Systematic review

Efficacy and safety of tranexamic acid versus placebo for preventing postpartum hemorrhage after cesarean section: systematic review and meta-analysis

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No conflicts of interest.

Abstract
Introduction. Postpartum hemorrhage is one of the leading causes of maternal morbidity and mortality worldwide. Tranexamic acid has been used as prophylaxis for postoperative blood loss. **Objective.** Evaluate the efficacy and safety of tranexamic acid in the prevention of postpartum hemorrhage in cesarean sections, compared to placebo. **Methodology.** A systematic review with meta-analysis was performed. The search was conducted in PubMed, Scopus, Web of Science, and EMBASE. The primary outcomes were the incidence of postpartum hemorrhage, total blood loss at the end of the study, and two hours postpartum. The risk of bias was assessed using RoB 2.0 and the GRADE methodology for certainty of evidence. Meta-analyses were performed using a random-effects model and the inverse variance method. Subgroup, sensitivity, and meta-regression analyses were performed. **Results.** Twenty-three randomized clinical trials were included. Tranexamic acid significantly reduced total blood loss at the end of the study (SMD = -0.97; 95 % CI: -1.64 to -0.30) and two hours postpartum (SMD = -1.19; 95 % CI: -1.62 to -0.76), with consistent results in the sensitivity analysis (I^2 = 0 %), especially if administered 10 to 20 minutes before the incision (MD = -170.10; 95 % CI: -229.28 to -110.93) and a reduction in the risk of postpartum hemorrhage (RR 0.84; 95 % CI: 0.76 to 0.93). **Conclusion.** The intervention reduced blood loss in cesarean sections when blood loss quantification and drug administration are performed in a standardized and consistent manner; it may decrease the need for blood transfusions and the use of additional uterotonics, without replacing active management of the third stage of labor. Protocol registration number. CRD42025648583.

Keywords
Postpartum Hemorrhage, Tranexamic Acid, Cesarean Section.

Resumen
Introducción. La hemorragia posparto es una de las principales causas de morbimortalidad materna en el mundo. El ácido tranexámico ha sido utilizado como profilaxis para la pérdida sanguínea postoperatoria. **Objetivo.** Evaluar la eficacia y seguridad del ácido tranexámico contra placebo en la prevención de la hemorragia posparto en cesáreas. **Metodología.** Se realizó una revisión sistemática con metaanálisis. La búsqueda fue realizada en PubMed, Scopus, Web of Science y EMBASE. Los desenlaces primarios fueron la incidencia de hemorragia posparto, pérdida total de sangre, al final del estudio y, a las dos horas posparto. El riesgo de sesgo se evaluó mediante RoB 2,0 y la metodología GRADE para la certeza de la evidencia. Los metaanálisis se realizaron con un modelo de efectos aleatorios y el método de varianza inversa. Se realizaron análisis de subgrupos, sensibilidad y metarregresión. **Resultados.** Se incluyeron 23 ensayos clínicos aleatorizados. El ácido tranexámico redujo la pérdida total de sangre al final del estudio (DME = -0,97; IC 95 %: -1,64 a -0,30) y a las dos horas posparto (DME = -1,19; IC 95 %: -1,62 a -0,76), con resultados consistentes en el análisis de sensibilidad (I^2 = 0 %), especialmente si se aplicó entre diez a 20 minutos antes de la incisión (MD = -170,10; IC 95 %: -229,28 a -110,93) y una reducción del riesgo de hemorragia posparto (RR 0,84; IC 95 %: 0,76 a 0,93). **Conclusión.** La intervención demostró una reducción significativa de la pérdida sanguínea durante la cesárea cuando tanto la cuantificación del sangrado como la administración del fármaco se realizaron de forma estandarizada y homogénea. Asimismo, se observó una posible disminución en la necesidad de transfusiones sanguíneas y en el uso de uterotónicos adicionales, sin que ello sustituya el manejo activo del tercer período del parto. Número del protocolo. CRD42025648583.

Palabras clave
Hemorragia Posparto, Ácido Tranexámico, Cesárea.

Introduction

Postpartum hemorrhage (PPH) is one of the leading causes of maternal morbidity and mortality worldwide, and is particularly relevant in women who have undergone cesarean section.[i] This type of hemorrhage is defined as blood loss greater than 1000 mL after delivery or accompanied by symptoms or signs of hypovolemia within 24 hours after birth.[ii]

In the most severe cases, it can lead to complications and the need for blood transfusions, hysterectomy, admission to intensive care units, or death.[iii] Despite advances in medical treatment, surgical techniques, and postoperative care, PPH remains a challenge in obstetrics, with direct implications for maternal health and healthcare system costs.[iv]

Globally, the proportion of cesarean deliveries is increasing, leading to a rise in cases of post-surgical hemorrhage.[v] According to recent statistics, cesarean sections account for approximately 30 % of deliveries in developed countries such as Canada and 20 % of all deliveries worldwide.[vi] It is estimated that between 1 % and 5 % of these procedures may be complicated by PPH.[vii] Maternal mortality attributed to PPH remains high in some regions, underscoring the urgent need for effective strategies to prevent and treat this complication.[viii]

PPH is the leading cause of maternal mortality in low-income countries and accounts for 26.4 % of all maternal deaths worldwide. Its prevalence varies by region, ranging from 2.4 % to 12.1 %.[ix]

In this context, tranexamic acid (TXA) has emerged as an option for reducing PPH in women undergoing cesarean section.[x] TXA is an antifibrinolytic agent that acts by inhibiting the premature dissolution of blood clots, which can help control excessive blood loss.[xi] Its use has become widespread in various surgical and trauma settings, and it has been proposed as a prophylactic intervention for PPH.[ix] However, evidence of its efficacy compared to placebo or standard treatment remains under investigation. It is important to include new studies to update the scientific evidence, consolidate current findings, and provide a more accurate assessment.[xii]

Therefore, the objective of this systematic review was to evaluate the efficacy and safety of TXA in the prevention of postpartum hemorrhage in women undergoing cesarean section, comparing its use with placebo or standard treatment. The aim was to provide a clear answer to the research question: Is tranexamic acid more effective than a placebo in reducing postpartum hemorrhage in women undergoing cesarean section?

