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Perioperative oxytocin infusion *versus* tranexamic acid and ethamsylate in reducing intraoperative blood loss during caesarean section: a systematic review and meta-analysis

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ABSTRACT

Objective. Review the efficacy of tranexamic acid and ethamsylate (TXAETH) infusion compared to oxytocin in reducing intraoperative blood loss during caesarean section.

Materials and Methods. Studies reporting TXAETH efficacy compared to oxytocin published up to November 24, 2023, were systematically searched across PubMed, EBSCOHost, and ProQuest. Three researchers independently extracted data. The extracted data were analysed using the MedCalc v19.5.1.

Results. In this meta-analysis, three articles were assessed involving 463 participants. There was a significant mean difference in intraoperative blood loss ($p = 0.030$, 95%CI 0.117-2.272) and postoperative haematocrit ($p = 0.004$, 95%CI -8.916 to -1.710). There was no significant mean difference in the duration of surgery ($p = 0.058$, 95%CI -0.012-0.739) and postoperative haemoglobin ($p = 0.197$, 95%CI -2.026-0.418).

Conclusions. Our studies demonstrate that using TXAETH reduced intraoperative bleeding and lowered haematocrit changes among participants. However, preoperative TXAETH has no significant advantage over the oxytocin group in terms of either the duration of surgery or postoperative haemoglobin.

INTRODUCTION

Caesarean section (CS) is a prevalent major surgical procedure, constituting nearly one-third of all births in the country. This trend is widespread globally, with increasing rates in many countries. Over time, global CS rates have risen from 7% in 1990 to 21% today, exceeding the WHO's recom-

mended 10%-15% ideal CS rate [1, 2]. However, patients undergoing caesarean delivery face an elevated risk of postpartum haemorrhage (PPH) compared to those having a vaginal delivery [3]. PPH stands as the major contributor to morbidity and mortality in childbirth, manifesting in approximately 1-6% of deliveries [4]. Uterine atony, responsible for 70-80% of all haemorrhagic

events, emerges as the predominant etiological factor in PPH [5-7]. Excessive bleeding occurring during a caesarean section has the potential to transform an otherwise standard surgical procedure into a challenging one [8].

Various drugs, such as ergometrine, oxytocin, misoprostol, carbetocin, and carboprost, have been studied to lower intraoperative blood loss during CS [9]. It is recommended to administer oxytocin post-foetal labour to stimulate uterine contractions, thereby lowering intraoperative blood loss and preventing PPH [10]. TXA, a synthetically derived lysine amino acid, acts as an antifibrinolytic by reversibly blocking lysine binding sites on the plasminogen proenzyme molecule. Commonly used to prevent and treat bleeding, TXA shows promising outcomes. Eth, an easily accessible synthetic haemostatic medication, enhances platelet adhesion and restores capillary endothelial resistance. It also exhibits anti-hyaluronidase activity, stabilizing capillary walls and reducing bleeding when platelets are deficient. Additionally, ethamsylate (Eth) functions at the initial stage of haemostasis by reinstating capillary endothelial resistance and enhancing platelet adhesiveness. This mechanism helps to reduce capillary bleeding [11]. TXA and ethamsylate (TXAEth) complement each other in haemostasis. Administering both intravenously could synergistically reduce intra- and post-operative blood loss [12]. The comparative effectiveness between oxytocin alone and the combined use of TXA and Eth remains unclear. This review aims to evaluate the efficacy of TXAEth infusion compared to oxytocin in reducing intraoperative blood loss during CS.

MATERIALS AND METHODS

Information sources

We conducted a comprehensive electronic search across various databases, including PubMed, EBSCO, and ProQuest, up to November 24, 2023. Our search method incorporated MeSH terms, keywords, and different variations of terms associated with “oxytocin”, “tranexamic acid”, “ethamsylate” and “cesarean section”. Additionally, we reviewed the reference lists of pertinent articles and reviews to identify any supplementary studies.

Search strategy

To conduct a systematic review and meta-analysis of studies analysing the comparison between perioperative oxytocin infusion *versus* TXA and Eth in reducing intraoperative blood loss during CS, we employed the following search terms: “oxytocin”, “tranexamic acid”, “ethamsylate” and “cesarean section”. These were limited to the title, abstract, and keywords.

