Provisionally accepted for publication

SYSTEMATIC REVIEW AND META-ANALYSIS

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

Short title: *Caesarean Blood Loss: Oxytocin vs. TXA & Ethamsylate*

Nicholas **Adrianto** [1,*], Ghea **Mangkuliguna** [1], Alfian **Prasetyo** [1], Candra Novi Ricardo **Sibarani** [2]

[1] School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Pluit Raya No.2, Penjaringan, North Jakarta, Daerah Khusus Ibukota Jakarta 14440, Indonesia.

[2] Department of Obstetrics and Gynaecology, The Regional General Hospital R. Syamsudin, Jl. Rumah Sakit No.1, Cikole, Sukabumi, West Java, 43113.

Corresponding author: Nicholas **Adrianto**, MD. School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Pluit Raya No.2, Penjaringan, North Jakarta, Daerah Khusus Ibukota Jakarta 14440, Indonesia.

Email: nicholasadrianto@yahoo.com.

ORCID: 0000-0001-7163-3102.

Doi: 10.36129/jog.2024.162

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 to 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.

Key words

Caesarean section; tranexamic acid; oxytocin; ethamsylate; blood loss.

Introduction

Cesarean 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 recommended 10%–15% ideal CS rate [1,2]. However, patients undergoing Caesarean delivery face an elevated risk of postpartum hemorrhage (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 hemorrhagic events, emerges as the

predominant etiological factor in PPH [5–7]. Excessive bleeding occurring during a cesarean 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-fetal labor 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 hemostatic 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 hemostasis 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 hemostasis. Administering both intravenously could synergistically reduce intra- and postoperative 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 analyzing 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 (see Supplementary Materials for a detailed search strategy)

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 gynecological 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 anemia. The outcomes of interest were the estimated amount of blood loss during the CS, the postoperative hemoglobin and hematocrit 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 (CNRS). 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 (NA, GM, and AP) 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 hemoglobin, and hematocrit 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 from: 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.

Demographically, the average maternal age ranges from 20-40 years, gestational age 38.0-41.0 weeks, and BMI 18.5-29.9 kg/m^2. 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 favorable. 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 TXAEth groups (P=0.030, 95% CI 0.117-2.272) regarding intraoperative blood loss (Figure 3). Robust 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).

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 hemoglobin

The pooled mean difference showed no statistically significant difference between the oxytocin group postoperative hemoglobin and the TXAEth group (P=0.197 (95% CI, -2.026 to 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 hematocrit

The pooled mean difference showed a statistically significant difference between the oxytocin group postoperative hematocrit and the TXAEth 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.

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 hemorrhage stands as a primary contributor to maternal morbidity and mortality [17]. In cases of traumatic bleeding, encompassing obstetrical hemorrhage, 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 TXAEth 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 hematocrit levels was observed between the two cohorts, there was no analogous difference in hemoglobin 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 TXAEth group compared to the oxytocin group (Table 2) [19,21]. This implies that TXAEth 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 TXAEth 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 TXAEth group owing to reduced intraoperative bleeding, thereby mitigating the time required for hemostasis [23].

Regarding safety, the incidence of PPH is lower in the TXAEth 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 TXAEth during and after CS has demonstrated safety, with no observed maternal or neonatal side effects, establishing them as a secure and efficacious intervention for managing obstetric hemorrhage [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.

Conclusion

Combining TXA and Eth is a safe and efficacious alternative for managing obstetric hemorrhage. The combination of TXAEth during CS indicated a notable decrease in intraoperative blood loss compared to the use of oxytocin alone. Furthermore, TXAEth was associated with higher postoperative hematocrit levels. The cost-effectiveness, accessibility, and diverse advantages of TXAEth make it a valuable medicine, providing enduring effects beyond the surgical procedure. To validate these findings, extensive research is required, involving larger multi-center 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 TXAEth and the use of oxytocin or Eth alone.

COMPLIANCE WITH ETHICAL STARNDARDS

Authors contribution:

N.A. – conceptualization, methodology, writing-review, and editing.

G.M. - conceptualization, methodology, writing-review, and editing.

A.P. - conceptualization, methodology, writing-review, and editing.

C.N.R.S. - conceptualization, methodology, writing-review, and editing.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Study register: PROSPERO registration number is CRD42023481950.

Disclosure of interest: The authors declare no conflict of interest.

Ethical approval: Not applicable.

Informed consent: Not applicable.

Data sharing: Data are available under reasonable request to the corresponding author.

