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Efficacy of Preoperative Tranexamic Acid Administration for Intraoperative Blood Loss Reduction in High-risk Cesarean Delivery: A randomized controlled trial

Nid Wongjariyakul, M.D.*,
Ussanee Sangkomkamhang, M.D.*

** Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen, Thailand*

ABSTRACT

Objectives: To evaluate the efficacy of preoperative tranexamic acid (TXA) in reducing intraoperative blood loss in high-risk cesarean deliveries.

Materials and Methods: A randomized controlled trial was conducted with 50 pregnant women with gestational age over 34 weeks and a high risk of postpartum hemorrhage (PPH) (e.g., previous cesarean delivery, fetal macrosomia, and placenta previa) who underwent cesarean delivery using spinal anesthesia. The intervention group received one gram of TXA intravenously before skin incision, and 0.9% sodium chloride solution was used in the placebo group. The primary outcome was the measurement of intraoperative blood loss.

Results: The TXA group showed significantly lower intraoperative blood loss when compared to the placebo group (495.8 ± 294.6 ml vs 925.6 ± 448.9 ml, mean difference: -429.8 ml, 95% confidence interval (CI): -645.8 to -213.9, $p < 0.001$). The incidence of blood loss > 1,000 ml was also significantly lower in the TXA group (8% vs 36%, relative risk = 0.22, 95% CI: 0.05 to 0.92, $p = 0.039$), and fewer significantly decreased hemoglobin levels were observed in the TXA group in comparison with the placebo group (1.1 ± 7.0 g/dL vs 6.9 ± 9.6 g/dL, mean difference: -5.7 g/dL, 95% CI: -10.5 to -0.9, $p = 0.020$). There was no difference in the requirement for additional uterotonic drugs (8% vs 28%, $p = 0.065$). No serious adverse effects were observed in this study.

Conclusion: TXA effectively reduced intraoperative blood loss in women at high risk of PPH who underwent cesarean deliveries.

Keywords: tranexamic acid, cesarean delivery, postpartum hemorrhage.

Correspondence to: *Nid Wongjariyakul, M.D., Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen 40000, Thailand. Email: nidwongjariyakul@gmail.com*

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ประสิทธิภาพของยาทราเนซามิกเอซิดเพื่อลดการเสียเลือดหลังผ่าตัดคลอดในสตรีที่มีความเสี่ยงสูงต่อการตกเลือดหลังคลอด: การทดลองแบบสุ่มที่มีกลุ่มควบคุม

ณิช วงศ์จริยกุล, อุษณีย์ สังคมกำแหง

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของยาทราเนซามิกเอซิดในการลดการสูญเสียเลือดระหว่างการผ่าตัดคลอดในกลุ่มเสี่ยงสูงต่อการตกเลือดหลังคลอด*

วัสดุและวิธีการ: *การศึกษานี้เป็นการทดลองแบบสุ่มที่มีกลุ่มควบคุมในสตรีตั้งครรภ์ 50 คน และได้รับการผ่าตัดคลอดร่วมกับการฉีดยาชาเข้าช่องน้ำไขสันหลัง มีอายุมากกว่า 18 ปี อายุครรภ์มากกว่า 34 สัปดาห์ และมีปัจจัยเสี่ยงสูงต่อการตกเลือดหลังคลอด (เช่น มีประวัติได้รับการผ่าตัดคลอดมาก่อน ทารกตัวโต ภาวะรกเกาะต่ำ) กลุ่มทดลองได้รับยาทราเนซามิกเอซิด ขนาด 1 กรัม ทางหลอดเลือดดำก่อนการผ่าตัด ส่วนกลุ่มควบคุมได้รับสารละลายน้ำเกลือ 0.9% ผลลัพธ์หลักคือการวัดปริมาณเลือดระหว่างการผ่าตัด*