Eligibility criteria

The literature search was conducted with a focus on clinical studies published in English. To meet the inclusion criteria, studies were required to satisfy the following conditions: 1) pregnant women with ≥ 38 weeks of gestation (GA); 2) free of other gynaecological problems (fibroid, malignancy); 3) patients must have undergone CS; and 4) the patients must receive either oxytocin or TXAEth perioperative. Our review excluded single case reports/series, editorials, commentaries, letters, and nonfull texts. The exclusion criteria encompassed conditions such as diabetes mellitus, hypertension in pregnancy, thyroid disease, cardiac and vascular disease, previous thromboembolic event, bleeding disorder, abnormal placentation (placenta previa, accreta spectrum), and anaemia. The outcomes of interest were the estimated amount of blood loss during the CS, the postoperative haemoglobin and haematocrit levels, and the duration of the surgical procedure.

Data extraction

Our study adhered to the reporting guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines and the Cochrane Risk of Bias Tool (Cochrane ROB-2) [13, 14].

All abstracts were assessed independently by two authors. Any discrepancies regarding the relevance of a particular study were resolved through discussion with a third author (C.N.R.S.).

In cases where multiple studies had the same participant group and addressed identical outcomes, we selected the study with the most comprehensive information while excluding the others to prevent duplication.

Three authors (N.A., G.M., and A.P.) independently evaluated the articles' quality in this systematic review and meta-analysis.

Statistical analysis

Meta-analysis of proportions was used to combine all the data and the reported pooled of estimated intraoperative blood loss, operation duration, postoperative haemoglobin, and haematocrit were calculated using a random-effects model. All meta-analyses were performed using MedCalc, version 19.5.1 [15]. The P-value for the overall effect, $p < 0.05$ with two-tailed, was considered statistically significant. I^2 was used to assess the heterogeneity of all the detailed studies. When it was lower than 50%, studies with acceptable heterogeneity were considered, and the random-effects model with the DerSimonian and Laird method was adopted.

Egger’s linear regression test and Begg’s rank correlation assessed publication bias for each pooled study group, when p was > 0.05 , there was no publication bias in the study. This systematic review and meta-analysis was registered in PROSPERO on November 21, 2023, with registration number CRD42023481950 (available at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=481950).

RESULTS

Study selection and data extraction

The electronic database search initially yielded 153 studies. After screening titles and abstracts, eight articles were identified for further evaluation. Eventually, three studies were included in this meta-analysis. The search process and selection criteria used in this study are shown in **Figure 1**.

Study characteristics

This systematic review and meta-analysis incorporated three primary studies (**Table 1**) involving 463 participants. All the included studies were randomized controlled trials. The administered oxytocin dosage ranged between 5-30 IU in all studies, with a pre-skin incision infusion of 1 gram of TXA and 250 mg of Eth. The review included studies conducted in both India and Egypt.