Methodology

Study design

A systematic review with meta-analysis was conducted in accordance with the recommendations of the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The protocol was prospectively registered on the PROSPERO (International Prospective Register of Systematic Reviews) platform under registration number CRD42025648583.

Searches

A systematic search was conducted in the PubMed, Scopus, Web of Science (WoS), and EMBASE databases, from their inception to December 31, 2024. An adapted search strategy was applied to each database, using free terms in all cases, MeSH thesauri in PubMed, and Emtree thesauri in EMBASE and Scopus (Supplementary Material). The main search terms were "postpartum hemorrhage," "tranexamic acid," and "cesarean section." No language or publication date restrictions were applied.

Eligibility criteria

All randomized controlled trials in a hospital setting that evaluated pregnant women and compared TXA prophylaxis with placebo or standard treatment were included.

Conference abstracts and retracted articles were excluded. Studies that included women with serious medical or surgical conditions, such as cardiac, hepatic, or renal complications; hematological disorders with a predisposition to bleeding; hypersensitivity to TXA; history of thromboembolism, preeclampsia, or antepartum hemorrhage; as well as cases of polyhydramnios, multiple pregnancies, fetal macrosomia, or ongoing anticoagulant treatment were also excluded.

Outcomes

The primary outcomes were total blood loss, defined as the estimated volume of blood loss at the end of the study; total blood loss at two hours, corresponding to the volume lost during delivery and in the two hours following delivery; and the incidence of postpartum hemorrhage, defined as a loss of more than 1000 mL or the need for red blood cell transfusion within two days after delivery. Studies that calculated blood loss using the gravimetric method or estimated blood loss (EBL) were considered.

Secondary outcomes included clinical and laboratory variables related to blood loss. The occurrence of mild adverse events, such as diarrhea, nausea, vomiting, and headache, as well as serious adverse events associated with the procedure, such as thromboembolic complications, hypersen-

sitivity reactions, and other medical complications, were systematically documented.

The length of hospital stay was also evaluated to estimate the impact of the intervention on recovery time, the proportion of patients requiring blood transfusion, and the need for additional administration of uterotonics.

Selection process

The records obtained from the electronic searches were exported to EndNote Web software, where they were consolidated into a library, and duplicates were removed. The library was then uploaded to the Rayyan platform for initial screening of titles and abstracts, applying the inclusion and exclusion criteria. The studies selected in the initial screening were evaluated in full text for a new review process, with the inclusion and exclusion criteria reapplied and justified. Subsequently, eligible studies were included in the systematic review, and the data extraction process was initiated. This stage was evaluated blindly and independently by reviewers XSL, DAT, HCG, CMG, KVA, and ZIA. Conflicts were resolved at each stage by team consensus.

Data extraction

Data from each study were extracted individually using a pre-designed format in a Microsoft Excel spreadsheet. For each analysis, information was collected on the author, year of publication, country, type of study, number of participants per intervention group, mean age per group, eligibility criteria, description of the intervention and control, and primary and secondary outcomes.

Risk of bias assessment

Risk of bias (RoB) was assessed using the RoB 2.0 tool by reviewers DAT, HCG, CMG, KVA, and ZIA. RoB was classified by domain as low, with some concerns, or high. Disagreements were resolved through discussion with a sixth reviewer (XSL).

Data synthesis

The meta-analysis was performed using a random-effects model, applying the inverse variance method to estimate the effects of TXA compared with placebo on primary and secondary outcomes. The variance between studies (τ^2) was estimated using the Paule-Mandel method.

Continuous outcomes were analyzed using mean differences (MD) or standardized mean differences (SMD), as appropriate, accompanied by their 95 % confidence intervals (95 % CI).

For dichotomous outcomes, the effect was quantified using relative risk (RR) with 95 % confidence intervals (95 % CI). In studies with no events in one or both groups, a continuity correction was applied. Confidence intervals were adjusted using the Hartung-Knapp-Sidik-Jonkman method for meta-analyses with more than five studies or the Profile Likelihood method for those with five or fewer.

Heterogeneity between studies was assessed using the I^2 statistic, considering low (< 30 %), moderate (30-60 %), and high (> 60 %) levels. Heterogeneity was explored using subgroup analysis and meta-regression using mixed-effects models. For sensitivity analysis, meta-analyses were performed under a fixed-effects model using the Mantel-Haenszel method, along with additional analyses excluding studies with high heterogeneity or specific characteristics that could influence the results. The presence of publication bias was assessed using funnel plots and Egger's test. The analysis was performed in R (version 4.4.2; www.r-project.org) using the "metabin" function of the "meta" package.

GRADE assessment

The certainty of the evidence and the level of recommendation were assessed using the GRADE methodology, which considered the domains of risk of bias, inconsistency, indirect evidence, imprecision, and publication bias. The assessment was performed for each outcome and summarized in summary of findings (SoF) tables, developed using the online software GRADEpro GDT (Supplementary Material).

Results

Study selection

A total of 1446 articles were identified in four databases, of which 736 duplicates were removed. After screening, 710 were evaluated by title and abstract, and 660 were excluded for not meeting the inclusion criteria. Fifty full-text articles were analyzed, and 27 were discarded due to irrelevant population (n = 12), inadequate intervention (n = 6), incompatible design (n = 3), conference abstracts (n = 3), or absence of the full-text document (n = 3). Finally, 23 randomized clinical trials (n = 19 935) were included for qualitative and quantitative analyses[xiii-xxxv] (Figure 1).

Characteristics of participants and included studies

The 23 randomized clinical trials included were published between 2009 and 2024 and conducted in various regions of the world, including Asia (India, Iran, Bangladesh, and Pakistan), Africa (Egypt and Nigeria), Europe (Italy and France), North America (the United States), and the Middle East (Turkey). Most of the studies were single-center, except for two large-scale multicenter studies conducted in the United States and France (Pacheco *et al.*, 2023, and Sentilhes *et al.*, 2021), which included 11 000 and 4431 participants, respectively.

Significant differences were observed between the mean ages of the groups in two studies (Vishal *et al.*, 2023 and Sentilhes *et al.*, 2021), as well as between the mean ages when comparing the different studies ($p < 0.05$).