ผลการศึกษา: *กลุ่มที่ได้รับยาทราเนซามิกเอซิด มีปริมาณเลือดระหว่างการผ่าตัดน้อยกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญ (495.8 ± 294.6 กับ 925.6 ± 448.9 มิลลิลิตร, ความแตกต่างเฉลี่ย: -429.8 มิลลิลิตร, 95% confidence interval (CI): -645.8 ถึง -213.9, p < 0.001) การเสียเลือดมากกว่า 1,000 มิลลิลิตร พบน้อยกว่าในกลุ่มที่ได้รับยาทราเนซามิกเอซิด (8% กับ 36%, ค่าความเสี่ยงสัมพัทธ์ = 0.22, 95% CI: 0.05 ถึง 0.92, p = 0.039) กลุ่มที่ได้รับยาทราเนซามิกเอซิด มีการลดลงของระดับฮีโมโกลบินที่น้อยกว่า (1.1 ± 7.0 กับ 6.9 ± 9.6 กรัมต่อเดซิลิตร, ความแตกต่างเฉลี่ย: -5.7 กรัมต่อเดซิลิตร, 95% CI: -10.5 ถึง -0.9, p = 0.020) กลุ่มยาหลอกมีการใช้ยากระตุ้นการหดรัดตัวของมดลูกมากกว่า (8% กับ 28%, p = 0.065) และ ไม่พบผลข้างเคียงที่รุนแรงในการศึกษานี้*

สรุป: *ยาทราเนซามิกเอซิดช่วยลดปริมาณเลือดออกระหว่างการผ่าตัดคลอด ในสตรีที่มีความเสี่ยงสูงต่อการตกเลือดหลังคลอด*

คำสำคัญ: *ยาทราเนซามิกเอซิด, การผ่าตัดคลอด, การตกเลือดหลังคลอด*

Introduction

Cesarean delivery (CD) is the most frequently performed major surgery globally. CD rates have risen from under 10% prior to the 1980s to over 30% in a wide range of developed countries during the past decade[1]. In 2022, the CD rate at Khon Kaen Hospital was 49%. CD is associated with a 2- to 5-fold elevated maternal morbidity relative to vaginal delivery[2]. These conditions include postpartum hemorrhage (PPH), infection, thromboembolism, and adverse effects related to anesthesia[3]. Intraoperative and postoperative hemorrhage represent critical complications inherent to women at high risk of PPH who undergo CD. Conditions such as placenta previa, multiple gestation, and severe preeclampsia considerably increase the risk of severe PPH, frequently requiring prompt blood transfusion[1,4]. In 2022, high-risk CD in Khon Kaen Hospital accounted for 674 cases (32.5%) from a total of 2,074 CD cases. These high-risk CD cases included previous CD (21.6%), prenatal anemia (5.1%), multiple gestation (2.0%), placenta previa (1.5%), fetal macrosomia (1.5%) and transverse presentation (0.6%)[5].

Uterotonic agents are commonly used to prevent and treat PPH. Oxytocin is the first-line agent, while additional uterotonics include methylergonovine (Methergine) and prostaglandins such as misoprostol (Cytotec) and carboprost tromethamine[6,7]. Traditionally, uterotonics were the primary drugs used to treat PPH, as it was assumed that uterine atony was the main cause. However, it is now understood that PPH can also involve coagulopathy in its pathophysiology[8].

Tranexamic acid (TXA), a synthetic lysine derivative, functions as an antifibrinolytic agent that reversibly blocks plasminogen activation. By inhibiting fibrinolysis, it aids in reducing bleeding[9]. TXA has been shown to be effective in preventing bleeding complications across various conditions, with minimal side effects[10]. Tranexamic acid is known to cross the placenta and is found in cord blood at concentrations similar to those in maternal blood. The Australian Therapeutic Goods Administration (TGA) classifies it as category B for pregnancy, signifying that it has been administered to a limited number of pregnant women without demonstrating an increased risk of malformations or other direct or indirect detrimental effects on the fetus[11].

In obstetrics, TXA has been utilized to manage bleeding related to pregnancy complications[12,13]. Multiple studies have shown that TXA has proven efficacy in reducing blood loss in CD in various indications[12,14,15]. Many of these studies focused on women at low or general risk for PPH, and most reported reduced intraoperative blood loss. However, research on women at high risk for PPH is relatively limited. Systematic review is thus required to obtain new evidence of the efficacy of TXA in high-risk populations. Only two studies have focused on women at high risk for PPH[16,17]. Based on this information, the efficacy of preoperative TXA administration in high-risk PPH pregnancies undergoing CD remains uncertain due to insufficient evidence. Therefore, the objective of this study was to evaluate the efficacy of preoperative administration of TXA in reducing intraoperative blood loss during high-risk CD.

Materials and Methods

The aim of the study was to examine the efficacy of administering TXA preoperatively to reduce intraoperative blood loss in high-risk CD. The study was designed as a double-blind, randomized, placebo-controlled trial, conducted at Khon Kaen Hospital between September and December 2023.