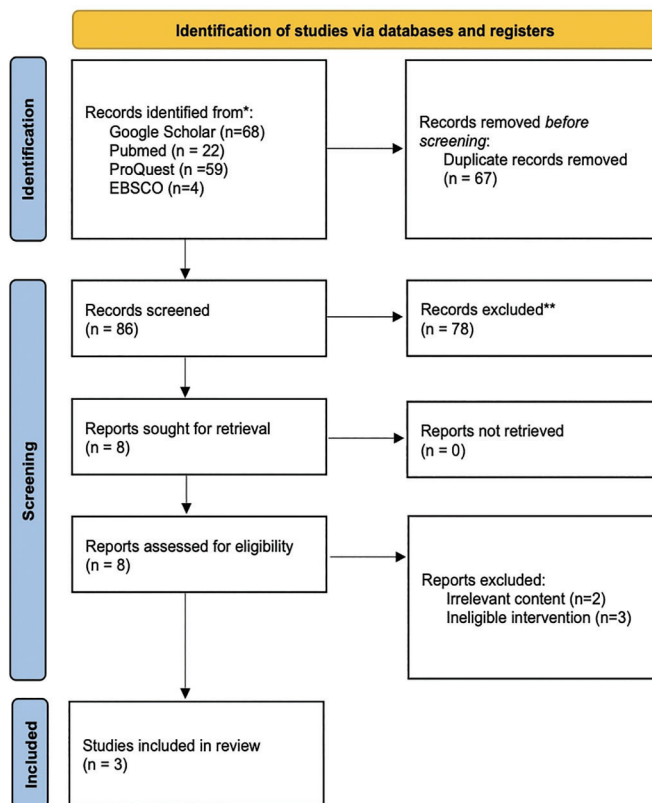


Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram. The diagram summarizes the search strategy and selection process to include articles eligible for this meta-analysis [13].

Demographically, the average maternal age ranges from 20-40 years, gestational age 38.0-41.0 weeks, and BMI 18.5-29.9 kg/m². Parity distribution showed variability, with percentages of primigravida and multigravida varying among the studies. The indications for CS included factors such as previous CS, macrosomic pregnancies, multiple pregnancies, maternal request, malpresentation, postdate pregnancies, cephalopelvic disproportion, and cases where vaginal delivery was not favourable.

The majority of included studies showed a low risk of bias. Only one study had high risk of bias arising from the randomization process, as well as some concerns in the deviation from the intended intervention and selection of the reported result (**Figure 2**).

Intraoperative blood loss

A statistically significant difference was observed between the oxytocin and TXA/Eth groups ($p = 0.030$, 95%CI 0.117-2.272) regarding intraoperative blood loss (**Figure 3**). Robust

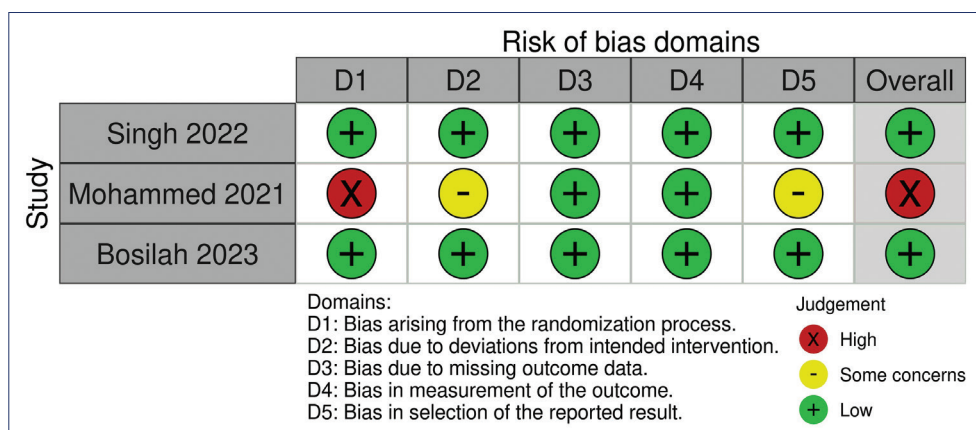


Figure 2. Risk of Bias Assessment using Cochrane ROB-2 Tool [14].

statistical assessments, including Begg’s test and Egger’s test of intercept, affirmed the absence of publication bias within the context of

this meta-analysis. Furthermore, marked heterogeneity was evident among the amalgamated studies ($Q = 80.50, p < 0.0001, I^2 = 97.52$).

Table 1. Study characteristics.