The methods used to estimate blood loss varied, with the most common being the weighing of surgical pads and towels (gravimetric method) and the use of formulas to calculate EBL. The duration of follow-up was 24 to 72 hours, in most studies; however, the trials by Lee *et al.*, (2023), Sentilhes *et al.*, (2021), and Pacheco *et al.*, (2023) included longer follow-up to assess thromboembolic events and other maternal complications[xviii,xxvii,xxxi] (Table 1).

Risk of bias assessment

Seven studies were identified as having a high risk of bias, and four as having some concerns. The studies with a high risk of bias had biases in the randomization process domain, as well as some concerns in the domains of deviations from the planned interventions and selection of reported outcomes. On the other hand, studies with some concerns showed limitations in the domains of the randomization process, deviations from the planned interventions, and the selection of reported outcomes (Figure 2).

Primary outcomes

Total blood loss

TXA significantly reduced total blood loss in patients undergoing cesarean section (SMD = -0.97, 95 % CI: -1.64 to -0.30; I^2 = 96.9 %; 11 studies, 6457 participants; very low certainty of evidence); however, heterogeneity was considerable (Figure 3). Subgroup analysis according to the method of blood loss estimation eliminated heterogeneity in the group using EBL ($p = 0.94$), suggesting that all heterogeneity originated from studies using the gravimetric method (Figure 4).

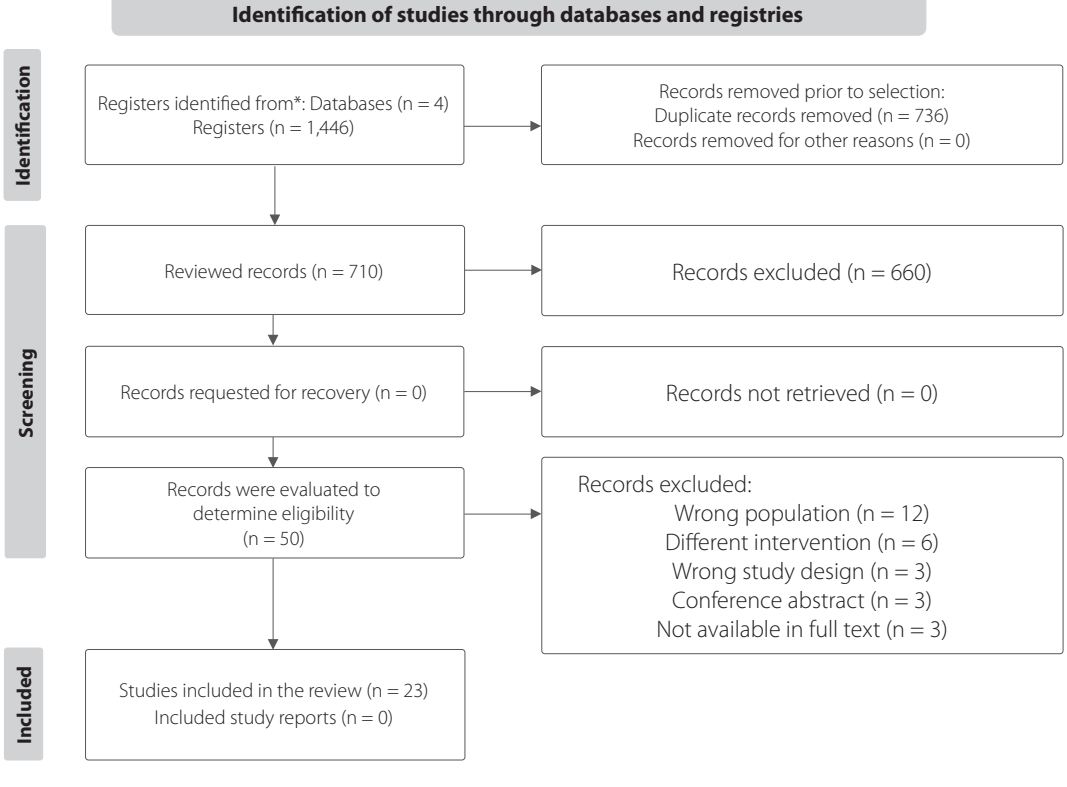

Figure 1. PRISMA flow diagram of study selection.

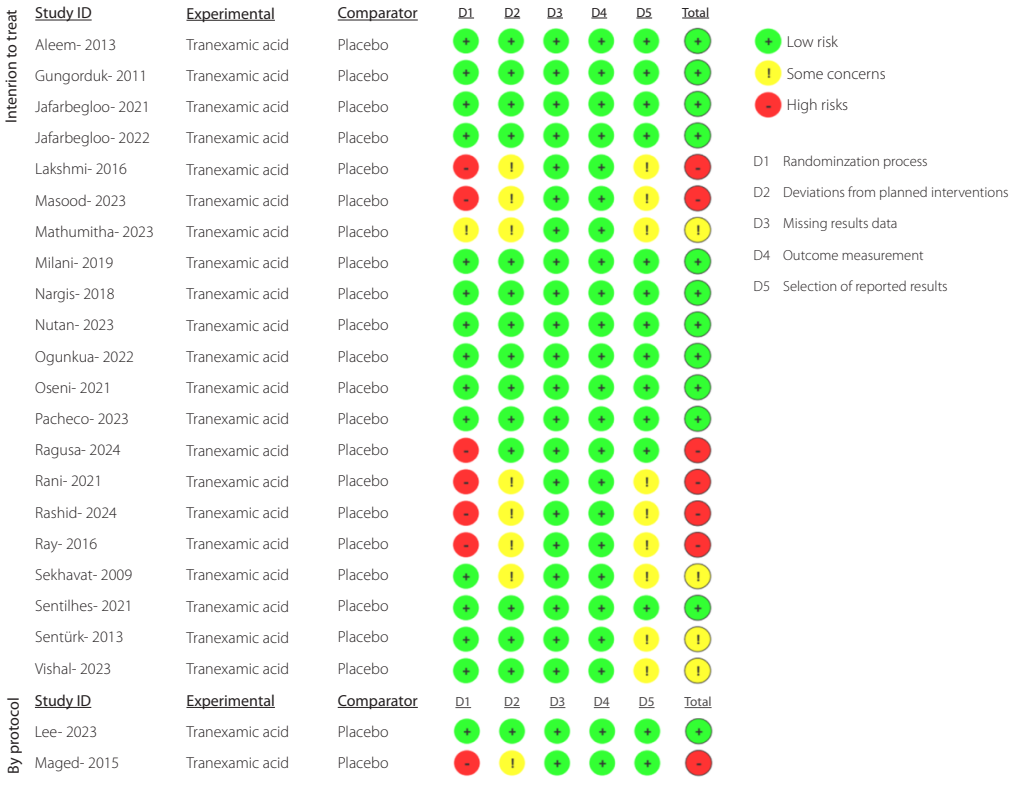

Figure 2. Risk of bias of the included studies.