The study included pregnant women who were 18 years or older, in their 34th week or later of pregnancy, scheduled for CD (either elective or emergency), and undergoing spinal anesthesia. In addition, they were required to present with one or more high-risk factors for PPH[18-23]. The factors that were considered included previous CD, transverse presentation, fetal macrosomia (estimated fetal weight exceeding 4.0 kg as determined by ultrasound), multiple gestation, placenta previa or low-lying placenta, prenatal anemia (hemoglobin levels below 9.9 g/dL), polyhydramnios (amniotic fluid index

exceeding 24 cm or a deep vertical pocket exceeding 8 cm), or a previous history of PPH. Women who had substantial medical conditions affecting the heart, liver, or kidneys, brain disorders, blood disorders, a known sensitivity to TXA, a history of or present venous or arterial thromboembolism, intrauterine fetal death, or major fetal anomalies were excluded from participating.

All participating women signed and dated an informed consent form after the study's risks and benefits were explained. All participants underwent a thorough evaluation, including a detailed medical history, general examination, and Leopold maneuvers to accurately assess risk factors and ensure compliance with the exclusion criteria. Upon admission, an obstetric ultrasound was conducted to assess fetal weight, detect anomalies, determine placental location, and measure amniotic fluid levels. Standard laboratory investigations, such as a complete blood count, were also performed.

On the day of surgery, participants were allocated to one of two groups through a process of randomization utilizing computer-generated random numbers by using block of 4. Allocation concealment was maintained by using sealed opaque envelopes. To ensure unbiased results, the participants, obstetricians, anesthesiologist, and outcome assessors were all blinded to the treatment allocation to ensure impartiality. All the ampules of TXA used throughout the study were produced by the same pharmaceutical company (T.P. Drug Laboratories (1969) Co., Ltd).

Nurses who were not involved in this study opened the envelopes, by which the participants were randomly assigned to one of the two groups. The nurses prepared the nameless solution (of both TXA and NSS) in the ward/labor room and sealed it within plastic containers when transferred to the operating room. TXA ampules were stored at a temperature of 25 °C in a dry container with clear colorless solution.

In the TXA group, participants received 1 gm TXA (1 gm/10 ml) (diluted with normal saline solution (NSS) 90 ml with intravenous administration 10-15 minutes before skin incision). In the placebo group, participants received 0.9% sodium chloride solution (NSS) (100 ml intravenous administration 10-15 minutes before skin incision). Both solutions were delivered by slow infusion over a period of 10 min via an infusion pump by an anesthesiologist.

All CD were performed under spinal anesthesia by a resident with at least one year of obstetric training or member of staff. The same surgical technique was consistently applied for all women, including a Pfannenstiel or low midline abdominal incision, an incision of the lower uterine segment, immediate umbilical cord occlusion after fetal extraction, repair of the uterine incision with one or two layers[24], and sequential closure of the abdominal wall. After fetal extraction, all participants received an intravenous bolus of 10 IU oxytocin, followed by an intravenous infusion of 20 IU of oxytocin, diluted in 1,000 ml of glucose 5% dextrose normal saline/2 at a rate of 120 ml/hr. If PPH occurred, one additional gram of tranexamic acid was administered by an anesthesiologist 30 minutes after the first dose[25]. The additional uterotonic agents were used when the uterus failed to contract adequately after delivery and there was an insufficient response to the first-line uterotonic agent (oxytocin)[6].

Intraoperative blood loss was measured by standardized operative nurses after completing the CD in the operating room. All participants received postoperative care following the standard protocol for CD under spinal anesthesia. Complete blood counts were collected at 24 hours after CD. Measurement of blood loss > 1,000 ml, operative time, additional uterotonic agents, blood transfusion, and adverse effects of TXA within 24 hours postpartum were recorded.