	Singh et al., 2022 [20]		Mohammed et al., 2021 [21]		Bosilah et al., 2023 [19]	
	Oxytocin (n = 131)	TXA + Eth (n = 132)	Oxytocin (n = 100)	TXA + Eth (n = 100)	Oxytocin (n = 100)	TXA + Eth (n = 100)
Country	India		Egypt		Egypt	
Study design	Single-centre, prospective, randomized, and double-blind study		Randomized controlled trial		Double-blinded, randomized, placebo-controlled trial	
Methods	Infusion of oxytocin 10 IU + 50 cc saline 0.9% (50 cc/hour)	Infusion of TXA 1 g + Eth 250 mg	Oxytocin 5 IU + 500 cc saline 0.9% (100 cc/hour)	Infusion of TXA 1 g + Eth 250 mg	Oxytocin 30 IU + 500 cc saline 0.9%	Infusion of TXA 1 g + Eth 250 mg
Mean age (Mean, SD)	29.0 ± 4.4	28.5 ± 4.3	29.0 ± 4.4	28.4 ± 4.3	30.85 ± 4.12	30.91 ± 4.43
BMI (kg/m ²)	28.5 ± 5.2	26.1 ± 5.6	28.9±3.1	26.2±3.0	27.15 ± 5.81	26.97 ± 5.98
GA (weeks, SD)	38.92 ± 0.40	38.87 ± 0.40	38.91±0.50	38.86±0.50	-	-
Parity						
Primigravida (%)	63 (48)	74 (56)	56 (56)	48 (48)	16 (16)	28 (28)
Multigravida (%)	68 (52)	58 (44)	44 (44)	52 (52)	84 (84)	72 (72)
Indication of CS						
Previous CS (%)	59 (45)	54 (41.0)	39 (39)	44 (44)	24 (24)	18 (18)
Macrosomic (%)	34 (26)	31 (23.4)	-	-	-	-
Multiple pregnancies (%)	27 (20.6)	25 (19)	-	-	-	-
Maternal request (%)	-	-	30 (30)	29 (29)	7 (0)	0 (0)
Malpresentation (%)	-	-	26 (26)	19 (19)	37 (37)	33 (33)
Postdate (%)	-	-	5 (5)	8 (8)	-	-
CPD (%)	-	-	-	-	-	-
In labour and not favourable vaginal delivery (%)	-	-	-	-	13 (13)	14 (14)
Other (%)	11 (8.4)	22 (16.6)	-	-	13 (13)	14 (14)

*TXA: Tranexamic acid; Eth: ethamsylate; IU: international unit; SD: standard deviation; BMI: body mass index; GA: Gestational age; CS: caesarean section; CPD: cephalopelvic disproportion.

Operation duration

The pooled showed no statistically significant difference in operation time ($p = 0.058$, 95%CI -0.012-0.739) (Figure 4). The absence of publication bias in this meta-analysis was confirmed by applying statistical tests, namely Begg’s test and Egger’s test of intercept. Additionally, significant heterogeneity was observed between the included studies ($Q = 11.795$, $p = 0.002$, $I^2 = 83.04$). The forest plot of the data is shown in Figure 4.

Postoperative haemoglobin

The pooled mean difference showed no statistically significant difference between the oxytocin

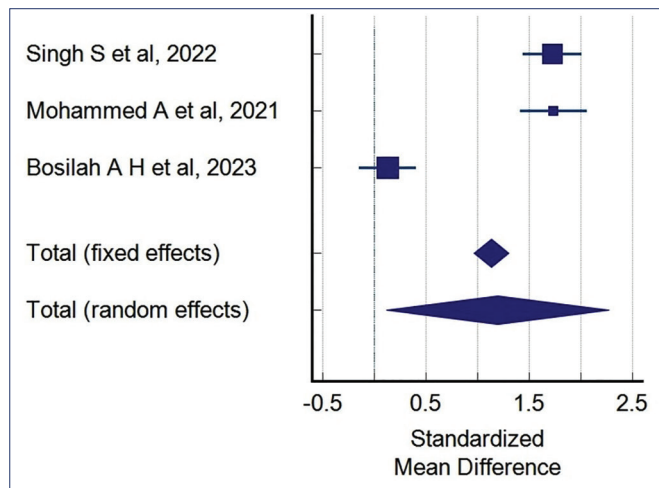


Figure 3. Result of perioperative oxytocin vs tranexamic acid and ethamsylate mean difference in intraoperative blood loss.