A meta-regression analysis was performed to identify predictors of heterogeneity. The model explained much of the observed heterogeneity (R^2 = 89.62 %), although significant residual heterogeneity persisted (I^2 = 87.93 %; τ^2 = 0.0996). While the model explained much of the heterogeneity, the residual heterogeneity indicates that factors not considered in the model persist and influence the variability between studies, reflecting the complexity of this scenario. Among the variables analyzed, the method of measuring blood loss, the timing of TXA administration, and the age of the participants were the factors that contributed most significantly to the observed heterogeneity (Supplementary Material).

The funnel plot showed an asymmetric distribution of studies, suggesting the possible presence of publication bias or unexplained heterogeneity. Egger's test showed a p-value of 0.0214, supporting the existence of asymmetry. This finding is consistent with the heterogeneity identified in the analysis (Supplementary Material).

A subgroup analysis was performed based on the method used to quantify blood loss, classified by EBL, gravimetric quantification, and studies that did not specify the method. Studies with EBL showed a significant reduction in bleeding with the use of TXA (MD = -104.91 mL; 95 % CI: -119.58 to -90.24; I^2 = 0 %; four studies, 5378 participants; moderate certainty of evidence). Similarly, the study without a specified method reported[xix] a significant decrease (MD = -131.67 mL; 95 % CI: -186.02 to -77.32; one study, 60 participants; moderate certainty of evidence). In contrast, studies using gravimetric quantification showed the greatest reduction in mean blood loss, albeit with high heterogeneity (MD = -195.71 mL; 95 % CI: -305.06 to -52.37; I^2 = 99.1 %; six studies, 998 participants; very low certainty of evidence). These results indicate that the overall heterogeneity originates mainly in the latter group (Figure 4).

In the subgroup analysis according to the timing of TXA administration, no significant difference in blood loss was found when the drug was administered after the start of the cesarean section (MD = -147.95 mL; 95 % CI: -399.65 to 103.75; I^2 = 98.9 %; four studies, 5016 participants; very low certainty of evidence), with high heterogeneity. In contrast, when administered 10 to 20 minutes before the start of the cesarean section, the reduction in bleeding was greater and statistically significant (MD = -151.65 mL; 95 % CI: -227.90 to -75.40; I^2 = 84.9 %; six studies, 1341 participants; low certainty of evidence). In the group without reporting the time of administration, the reduction was -269.05 mL (95 % CI: -301.86 to -236.24; one study, 100 participants; low certainty of evidence) (Supplementary Material).

Table 1. Characteristics of the included studies.

Author and year of publication	Country	Study design	Number of center s	Follow-up duration	Inclusion period	Number of participants	Age, mean (SD)	Method for calculating blood loss	Time of drug administration (15 minutes before or after incision)
Aleem- 2013[xii]	Egypt	Randomized controlled trial with concealed allocation, single- blind	1	24 hours	August 2010 to December 2011	740	Study group 26.34 (5.16) Control group 26.62 (5.05)	Gravimetric method	Before
Gungorduk-2011[xiv]	Turkey	Prospective, randomized, double-masked, controlled study	1	3 and 6 weeks	June 1, 2009, to September 30, 2009	660	Study group 26.3 (3.5) Control group 26.6 (3.6)	EBL	Before
Jafarbegloo-2021[xv]	Iran	Randomized, controlled, double- blind clinical trial	1	72 hours	August 15, 2016 to April 30, 2017	50	Study group 30.48 (4.71) Control group 31.46 (4.85)	Gravimetric method	Before
Jafarbegloo-2022[xvi]	Iran	Randomized controlled trial, double-blind	1	72 hours	August 15, 2016 to April 30, 2017	50	Study group 30.48 (4.71) Control group 31.46 (4.85)	Gravimetric method	Before
Lakshmi- 2016[xvii]	India	Randomized controlled trial, open-label	1	24 hours	June 2014 to May 2015	120	Study group 26.77 (2,807) Control group 26.82 (2.801)	Gravimetric method	After
Lee- 2023[xviii]	Singapore	Double-blind, randomized, controlled trial	1	6 weeks	June 2020 to October 2021	200	Study group 33.6 (4.5) Control group 33.9 (4.1)	EBL	Before
Maged- 2015[xxi]	Egypt	Single-blind, randomized, controlled study	1	4 weeks	November 1, 2013 to November 30, 2014	214	Study group 24.9 (4.6) Control group 25.3 (4.7)	EBL	Before
Masood- 2023[xix]	Pakistan	Randomized controlled trial, open-label	1	Not reported	December 17, 2018 to June 17, 2019	60	Study group 36.41 (13.89) Control group 34.31 (5.13)	Not reported	Before
Mathumitha-2023[xx]	India	Randomized controlled trial	1	2 hours	Not reported	50	Study group 26.4 (2.75) Control group 27.52 (3.07)	Gravimetric method	Before
Milani- 2019[xxii]	Iran	Randomized double-blind controlled trial	1	24 hours	2015 to 2016	60	Study group 29.33 (5.59) Control group 31.2 (5.53)	Gravimetric method	Before
Nargis- 2018[xxiii]	Bangladesh	Randomized controlled trial, double-blind	1	24 hours	June 2016 to May 2017	120	Study group 25.34 (3.8) Control group 25.68 (3.3)	Gravimetric method	After
Nutan- 2023[xxiv]	India	Randomized double-blind controlled trial	1	48 hours	April 2021 to August 2022	72	Study group 29.42 (2.81) Control group 29.44 (3.71)	Gravimetric method	Before
Ogunkua-2022[xxv]	United States	Double-blind, randomized, controlled trial	1	24 hours	June 17, 2019 to October 2020	110	Study group 29.8 (5.2) Control group 28.7 (5.2)	EBL	Before
Oseni- 2021[xxvi]	Nigeria	Double-blind, randomized, controlled trial	1	5 days	December 2017 to June 2018	244	Study group 27.6 (4.6) Control group 27.5 (4.6)	Gravimetric method	Before