Supplementary file: https://drive.google.com/drive/folders/1-trp_t1f0y6KME7wsnP84KpOl0_D7Ye9?usp=share_link

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Table 1. Study characteristics

	Singh S et al, 2022 [20]		Mohammed A et al, 2021 [21]		Bosilah A H 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-center, 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 labor and not favorable 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, Cesarean section; CPD, Cephalopelvic disproportion

Table 2. Efficacy

	Singh S et al, 2022 [20]		Mohammed A et al, 2021 [21]		Bosilah A H 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)
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 ±	33.20 ±	31.4 ± 2.5	31.0 ± 2.5	32.41 ±	32.41 ±

	0.39	0.39			2.46	2.43
Postoperative HCT (%)	25.10 ± 0.30	30.7 3 ± 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, Hemoglobin; HCT, Hematocrit

Table 3. Safety

	Singh S et al, 2022 [20]		Mohammed A et al, 2021 [21]		Bosilah A H 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)
Postpartum hemorrhage (%)	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)
Cesarean hysterectomy (%)	-	-	-	-	0 (0)	0 (0)

*TXA, Tranexamic acid; Eth, ethamsylate

Fig.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].

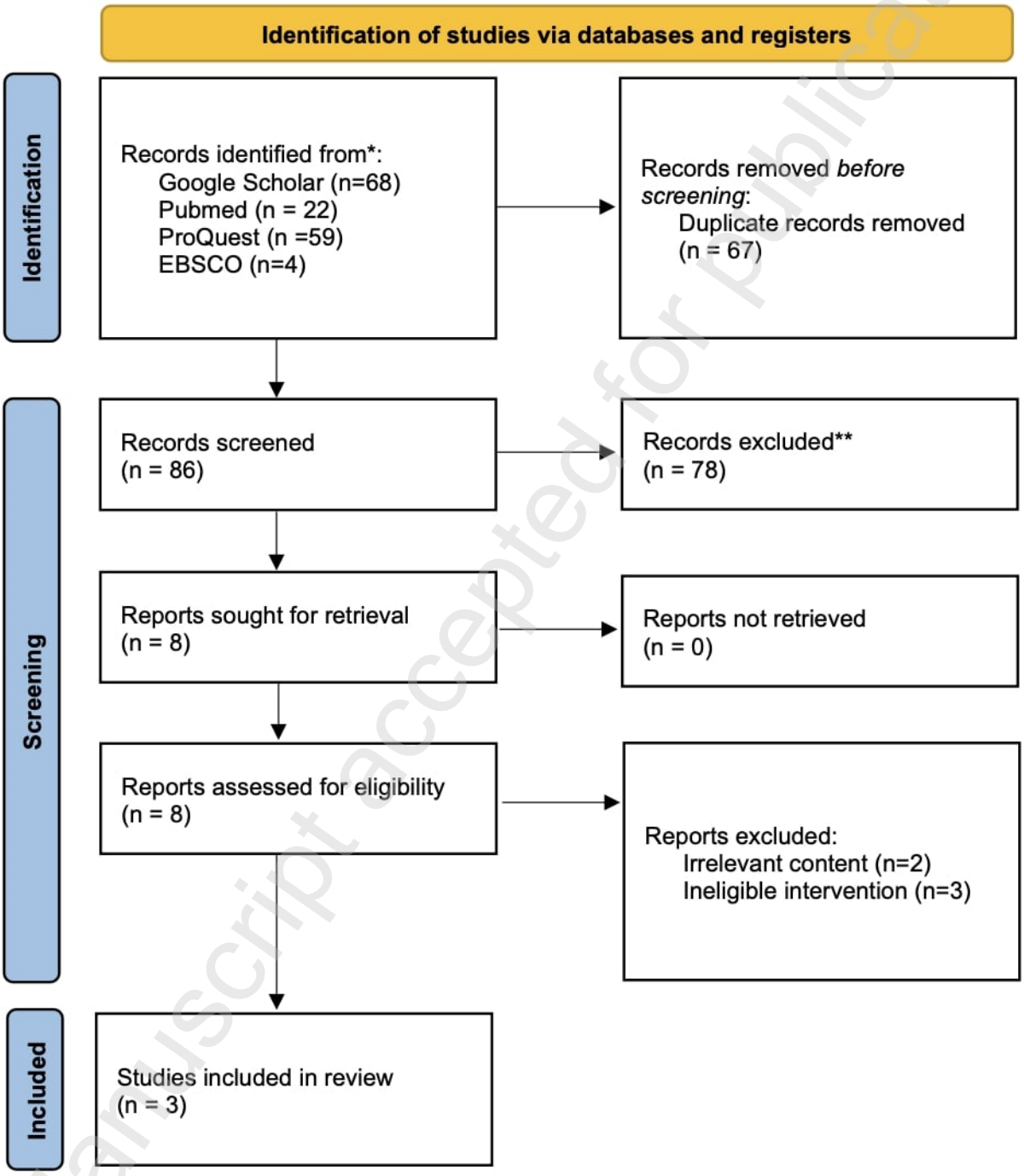

Fig 2. Risk of Bias Assessment using Cochrane ROB-2 Tool [14].