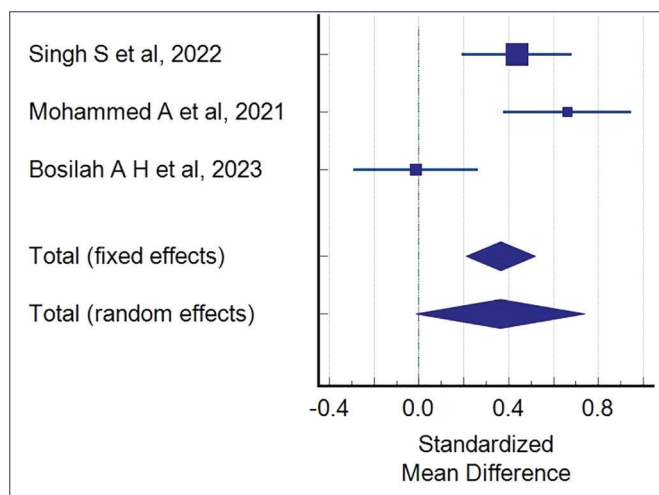


Figure 4. Result of perioperative oxytocin vs tranexamic acid and ethamsylate mean difference in operation duration.

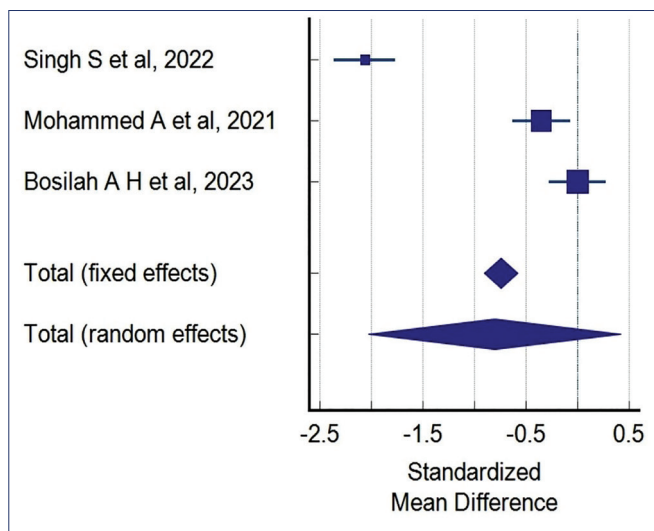


Figure 5. Result of perioperative oxytocin vs tranexamic acid and ethamsylate mean difference in postoperative haemoglobin.

group postoperative haemoglobin and the TX-AEth group ($p = 0.197$, 95%CI -2.026-0.418). The pooled studies were heterogeneous ($Q = 110.58$, $p < 0.0001$, $I^2 = 98.19$). The forest plot of the data is shown in Figure 5.

Postoperative haematocrit

The pooled mean difference showed a statistically significant difference between the oxytocin group postoperative haematocrit and the TX-AEth group ($p = 0.004$, 95%CI -8.916 to -1.710). The pooled studies were heterogeneous ($Q = 520.8176$, $p < 0.0001$, $I^2 = 99.62$). The forest plot of the data is shown in Figure 6.

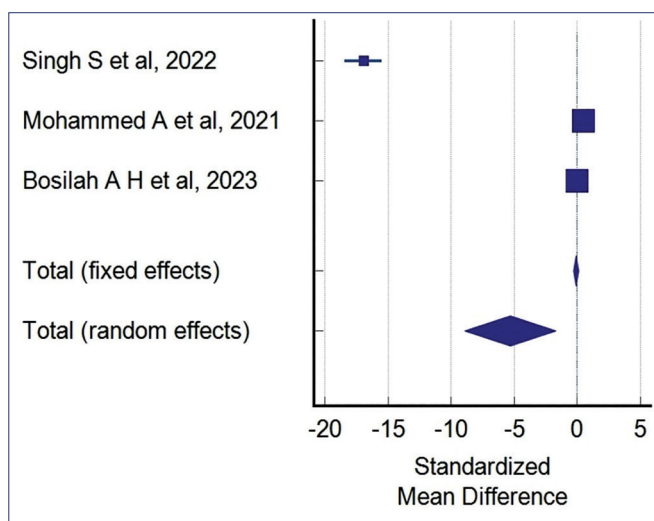


Figure 6. Result of perioperative oxytocin vs tranexamic acid and ethamsylate mean difference in postoperative haematocrit.