Author and year of publication	Country	Study design	Number of center s	Follow-up duration	Inclusion period	Number of participants	Age, mean (SD)	Method for calculating blood loss	Time of drug administration (15 minutes before or after incision)
Pacheco- 2023	United States	Multicenter controlled trial, double-blind, randomized	31	7 days and at 6 weeks	March 2018 to July 2021	11 000	Study group 30.1 (5.8) Control group 30.1 (5.8)	Visual method and data obtained from the anesthesia record and surgical report	After
Ragusa- 2024	Italy	Multicenter, randomized, open- label controlled trial randomized, open- label	2	7 days and 40 days	January 7, 2020 to June 30, 2023	231	Study group 32.25 (2.03) Control group 32.25 (2.03)	Gravimetric method	After
Rani- 2021	India	Controlled, randomized, open-label clinical trial	1	24 hours	January 2019 to January 2020	100	Study group 25.0 (4.71) Control group 25.88 (5.39)	Gravimetric method	Before
Rashid- 2024	India	Randomized controlled clinical trial	1	24 hours	January 2021 to June 2022	100	Study group 23.21 (3.12) Control group 23.54 (3.74)	Gravimetric method	Not reported
Ray- 2016	India	A randomized, controlled, open-label clinical study	1	24 hours	May 2012 to April 2013	100	Study group 25.0 (4.71) Control group 25.88 (5.39)	Gravimetric method	Before
Sekhavat- 2009	Iran	Prospective, randomized controlled clinical trial	1	24 hours	June 2004 to April 2005	90	Study group 26.2 (4.7) Control group 27.1 (4.1)	Gravimetric method	Before
Sentilhes- 2021	France	Multicenter, randomized, placebo-controlled, double-blind trial	27	48 hours	March 2018 to January 2020	4431	Study group 33.3 (5.3) Control group 33.5 (5.3)	EBL	After
Sentürk- 2013	Turkey	Randomized, double-blind clinical trial	1	48 hours and 2 weeks	October 5, 2010 to December 5, 2010	223	Study group 30.20 (6.83) Control group 29.22 (6.93)	Gravimetric method	Before
Vishal- 2023	India	Prospective, randomized, double-blind, controlled	1	48 hours	December 2018 to June 2021	910	Study group 24.2 (3.9) Control group 24.5 (3.85)	Gravimetric method	Before

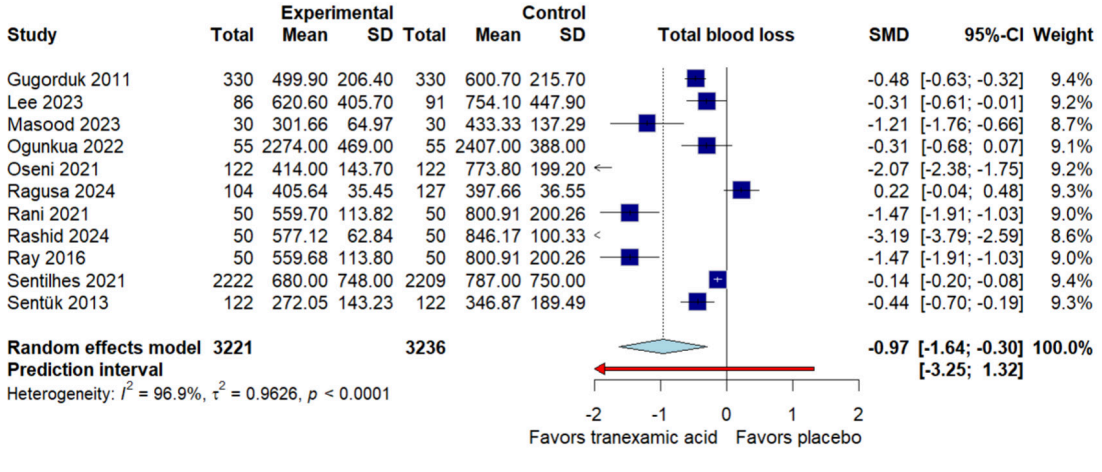

Figure 3. Total blood loss

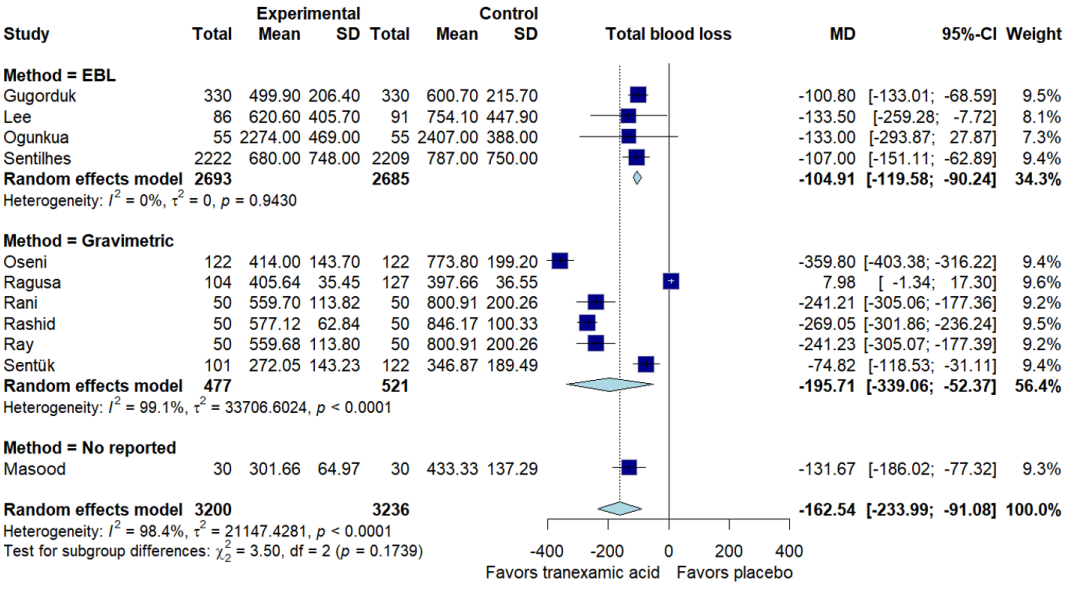

Figure 4. Subgroup analysis of total blood loss.