The primary outcome was measurement of intraoperative blood loss, which was measured from the time of placental delivery until skin closure by standardized operative nurses using the gravimetric method[26-28]. Total intraoperative blood loss was determined by weighing the blood-soaked materials

used during CD, subtracting the weight of the dry materials before the procedure, and adding the amount of blood collected in the suction bottle. One gram of weight increase in blood-soaked surgical gauze was considered equivalent to one milliliter of blood loss. Secondary outcomes included intraoperative blood loss > 1,000 ml, hemoglobin level change before and 24 hours after CD, operative time, intraoperative or postoperative blood transfusion within 24 hours, additional uterotonic agents within 24 hours, adverse effects of TXA, and the length of hospital stay (LOS).

$$n_1 = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 \left[\sigma_1^2 + \frac{\sigma_2^2}{r}\right]}{\Delta^2}$$
$$r = \frac{n_2}{n_1},\ \Delta = \mu_1 - \mu_2$$

The calculation of sample size for this study was based on a pilot study with 15 women per group. The average blood loss in the treatment group was 443.6 ml with a standard deviation (SD) of 160.7 ml, whereas the control group exhibited a mean blood loss of 933.9 ml with an SD of 469.9 ml. With a power of 90% and an alpha error of 5%, accounting for a 10% dropout rate, the study required a total population of 50 women, with 25 women per group. Continuous outcome data was reported as mean ± SD or median and interquartile length, as appropriate. Comparisons between groups at a single time point were conducted using the student t-test for normally distributed data or the Mann-Whitney U test for data that was not normally distributed. Dichotomous outcomes were analyzed using the chi-square test or Fisher's exact test if expected cell counts were less than 5. The treatment effect was reported as the mean difference (MD) along with a 95% confidence interval (CI), and p values below 0.05 were considered statistically significant. STATA version 18 was used for all analyses.

Based on the ethical principles of research on the basis of protecting the human rights, security and human dignity of each person, this proposal was submitted to Khon Kaen Hospital. Ethical approval was obtained from the Institutional Review Board for Human Research.

Results

Between September and December 2023, 50 eligible high risk PPH women who underwent CD under spinal anesthesia were enrolled in the study. None of them were excluded from the study. A total of 50 eligible women were randomly assigned into two groups: 25 to the TXA group and 25 to the placebo group. There were no dropouts (Fig. 1).

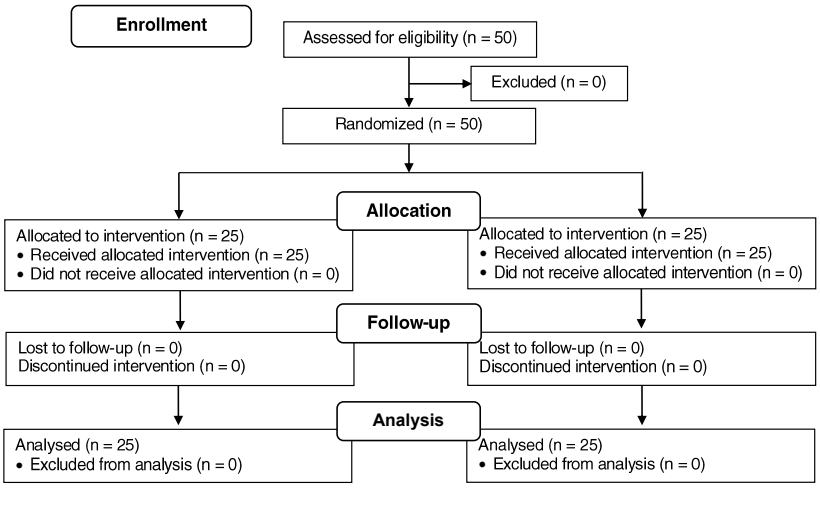

Fig. 1. Consort flow diagram.

No statistical difference was observed between women receiving TXA and those receiving the placebo in terms of maternal age, body mass index (BMI), mode of previous delivery, preoperative hemoglobin concentration, type of CD, skin incision, or surgeon, with all p values > 0.05. Previous CD was the most common risk factor in both groups, with fetal macrosomia and prenatal anemia following in frequency (Table 1).

Table 1. Demographic characteristics.