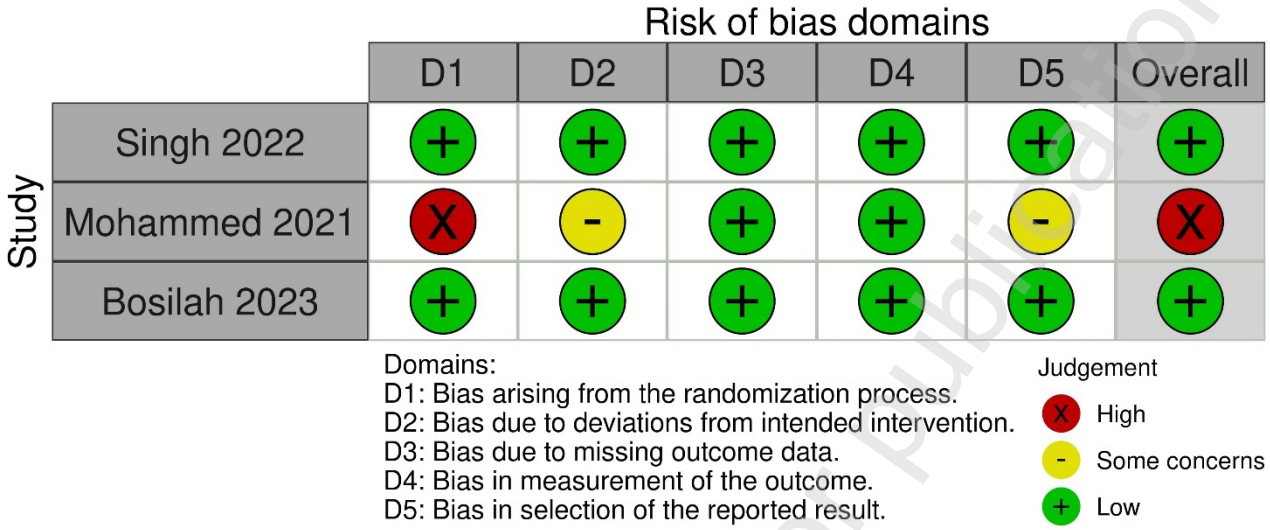

Fig 3. Show the result of perioperative oxytocin vs tranexamic acid and ethamsylate mean difference in intraoperative blood loss.

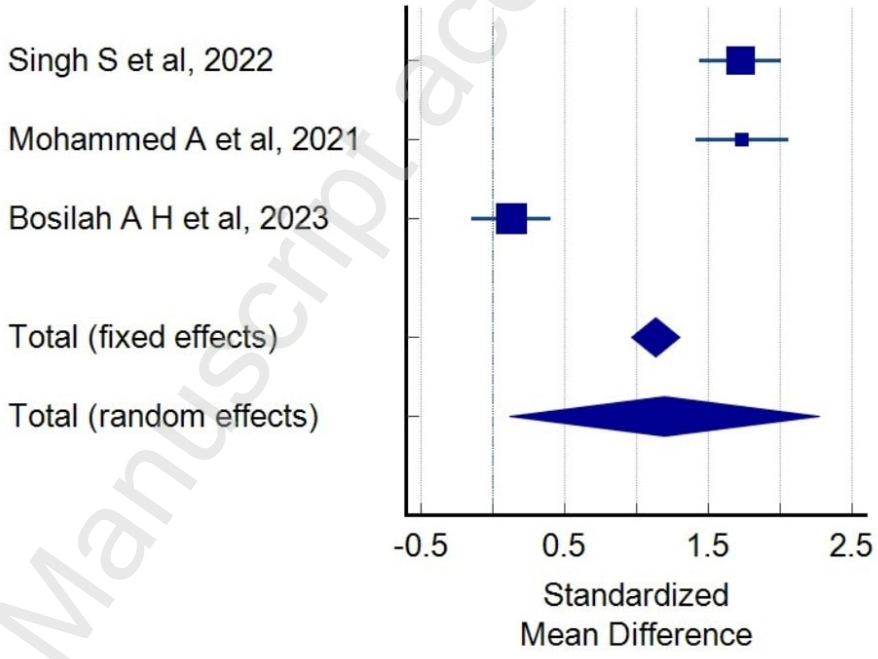

Fig 4. Show the result of perioperative oxytocin vs tranexamic acid and ethamsylate mean difference in operation duration.