Total blood loss at two hours

Blood loss at two hours postpartum showed a significant decrease (SMD -1.25, 95 % CI: -1.72 to -0.78; I^2 = 93.8 %; eight studies, 2202 participants; moderate certainty of evidence) (Figure 5). Meta-regression (n = 8) explained 100 % of the heterogeneity (τ^2 = 0; I^2 = 0 %). The residual heterogeneity test was not significant (p = 0.84), while the moderator test was (p < 0.0001). Single-blinding studies were the primary source of variability in this outcome (Supplementary Material).

In the subgroup meta-analysis according to blinding level, double-blind studies showed no heterogeneity, while single-blind studies accounted for 54.3 % of the total heterogeneity. The remaining heterogeneity was attributed to the method of quantifying blood loss and the age of the participants. In this group, six of the eight studies calculated loss using the gravimetric method, one used EBL, and the other did not report the measurement method. Six studies administered the drug 10 to 20 minutes before incision (MD -177.23, 95 % CI: -245.59 to -108.87; I^2 = 78.3 %; six studies, 552 participants; low certainty of evidence) (Supplementary Material).

Sensitivity analysis for this outcome showed a considerable decrease in heterogeneity when excluding the study by Aleem *et al.* (2013), identified as the main source of variability, and that by Maged *et al.* (2015), which calculated blood loss using EBL. The remaining studies estimated blood loss using the gravimetric method. A significant reduction in total blood loss was observed (SMD = -0.97; 95 % CI: -1.18 to -0.77; I^2 = 10.9 %; six studies, 1262 participants; moderate certainty of evidence), with low heterogeneity (Figure 6).

Postpartum hemorrhage

The use of TXA was associated with a relative reduction in the risk of PPH compared with the control group (RR 0.84; 95 % CI: 0.76 to 0.93; I^2 = 28.2 %; 13 studies, 17 863 participants; low certainty of evidence) (Figure 7). The funnel plot showed an asymmetric distribution of studies. The Egger test confirmed this asymmetry, with a p-value < 0.05 (Supplementary Material).

Secondary outcomes

The use of TXA was associated with a lower need for additional interventions, such as the use of uterotonics (RR 0.67; 95 % CI: 0.49 to 0.91; I^2 = 56 %; 11 studies, 18 685 participants; low certainty of evidence) and blood transfusion (RR 0.57; 95 % CI: 0.33 to 0.99, I^2 = 30 %; nine studies, 17 723 participants; low certainty of evidence) (Supplementary Material).

No significant differences were identified between the use of TXA and length of hospital stay (SMD -0.14; 95 % CI: -0.59 to 0.30; I^2 = 95 %; five studies, 13 499 participants; very low certainty of evidence) (Supplementary Material).

The use of TXA was associated with an increased risk of side effects compared with the control group (RR 1.50; 95 % CI: 1.01 to 2.24; I^2 = 91.6 %; 15 studies, 18 788 participants; very low certainty of

evidence). Adverse effects assessed included nausea, vomiting, headache, and diarrhea (Supplementary Material).

There was no evidence of a significant association between TXA use and an increase in the occurrence of serious adverse events, such as thromboembolism (RR 1.16; 95 % CI: 0.86 to 1.55; I^2 = 0 %; 15 studies, 17.706 participants; very low certainty of evidence) (Supplementary Material).

Discussion

PPH is one of the leading causes of maternal morbidity and mortality worldwide, especially in low- and middle-income countries.[ix] In this context, cesarean delivery carries an inherently higher risk of PPH compared with vaginal delivery.[vii] This systematic review and meta-analysis evaluated the efficacy and safety of TXA compared with

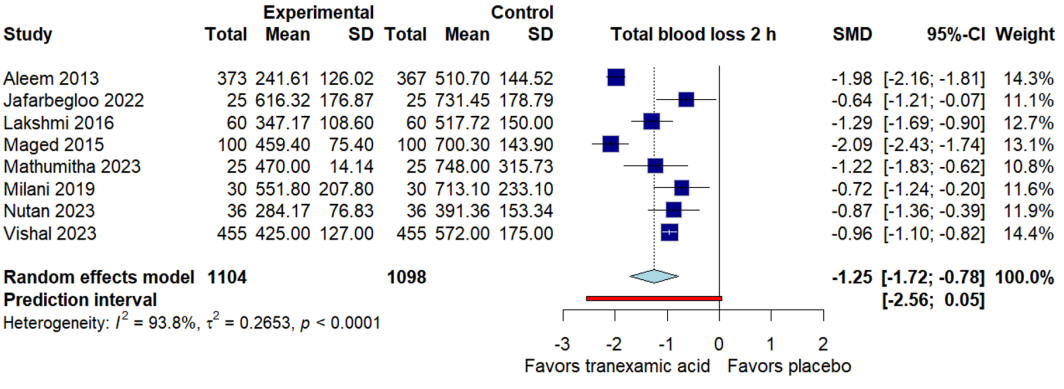

Figure 5. Total blood loss at two hours

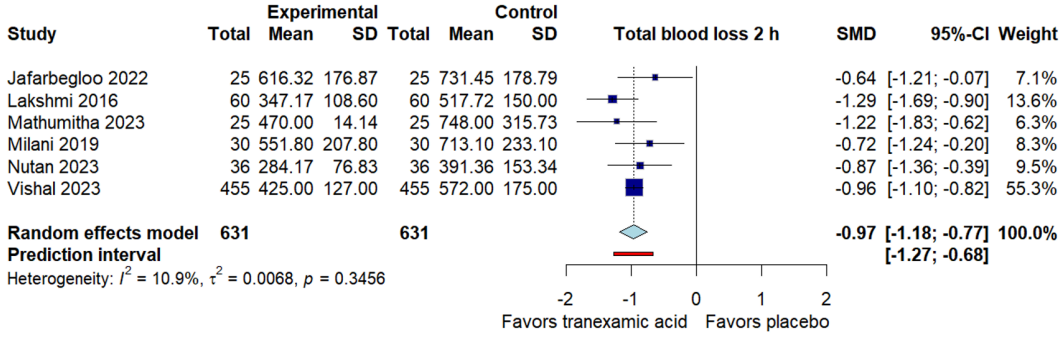

Figure 6. Sensitivity analysis of total blood loss at two hours.