Characteristics	TXA group (n = 25)	Placebo group (n = 25)	p value
Age (years), mean ± SD	28.9 ± 5.0	29.9 ± 5.2	0.479
BMI (kg/m^2), mean ± SD	29.5 ± 5.4	28.6 ± 4.1	0.526
Mode of previous deliveries, n (%)			0.776
No previous delivery	3 (12)	1 (4)	
Vaginal delivery	4 (16)	5 (20)	
1 previous CD	17 (68)	19 (76)	
≥ 2 previous CD	1 (4)	0 (0)	
High risk identification, n (%)			0.945
Previous cesarean delivery	17 (68)	18 (72)	
Fetal macrosomia	3 (12)	2 (8)	
Prenatal anemia	2 (8)	1 (4)	
Previous history of PPH	1 (4)	2 (8)	
Multiple gestation	1 (4)	1 (4)	
Transverse presentation	0 (0)	1 (4)	
Placenta previa/low-lying	1 (4)	0 (0)	
Preoperative hemoglobin concentration (g/dL), mean ± SD	12.0 ± 1.2	12.1 ± 1.2	0.374
Type of cesarean delivery, n (%)			1.000
Elective	17 (68)	17 (68)	
Emergency	8 (32)	8 (32)	
Skin incision, n (%)			0.563
Pfannenstiel	14 (56)	16 (64)	
Low midline	11 (44)	9 (36)	
Surgeon, n (%)			0.390
Staff	12 (48)	9 (36)	
Resident	13 (52)	16 (64)	

TXA: tranexamic acid, SD: standard deviation, BMI: body mass index, CD: cesarean delivery, PPH: postpartum hemorrhage

The measurement of intraoperative blood loss was 495.8 ± 294.6 ml and 925.6 ± 448.9 ml in the TXA group and the placebo group, respectively. The MD was -429.8 ml (95%CI: -645.8 to -213.9). Measurement of intraoperative blood loss was statistically significantly lower in the TXA group compared to the placebo group (p < 0.001) (Table 2).

Table 2. Primary and secondary outcomes.

	TXA group (n = 25)	Placebo group (n = 25)	Mean Difference	95% CI	p value
Measurement of intraoperative blood loss (ml), mean ± SD	495.8 ± 294.6	925.6 ± 448.9	-429.8	-645.8 to -213.9	<0.001
Hemoglobin change (g/dL), mean ± SD	1.1 ± 7.0	6.9 ± 9.6	-5.7	-10.5 to -0.9	0.020
Operative time (min), mean ± SD	44.7 ± 12.9	61.5 ± 19.7	-26.3	-26.0 to -7.5	<0.001
Intraoperative/ postoperative blood transfusion, n (%)	0 (0)	2 (8)			0.148
Additional uterotonic agents, n (%)	2 (8)	7 (28)			0.065
Adverse effects of TXA, n (%)					0.570
None	16 (64)	14 (56)			
Dizziness	6 (24)	7 (28)			
Nausea/Vomit	1 (4)	4 (16)			
Headache	2 (8)	0 (0)			
LOS (days), mean ± SD	3.0 ± 0.7	3.1 ± 0.7			0.240

TXA: tranexamic acid, CI: confidence interval, SD: standard deviation, LOS: length of hospital stay

Excessive blood loss of more than 1,000 ml in the TXA and placebo group were 8% and 36%, respectively. The relative risk was 0.22, and 3.57 was the number needed to treat. Excessive blood loss of more than 1,000 ml was statistically significantly lower in the TXA group (95%CI -645.8 to -213.9, p = 0.039) (Table 3).

In addition, the operative time in the TXA group and the placebo group was 44.7 ± 12.9 min vs 61.5 ± 19.7 min, respectively. The respective hemoglobin level changes before and 24 hours after CD in the TXA group and the placebo group were 1.1 ± 7.0 g/dL and 6.9 ± 9.6 g/dL. The operative time and the hemoglobin level changes were significantly lower in the TXA group, with p <0.001 and 0.020 indicating statistical significance, respectively (Table 2).

The two study groups showed no significant differences in terms of blood transfusion requirements, or length of hospital stay. Although the need for additional uterotonic agents was greater in the placebo group compared to TXA group, this difference did not reach statistical significance (p = 0.065). Adverse effects associated with TXA included dizziness, nausea/vomiting and headache (Table 2). No serious adverse events were reported in this study.

Table 3. Blood loss >1,000 ml.

	TXA group (n = 25)	Placebo group (n = 25)	Relative risk	NNT	95% CI	p value
Measurement of blood loss > 1,000 ml, n (%)	2 (8)	9 (36)	0.22	3.57	0.05 to 0.92	0.039

TXA: tranexamic acid, NNT: number needed to treat, CI: confidence interval

Discussion

Our study aimed to evaluate the efficacy of preoperative TXA in reducing blood loss in women at high risk of PPH undergoing CD. The findings indicated that preoperative TXA administration significantly reduced measurement of intraoperative blood loss and the occurrence of PPH compared to the placebo.