DISCUSSION

The prevalence of CS has increased from approximately 7% in 1990 to the current rate of 21%, as per recent World Health Organization research, and is projected to rise to almost 29% by 2030. Additionally, the occurrence of obstetric bleeding during or after CS is noted to be twice that observed in vaginal delivery [1, 16]. Obstetric haemorrhage stands as a primary contributor to maternal morbidity and mortality [17]. In cases of traumatic bleeding, encompassing obstetrical haemorrhage, the utilization of TXA has been associated with a reduction in overall mortality. Additionally, following placental delivery, there is an elevation in fibrinolytic activity, as indicated by increased levels of tissue plasminogen activator and D-dimer [18].

In this study of intraoperative blood loss, the TXA-Eth group demonstrated significantly lower intraoperative blood loss than the oxytocin group. This result is consistent in all included studies [19-21]. It is affirmed that TXA and Eth are associated with a significant reduction in intraoperative blood loss compared to a placebo [22]. Another study also revealed that TXA and Eth could minimize postoperative bleeding with minimal adverse effects [23,24]. Our study supports the WOMAN Trial, strengthening the place of TXA in PPH. The WOMAN trial compared 1 gram of TXA or placebo and concluded that TXA decreased death due to bleeding (155 [1.5%] vs 191 [1.9%]) [25]. However, one study included emergency CS, which has differing risks of PPH, potentially influencing heterogeneity [19, 26, 27].

Although a statistically significant distinction in postoperative haematocrit levels was observed between the two cohorts, there was no analogous difference in haemoglobin levels. Nevertheless, the decline in both Hb (-0.5 ± 0.2 and -1.77 ± 1.16 vs -0.9 ± 0.2 and -1.78 ± 1.12) and Hct (-1.5 ± 1.4 and -5.84 ± 3.91 vs -2.57 ± 1.6 and -5.84 ± 3.91) was less pronounced in the TXA-Eth group compared to the oxytocin group (Table 2) [19, 21]. This implies that TXA-Eth might exhibit greater efficacy in mitigating blood loss during surgical procedures. Eth and TXA exhibit a synergistic effect in hemostasis when administered intravenously together. This combined approach proves effectively minimizes intra- and postoperative blood loss [12]. In this investigation, no statistically significant variance was noted in the surgical duration. Nevertheless, the Duration of Surgery (DOS) exhibited a shorter duration in the TXA-Eth group within two incorporated studies than the oxytocin group [20, 21]. This finding aligns with other research indicating that the DOS was shorter in the TXA-Eth group owing to reduced intraoperative bleeding, thereby mitigating the time required for hemostasis [23].

Regarding safety, the incidence of PPH is lower in the TXA-Eth group than in the oxytocin group (Table 3) [19, 20]. Nonetheless, TXA in combination with Eth demonstrated a heightened occurrence of thrombotic events, although it is essential to note that only one study reported such incidents. Further investigation and in-depth analysis are warranted to gain a more comprehensive understanding of these events. The administration of TXA-Eth during and after CS has demonstrated

Table 2. Efficacy.

