$). A 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 for nonthromboembolic 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, <.001). The credibility of the evidence was judged to be low because of potential concerns around the risk of

bias, inconsistency, and publication bias (Table 2). In a sensitivity analysis with exclusion of low-quality studies, the results remained the same (Supplementary Figure 22).

Thromboembolic events

A total of 28 studies assessed thromboembolic events, but because the trials were largely underpowered to detect this rare outcome, only 3 observed any events (Supplementary Table 3). Hence, we synthesized this outcome qualitatively. Xu et al⁷⁶ reported a similar incidence of deep vein thrombosis in the TXA arm (2/88) and the placebo arm (2/86) ($P=.38$). Sentilhes et al⁸⁴ reported that the risk for thromboembolic events did not differ significantly between the 2 groups (RR, 4.01; 95% CI, 0.85–18.88). Pacheco et al²⁵ reported that the proportion of patients with a thromboembolic event was comparable between the 2 groups (8/5069 vs 13/4996).²⁵

Maternal morbidity

Eighteen trials assessed maternal morbidity but most reported no events (Supplementary Table 3). Shady and Sallam⁶⁷ reported that fewer women in the TXA group needed additional surgical interventions (17.5% vs 52.5% uterine and internal iliac artery ligation). Abbas et al⁷⁹ and El-Sttar et al³⁹ 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 al⁸⁴ 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). Pacheco et al²⁵ reported that the number of patients who required surgical or radiological interventions, such as a laparotomy, hysterectomy, or intrauterine balloon tamponade, to control bleeding was similar between the 2 groups (233/5525; 4.2% vs 231/5470; 4.2%).

Maternal mortality

Six trials assessed maternal mortality but only 1 trial reported any events (Supplementary Table 3). Pacheco et al²⁵ reported that the risk of maternal deaths was similar between the 2 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 al⁷¹ reported that there was 1 case of intra-uterine fetal death in the placebo group, and 1 neonate in the TXA group developed seizures within the first 24 hours because of maternal chorioamnionitis and was diagnosed with early neonatal sepsis. El-Gaber et al⁸⁰ reported no difference in either the rate of NICU admission (2.4% vs 2%) or neonatal respiratory distress syndrome (5.6% vs 5.2%) between the 2 groups.

Comparison 2: Tranexamic acid vs prostaglandin analogs. Only 2 studies (360 patients) used prostaglandin analogs, such as misoprostol, as the comparator (Supplementary Table 3).^{60,72} Tabatabaie et al⁷² reported the mean total blood loss determined by the gravimetric method (500.90 ± 102.24 in the TXA group vs 390.08 ± 164.09 in the misoprostol group; $P < .001$). Pakniat et al⁶⁰ 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 nonthromboembolic adverse events (43 in the TXA group vs 35 in the misoprostol group). Both studies reported a reduction in the hemoglobin levels. Tabatabaie et al⁷² found a smaller reduction in the hemoglobin levels in the TXA group than in the misoprostol group (-1.02 ± 0.35 vs -1.19 ± 0.52 g/dL; $P < .001$). Pakniat et al⁶⁰ reported a greater reduction in the hemoglobin levels in the TXA group than in the misoprostol group (-2.45 ± 0.84 vs -2.14 ± 1.38 g/dL; $P < .001$).

Comment

Main findings

In this meta-analysis that included 50 RCTs, we evaluated the efficacy of prophylactic administration of TXA to

reduce PPH in groups of low- and high-risk women who underwent cesarean delivery. We found that administration of TXA probably reduced the risk of blood loss >1000 mL in low-risk patients, and the reduction was likely greater among high-risk patients. We also found that TXA might reduce the mean total blood loss slightly in low-risk patients and might 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 when compared with administration before skin incision, which led to large reductions in blood loss >1000 mL and need for blood transfusion.

The TXA safety data suggest that there was a high risk for 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 based on the GRADE approach demonstrated that the quality of evidence in the low-risk group was low to very low for all outcomes, whereas 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 a cesarean delivery.^{9,26,85} However, in contrast with the previous meta-analysis by Bellos and Pergialiotis⁹ in low-risk patients that reported a higher level of certainty of evidence based on their assessment of the RCTs to be 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 RCT in this subpopulation.

Two of the largest trials on this topic⁸⁴ with a total of 4431 and 11000 participants, respectively, reported no substantial benefits of TXA in reducing the risk for 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.

However, the neutral findings of the large RCTs might be a consequence of 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, because 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 has greater benefit for high-risk populations. Our review also sought to compare the use of TXA and misoprostol; however, because only 2 trials addressed this comparison and because of conflicting results between them,^{60,72} no conclusion can be drawn on the comparative effectiveness of TXA and misoprostol.

Overall, TXA can be considered a cost-effective drug that is 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 the 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, and women for whom blood loss had to 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 examined high-risk patients who have mostly been excluded from previous reviews, and it also examined TXA in comparison 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 were also not reported in most trials because of a lack of postdischarge 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 because it shows a statistically significant reduction in the need for blood transfusion and the risk of bleeding >1000 mL. This, combined with the fact that TXA has a low cost and is easy to administer, further promises positive impacts in healthcare. Nevertheless, because of the low quality of the evidence that supports these findings, additional high-quality data are required before it can be administered prophylactically in all women who undergo cesarean deliveries. Although most trials, including the 2 largest trials, report statistically significant reductions in the 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. In addition, more studies in high-risk patients are required and the ongoing Tranexamic Acid for Preventing Blood Loss Following a Cesarean Delivery in Women With Placenta Previa trial (NCT04304625) and the World Maternal Antifibrinolytic 2 Trial⁹² will provide valuable evidence in this regard. Further research is also needed to shed light on the pharmacokinetics and the timing of administration of TXA and to compare the efficacy of TXA with other uterotonic agents, especially misoprostol. The ongoing Pharmacokinetics and Pharmacodynamics of Tranexamic Acid in Women Having Cesarean Section Birth trial⁹³ will help to provide more evidence in this regard. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ajogmf.2023.101049.

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