No substantial differences were observed in the demographic characteristics, such as maternal age, BMI, mode of previous deliveries, preoperative hemoglobin concentration, type of CD, skin incision, and surgeon, between the TXA and placebo groups. This suggests that the initial features of the groups were similar, which guarantees the accuracy of the compared results. Previous CD, fetal macrosomia, and prenatal anemia were the most frequently seen high-risk factors, which aligned with earlier research studies that have emphasized these as notable risk factors for PPH[16-23]. Previous CD still remains the most common risk factor for PPH in Khon Kaen Hospital.

The primary outcome of the study showed that the TXA group had a considerably lower amount of intraoperative blood loss compared to the placebo group. This finding was consistent with prior research that has shown the effectiveness of TXA in reducing intraoperative blood loss during CD[16,17].

In the secondary outcomes, the TXA group experienced a shorter duration of surgery, indicating that the decreased blood loss potentially enhanced the efficiency of the surgical procedure. Moreover, in the TXA group, the occurrence of PPH (intraoperative blood loss > 1,000 ml) was effectively mitigated, which was the main result of this study. The need for additional uterotonic agents was greater in the placebo group compared to the TXA group with clinical significance but no statistical significance. This reduction in the use of additional uterotonic agents has important implications, as it may reduce the risk of the side effects associated with these drugs and simplify the management of hemorrhage in the operating room.

This parallels the findings of Ortuanya et al[29], which evaluated the use of prophylactic TXA for reducing intraoperative blood loss in CD among high-risk women. In their study, the TXA group experienced significantly lower mean blood loss compared to the placebo group (442.9 ± 200.9 ml vs 801.2 ± 258.6 ml; p = 0.001), reduced incidence of PPH (1.0% vs 19.0%; p = 0.001), and decreased need for additional uterotonic agents (39.0% vs 68.0%; p = 0.001). These findings and those of this current study demonstrated the effectiveness of TXA in minimizing both intraoperative blood loss and the risk of PPH in high-risk CD patients.

Our findings aligned with previous studies, such as the research conducted by Shalaby et al[16], which observed a notable disparity in intraoperative blood loss between the placebo group (896.8 ± 519.6 ml) and the TXA group (583.2 ± 379.6 ml) (p < 0.001) in women at high risk of PPH who underwent CD. In a related study, Abdel-Fatah et al[17] discovered a noteworthy decrease in intraoperative blood loss during CD when using preoperative TXA in pregnancies at high risk of PPH. The group that received TXA had an average blood loss of 484.8 ml, whereas the control group had 705 ml (p < 0.001).

In contrast, the research by Madar et al[30] examined the effect of preoperative TXA administration in women with multiple pregnancies undergoing CD. Their results showed that estimated blood loss exceeding 1,000 ml occurred in 62 of the 147 women (42.2%) in the TXA group and 67 of the 152 women (44.1%) in the placebo group (adjusted relative risk (RR) = 0.97; 95% CI 0.68 to 1.38; p = 0.86), indicating no significant difference between the two groups. This difference in outcomes could be attributed to variations in the populations studied. Our research focused on women with specific high-risk factors for PPH, in which TXA demonstrated clear effectiveness in reducing intraoperative blood loss and the occurrence of PPH.

Our study's findings also aligned with a comprehensive analysis conducted by Al-dardery et al[12], which involved 59 randomized controlled trials

(RCTs) and demonstrated that TXA effectively decreased overall blood loss in CD when compared to the placebo (standardized MD = -2.11, 95% CI -3.09 to -1.14, p < 0.001). This meta-analysis further confirmed the safety profile of TXA, demonstrating no substantial rise in side effects such as nausea or vomiting.

In research by Eyeberu et al[14], the effects of TXA on African women undergoing CD were explored. The study revealed that TXA had a substantial impact on mitigating blood loss both during and after the procedure (standardized MD = -1.93, 95% CI -2.40 to -1.47). This meta-analysis provides more evidence of the effectiveness of TXA in various groups and circumstances, reaffirming its importance in the management of blood loss during cesarean procedures.

The findings of Bellos et al[31] provided additional support for our results. Their meta-analysis encompassed 36 studies involving 10,659 women. The study revealed that the administration of TXA resulted in notable reductions in total blood loss (MD = -189.4 ml, 95% CI -218.6 to -160.2), hemoglobin drops, risk of blood loss over 1,000 ml, transfusion requirements, and the need for supplementary uterotonic agents.