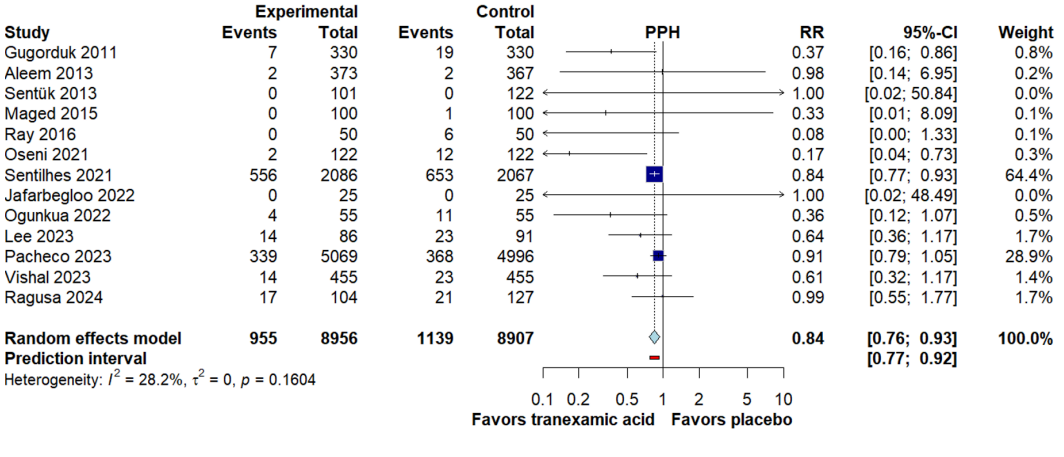

Figure 7. Incidence of postpartum hemorrhage

placebo for the prevention of PPH after cesarean section, providing a comprehensive analysis of 23 randomized clinical trials involving 19 935 participants.

The use of TXA was associated with a significant reduction in total blood loss compared with placebo. Although high heterogeneity was observed between studies, subgroup, sensitivity, and meta-regression analyses identified the main source of variability. This was mainly related to the methodology used to quantify blood loss, the timing of drug administration, and differences in mean age between groups. These findings explain most of the observed heterogeneity and reinforce the robustness of the results, increasing confidence in the effectiveness of the treatment.

The results of this study are consistent with the evidence previously reported in 2023 by Ammar Al Naimi *et al.*, who documented a significant reduction in blood loss with the use of TXA; however, they highlighted the influence of the clinical context on the magnitude of the observed benefit.[xxxvi] This finding is particularly relevant, given the methodological variability identified in the present

Analysis, which suggests that both clinical conditions and methodological approaches can significantly influence treatment effectiveness. Similarly, in 2015, Asim Alam *et al.*, pointed out that the efficacy of TXA may depend on the specific technique used for the cesarean section, the indication for the cesarean section, and the surgical hemostasis techniques employed, an aspect that is also reflected in the subgroup analyses performed in this study.[xxxvii]

This high heterogeneity has also been reported by previous studies with similar methodological characteristics,[xxxviii-xli] suggesting that it is an inherent limitation of the design and variability in methods of quantifying blood loss.[xlii] In particular, as a result of differences in inclusion criteria, the timing of TXA administration, and operational definitions of bleeding.[xxxvi] Despite this, the direction of the effect was consistent, reinforcing the strength of the evidence in favor of using TXA to reduce intraoperative and postoperative blood loss.[xxxviii-xl,xliii]

When analyzing only the studies that used the EBL calculation method,[xiv,xviii,xxv,xxxi] the effect and directionality remained consistent with considerably less heterogeneity. Greater certainty of evidence was evident according to the GRADE methodology, which strengthens confidence in this finding. In contrast, the group that weighed pads or measured aspiration fluids continued to show very high heterogeneity and, consequently, a very low level of evidence.[xxvi,xxviii,xxix,xxxii,xxxiv,xxxv]

A clinically important finding was that TXA administered 10 to 20 minutes prior to incision and assessed by EBL showed a significant reduction in blood loss, representing evidence of moderate certainty.[xiv,xviii,xxv] However, the timing of the intervention alone did not reduce heterogeneity, and even the group that administered the drug after the incision showed no significant results.[xxv,xxvi,xxviii,xxxi]

This temporal consideration has important clinical implications for developing drug administration protocols in the preoperative context. Standardizing interventions, definitions, and measurement methods will allow us to understand the actual effect of the intervention and provide a higher level of evidence for future research. Therefore, it is important to continue to investigate the appropriate timing of the intervention.

The difference observed in blood loss two hours after cesarean section provides additional information on the sustained effect of TXA during the immediate postoperative period, a critical time for the development of PPH. However, this outcome also showed high heterogeneity, which was attributed to the different methods of quantifying blood loss. Additionally, the meta-regression performed for this outcome explained all the observed heterogeneity, identifying that the type of blinding used in the studies was a determining factor in the variability of the reported results. A metaepidemiological study determined that simple blinding or blinding failures can lead to overestimations of the effect in surgical clinical trials, with greater heterogeneity between studies.[xliv]

The analysis, differentiated by type of blinding, showed that double-blind studies, despite using the weighing method to quantify blood loss, exhibited low heterogeneity and demonstrated a higher level of evidence. In the sensitivity analysis, when studies with simple or open blinding were excluded, heterogeneity was substantially reduced, reaching zero heterogeneity.

This analysis reinforces what has been demonstrated in other studies, where standardization of interventions, measurement methods, and operational definitions is essential to improve the accuracy and comparability of results, as well as to increase confidence in the evidence generated.[xxxvi]

In this regard, previous research highlights the need for careful methodological design in studies of obstetric hemorrhage

prophylaxis, considering that outcomes may be subject to the influence of numerous clinical, surgical, and logistical factors.[xliii,xliv] Likewise, reducing heterogeneity by excluding studies with methodological limitations or with non-homogeneous administration times highlights the need to establish uniform protocols in future research in order to maximize the hemostatic effect of treatment and reduce variability between studies.