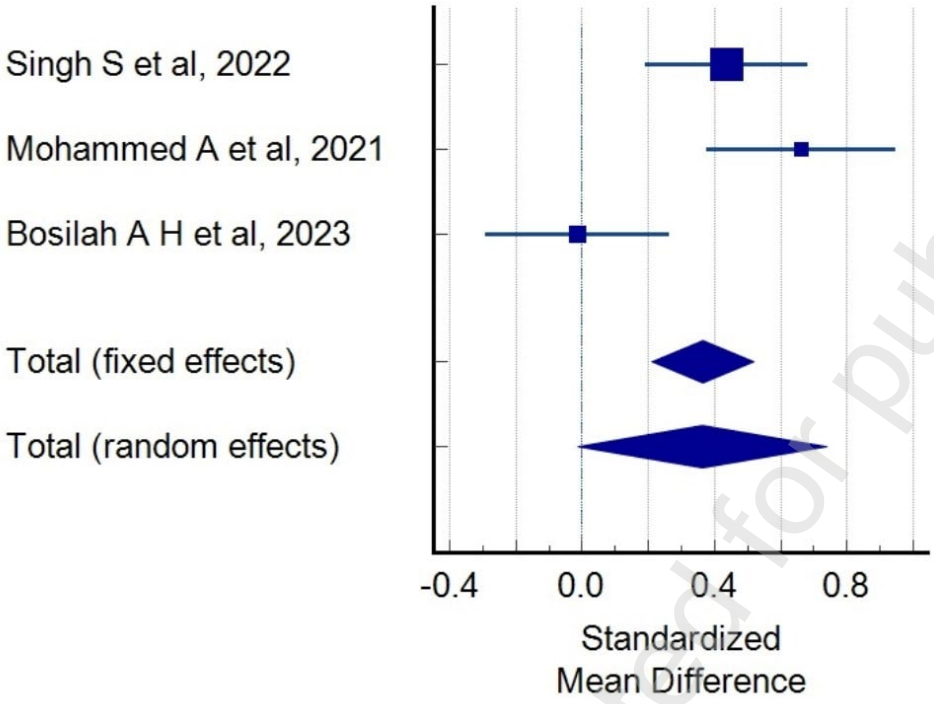

Fig 5. Show the result of perioperative oxytocin vs tranexamic acid and ethamsylate mean difference in postoperative hemoglobin.

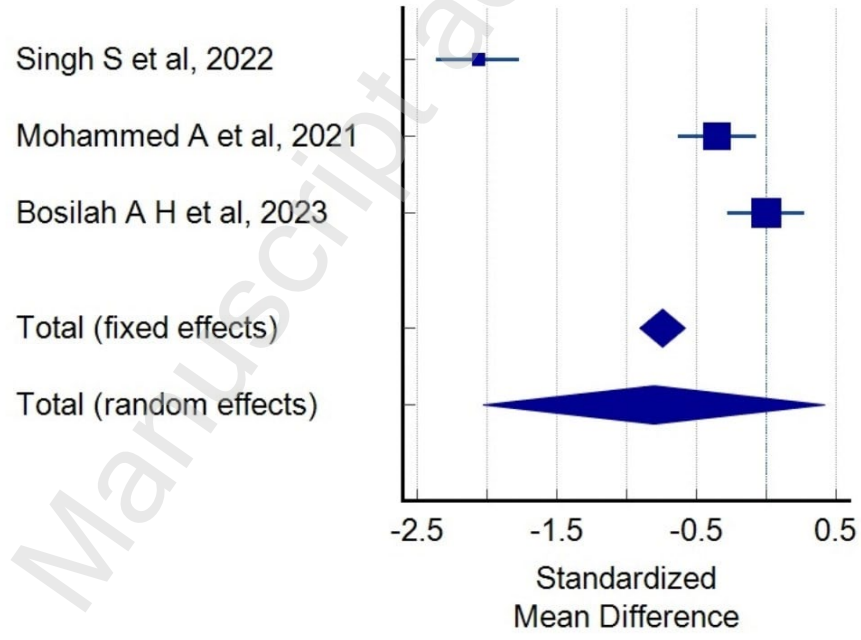

Fig 6. Show the result of perioperative oxytocin vs tranexamic acid and ethamsylate mean difference in postoperative hematocrit.