In addition, research by Chatdoa et al[32] revealed a noteworthy decrease in intraoperative blood loss in the TXA group compared to the control group (740.5 ± 139.5 ml vs 853.5 ± 163.6 ml, p = 0.002). Their study focused on women who were undergoing elective CD and had a history of previous CD. This supports our research, in which the most common high-risk PPH factor was previous CD, and emphasizes the importance of TXA in addressing blood loss in previous CD populations, which is increasingly found as a high-risk PPH factor worldwide.

In a study by Sentilhes et al[33], women undergoing CD were given an intravenous prophylactic uterotonic agent along with either tranexamic acid (1 gm) or a placebo. The estimated blood loss exceeding 1,000 ml occurred in 556 out of the 2,086 women (26.7%) in the TXA group and in 653 out of the 2,067 women (31.6%) in the placebo group (adjusted RR = 0.84; 95% CI 0.75 to 0.94; p = 0.003). However, there were no significant differences between the two groups in terms of the mean blood loss measured using gravimetric methods. This contrast may be attributed to our stricter definition of high-risk factors, which included a higher prevalence of PPH. Furthermore, our research focused on the impact of TXA alone, allowing us to better assess its direct effects on intraoperative blood loss.

Oseni et al[34] also found that TXA had a significant impact on reducing intraoperative blood loss in emergency CD. In the TXA group, only 2 (1.6%) patients experienced blood loss over 1,000 ml, compared to 12 (9.8%) in the control group (p = 0.01). This discovery provides further evidence of the efficacy of TXA in various scenarios involving CD.

In contrast, the research conducted by Ruka et al[35] did not observe any notable variation in intraoperative blood loss in elective CD between the TXA (454.6 ml) and placebo groups (467 ml). There could be various reasons for this discrepancy, such as variations in the number of participants, the methodology used in the study, or the characteristics of the patients involved.

The study found that the negative impacts of TXA were mostly modest, such as dizziness, nausea/vomiting, and headache. The results aligned with the safety characteristics of TXA documented in prior research conducted by Shalaby et al and Abdel-Fatah et al[16,17], which similarly reported the safety record of TXA with rare occurrences of severe adverse effects. The minimal occurrence of negative outcomes in our study strengthened the assurance of the safety of TXA utilization in CD.

Preoperative administration of TXA has been shown to significantly reduce intraoperative blood loss, thereby potentially lowering the need for additional interventions such as blood transfusions. This reduction in blood loss not only leads to direct cost savings by decreasing the resources required for blood products but also minimizes the hospital

stay and recovery time for the patient. Moreover, patients who experience PPH often require additional medical interventions, which can further increase hospital costs and impact overall patient outcomes. By implementing a preoperative protocol for high-risk patients, healthcare providers may achieve better resource allocation and improved clinical outcomes, ultimately resulting in a more cost-effective approach to managing CD.

In contrast, intraoperative administration of TXA, while beneficial, may not provide the same level of efficacy as preoperative administration. Intraoperative TXA is administered after blood loss has already begun, which can result in less effective hemostatic control. The timing of administration is crucial, as preoperative TXA allows for optimal plasma levels of the drug before surgical intervention, enhancing its effectiveness in preventing excessive blood loss. Furthermore, preoperative TXA may mitigate the stress response to surgical trauma and enhance coagulation pathways before the onset of surgical bleeding.

The strengths of our study were that it was conducted as a randomized controlled trial with a double-blinded placebo control. The sample size was calculated accurately based on data from the pilot study, and there were no dropouts. Additionally, intraoperative blood loss was calculated using a measurement formula, resulting in minimal error.

On the contrary, the limitations of our study were that it used a single-center approach, which may limit the broader applicability of the findings. Moreover, there was a potential confounding factor, which was that the most common high-risk PPH factor was the previous CD. Due to the time constraints for data collection and the calculated sample size, the majority of the participants gathered at the time of the study consisted of individuals with previous CD.

Consequently, we suggested that preoperative TXA administration can be used in women at high risk of PPH undergoing CD to reduce intraoperative blood loss, without serious adverse effects. Further studies are needed to stratify women at high risk of PPH to cover other high-risk groups.

Conclusion

TXA effectively reduced intraoperative blood loss and the occurrence of PPH during high-risk CD under spinal anesthesia, without serious adverse effects.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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