One of the most relevant findings from a clinical perspective was the significant reduction in the incidence of PPH. In addition to the direct benefit on blood loss, there was a reduced need for complementary therapeutic interventions, such as the additional use of uterotonics [xiii,xiv,xvii,xviii,xxi,xviii,xvii,xxix,xxxi-xxxiii] or the administration of transfusions.[xiv,xvii,xviii,xxiii,xxiv,xxvii,xxxi-xxxiii]

Traditionally, uterotonics such as oxytocin have been the mainstay of PPH prevention. However, recent studies from 2024 by Ragusa *et al.*, included in this research, suggest that TXA may effectively complement standardized strategies.[xxviii] The mechanism of action of TXA, which inhibits fibrinolysis rather than promoting uterine contractions, may provide useful synergy in the comprehensive prevention of PPH.[xxxviii] These findings suggest that prophylaxis with TXA translates into significant clinical outcomes, beyond just reducing mean blood loss.

The evaluation of the safety profile of TXA showed a higher frequency of mild side effects in the intervention group compared to the placebo group. These events are consistent with those reported in 2025 by Guinness *et al.*, and included nausea, vomiting, headache, and diarrhea, which were generally mild, self-limiting, and manageable in the perioperative setting.[xxxix]

No significant differences in serious adverse events were identified between the groups. This finding is consistent with the results of Al Naimi *et al.*, in 2024. It supports the safety profile of TXA when used as prophylaxis in the obstetric population,[xxxvii] suggesting a favorable risk-benefit ratio.[xlvi]

Unlike the outcomes related to the reduction of hemorrhagic complications, no significant differences were observed in the length of hospital stay between the groups treated with TXA and placebo. This result reflects the multifactorial complexity of the determinants of hospitalization in the obstetric setting. Similar results have been reported by the 2015 meta-analysis by Alam *et al.*, who suggest that the length of stay after cesarean section may be influenced by factors unrelated to hemorrhagic complications, such as institutional protocols, obstetric risk, and postpartum outcomes for both the mother and the newborn.[xlvii]

The high heterogeneity observed suggests significant differences in postoperative management practices between different centers and healthcare systems. This variability limits the interpretation of the combined effect and suggests that hospital stay may not be a sensitive indicator for evaluating the effectiveness of hemostatic interventions in this context.

However, the combined sample included in this investigation provided sufficient statistical power to evaluate the primary outcomes. Analyses of rare adverse effects, sensitivity analyses, subgroup analyses, and meta-regression were performed. In addition, the involvement of a clinical expert in all stages of the study ensured proper technical implementation of the process.

Some limitations were found in this research. High heterogeneity was identified among the included studies, a common situation in this type of research. This was addressed through subgroup analyses and meta-regressions, which explained much of the variability; however, residual heterogeneity persisted in some secondary outcomes. Previous studies have attributed this variability to factors such as the country's economic level, population characteristics, and health care conditions, which may limit the generalizability of the results.[xxxvii,xlii,xlvii]

In addition, most of the studies included in this research excluded women with significant risk factors for hemorrhage or thrombosis. This restriction is relevant, as patients with risk factors for PPH could be candidates for this intervention. The exclusion was intended to analyze a homogeneous population to evaluate the drug's effectiveness under comparable conditions, which is crucial for providing the study with solidity and reducing possible confounding factors associated with postpartum hemorrhage. By demonstrating the effectiveness of the drug in a population such as the one described above, this finding is also applicable to patients with various risk factors.[xlviii]

Multiple sources of variability were found in the intervention protocols, the methodologies for measuring outcomes, the characteristics of the populations studied, and the geographical contexts. These factors could limit the accuracy of some combined estimates and increase heterogeneity between and within studies. However, this research addressed the causes of heterogeneity through subgroup analysis, sensitivity analysis, and meta-regression. These methods allowed for a more accurate estimation of the effect of the intervention, improved

interpretation of the results, and more robust and valuable conclusions.

The consistent results on preventing postpartum hemorrhage in cesarean sections support the need for further research to optimize its application in clinical practice, guide future studies in at-risk populations, and generate evidence-based recommendations.

However, future research must determine the most appropriate and standardized dosing regimens, as well as the efficacy of repeated doses, weight-adjusted regimens, alternative routes of administration — such as oral or intrauterine —and the optimal timing of administration in relation to specific phases of the surgical procedure.[xl]

Another line of research is the evaluation of the efficacy and safety of TXA in high-risk populations. Because many studies systematically excluded women with pre-existing conditions, knowledge about the risk-benefit balance of the drug in these groups remains limited. Conducting clinical trials and new systematic reviews that specifically include these populations would allow for more precise and clinically relevant indications to be established.

Likewise, the analysis of the combined administration of TXA with other conventional hemostatic strategies, including uterotonics, topical agents, intrauterine balloons, or compressive surgical techniques, represents a line of research with high clinical potential. Evaluating their possible interactions could identify beneficial synergistic effects or, failing that, warn of ineffective or potentially harmful combinations.

Finally, it is essential to promote greater methodological standardization in research on PPH. The lack of uniformity in clinical definitions, methods for quantifying blood loss, and criteria for diagnosing and reporting adverse effects limits the synthesis of results and the development of sound clinical recommendations. Promoting the homogenization of these aspects would strengthen the evidence base and allow for a more effective, safe, and contextualized application of tranexamic acid in obstetric care.

Conclusion

TXA reduces total blood loss during and after a cesarean section when the estimate is made using a standardized quantification method, and its effect is more consistent when both the quantification method and the timing of application are standardized and implemented together.

TXA may result in a reduction in the incidence of postpartum hemorrhage in women undergoing cesarean section. Evidence suggests that it may also reduce the need for blood transfusions and the additional use of uterotonics, without replacing the standard treatment of active management of the third stage of labor, which should remain a key intervention in the prevention of postpartum hemorrhage.

Evidence suggests that TXA results in an increase in mild side effects such as nausea, vomiting, diarrhea, and headache; however, it has no effect on hospital stay. Likewise, TXA may have little or no effect on serious adverse events, although the available evidence on this outcome is very uncertain.

The evidence is very uncertain regarding the effect of TXA on reducing total blood loss when different methods of quantifying blood loss are included, which increases the variability of the analysis and reduces the magnitude of the combined effect. Similarly, the evidence is very uncertain when the loss is estimated using gravimetric quantification.

Supplementary material

The online version contains supplementary material available at:

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