	Singh et al., 2022 [20]		Mohammed et al., 2021 [21]		Bosilah et al., 2023 [19]	
	Oxytocin	TXA + Eth	Oxytocin	TXA + Eth	Oxytocin	TXA + Eth
	(n = 131)	(n = 132)	(n = 100)	(n = 100)	(n = 100)	(n = 100)
Blood loss (mL)	613.7 ± 123.7	406.2 ± 116.5	614.5 ± 120.7	407.1 ± 117.3	625.26 ± 144.06	605.34 ± 158.8
Operation duration (minutes)	48.5 ± 9.3	44.3 ± 9.8	49.1 ± 9.9	42.8 ± 9.0	64.35 ± 18.72	64.6 ± 19.61
Preoperative Hb (mg/dL)	10.78 ± 1.34	11.07 ± 0.14	10.8 ± 0.8	10.7 ± 0.8	10.81 ± 0.81	10.81 ± 0.81
Postoperative Hb (mg/dL)	8.29 ± 1.18	10.02 ± 0.10	9.9 ± 0.8	10.2 ± 0.9	9.03 ± 1.2	9.03 ± 1.27
Reduction mean (mg/dL)	-	-	-0.9 ± 0.2	-0.5 ± 0.2	-1.78 ± 1.12	-1.77 ± 1.16
Preoperative HCT (%)	32.23 ± 0.39	33.20 ± 0.39	31.4 ± 2.5	31.0 ± 2.5	32.41 ± 2.46	32.41 ± 2.43
Postoperative HCT (%)	25.10 ± 0.30	30.73 ± 0.36	30.6 ± 2.1	29.5 ± 2.7	26.57 ± 3.96	26.79 ± 4.09
Reduction (%)	-	-	-2.57 ± 1.6	-1.5 ± 1.4	-5.84 ± 3.91	-5.62 ± 3.94
Hospital stay (hours/days)	-	-	12.3 ± 1.1	11.9 ± 0.7	2.25 ± 2.06	2.3 ± 2.16
Blood transfusion (%)	14 (10.6)	1 (0.75)	-	-	14 (14)	11 (11)

TXA: Tranexamic acid; Eth: ethamsylate; Hb: Haemoglobin; HCT: Haematocrit.

Table 3. Safety.

	Singh <i>et al.</i> , 2022 [20]		Mohammed <i>et al.</i> , 2021 [21]		Bosilah <i>et al.</i> , 2023 [19]	
	Oxytocin (n=131)	TXA + Eth (n = 132)	Oxytocin (n = 100)	TXA + Eth (n = 100)	Oxytocin (n=100)	TXA + Eth (n = 100)
Postpartum haemorrhage (%)	3 (2.30)	0 (0)	-	-	30 (30)	23 (23)
Postoperative fever (%)	-	-	-	-	26 (26)	20 (20)
Postoperative thrombosis (%)	-	-	-	-	3 (3)	14 (14)
Postoperative infection (%)	-	-	-	-	18 (18)	20 (20)
Caesarean hysterectomy (%)	-	-	-	-	0 (0)	0 (0)

TXA: Tranexamic acid; Eth: ethamsylate.

safety, with no observed maternal or neonatal side effects, establishing them as a secure and efficacious intervention for managing obstetric haemorrhage [22, 28].

Strength and limitation of the study

The strength of this research lies in its novelty as the inaugural systematic review and meta-analysis, along with meticulous attention to methodological and statistical methodologies. However, our review uncovers several limitations. The limited sample size, variability in parity, and scarcity of studies collectively impede the generalizability of our conclusions. Additionally, the geographical confinement of the studies included in our review raises the possibility of regional disparities in results. Another overarching limitation is the lack of data on oxytocin storage conditions; none of the studies reported whether it was stored at ambient temperature or in a refrigerated environment. Moreover, the differences in oxytocin dosages, timing of administration, and infusion rates among the included studies contribute to variability in outcomes. Moreover, not all studies documented the necessity for transfusion and safety outcomes, adding to the limitations.

CONCLUSIONS

Combining TXA and Eth is a safe and efficacious alternative for managing obstetric haemorrhage. The combination of TXA&Eth during CS indicated a notable decrease in intraoperative blood loss compared to the use of oxytocin alone. Furthermore, TXA&Eth was associated with higher

postoperative haematocrit levels. The cost-effectiveness, accessibility, and diverse advantages of TXA&Eth make it a valuable medicine, providing enduring effects beyond the surgical procedure. To validate these findings, extensive research is required, involving larger multi-centre randomized trials and an examination of the optimal timing of administration, whether post-delivery or before skin incision and comparing the combination of oxytocin and TXA&Eth and the use of oxytocin or Eth alone.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

N.A., G.M.: writing – original draft. All authors: Conceptualization, methodology, writing – review & editing.

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None.

Study registration

The PROSPERO registration number is CRD42023481950.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

N/A.

Data sharing

Data are available under reasonable request to the corresponding author. Supplementary file are available at: https://drive.google.com/drive/folders/1-trp_t1f0y6KME7wsnP84KpOI0_D7Ye9?usp=share_link

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