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Effect of Prophylactic Tranexamic Acid on Perioperative Blood Loss in High-Risk Cesarean Delivery: A Randomized Controlled Study

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Abstract

Background

Postpartum hemorrhage (PPH) remains a major cause of maternal morbidity and mortality. Although tranexamic acid (TXA) is recommended for the treatment of established PPH, the clinical benefit of its prophylactic administration during cesarean delivery, particularly in women at increased risk of hemorrhage, remains uncertain.

Methods

Women aged 18–45 years with American Society of Anesthesiologists physical status II and at increased risk of PPH who were scheduled for elective cesarean delivery under spinal or general anesthesia were enrolled. The anesthesia technique was selected before randomization. Participants were subsequently stratified by anesthesia type and randomized within each stratum to receive either 1 g intravenous TXA after umbilical cord clamping or no TXA. All patients received a standardized uterotonic regimen. The primary outcome was estimated blood loss calculated using perioperative hematocrit values. Secondary outcomes included the incidence of blood loss > 500 and > 1000 mL, blood transfusion, perioperative changes in hemoglobin and hematocrit, additional uterotonic requirements, adverse events, and thromboembolic events during the three-month follow-up period. Eighty-four women were enrolled, and 83 were included in the final analysis.

Results

Estimated blood loss was 511 mL in the spinal anesthesia–TXA group, 590 mL in the spinal anesthesia control group, 579 mL in the general anesthesia–TXA group, and 617 mL in the general anesthesia control group. No statistically significant differences were observed among the groups in estimated blood loss, the incidence of blood loss > 500 or > 1000 mL, transfusion requirements, perioperative hemoglobin or hematocrit changes, or additional uterotonic use (all $P > 0.05$). Adverse-event rates were also comparable among groups. No thromboembolic events were identified during the three-month follow-up period.

Conclusions

In women at increased risk of PPH undergoing elective cesarean delivery, 1 g intravenous TXA administered after umbilical cord clamping was not associated with a statistically significant reduction in estimated blood loss or other hemorrhage-related outcomes under either spinal or general anesthesia. Given the limited sample size, the absence of statistically significant differences should be interpreted cautiously and does not exclude a potential prophylactic benefit of TXA.

Trial Registration

ClinicalTrials.gov, NCT07870499. Registered on October 6, 2026. Retrospectively registered.

INTRODUCTION

Postpartum hemorrhage (PPH) remains a major obstetric emergency and one of the leading causes of maternal morbidity and mortality worldwide (1, 2). Although several definitions have been proposed, severe PPH is commonly characterized by blood loss of ≥ 1000 mL following delivery (3). With the increasing global rate of cesarean delivery (4), perioperative hemorrhage has become an important concern, particularly in women with established risk factors for PPH (5).

Tranexamic acid (TXA) is a synthetic lysine analogue that exerts its antifibrinolytic effect by reversibly binding to lysine-binding sites on plasminogen, thereby inhibiting fibrinolysis (6). Its efficacy in reducing perioperative blood loss has been demonstrated in a variety of surgical settings (7). The potential role of prophylactic TXA in cesarean delivery was first reported by Gai et al., who demonstrated a reduction in intraoperative and postpartum blood loss (8). Subsequently, Naeiji et al. also reported reduced blood loss following prophylactic TXA administration in women undergoing elective cesarean delivery (9).

Despite these findings, the clinical benefit of prophylactic TXA during cesarean delivery remains uncertain. In the large multicenter TRAAP2 trial, prophylactic TXA reduced the composite primary outcome of calculated blood loss > 1000 mL or red-cell transfusion; however, no significant reductions were observed in gravimetrically measured blood loss, clinically assessed PPH, additional uterotonic use, or blood transfusion (10). The timing of administration may also influence efficacy. In an updated systematic review and meta-analysis, Cheema et al. reported that TXA administered before skin incision was associated with a greater reduction in blood loss, whereas administration after umbilical cord clamping did not demonstrate the same magnitude of benefit (11).

This issue may be particularly relevant in women at high risk of PPH. Recent randomized controlled trials in high-risk parturients demonstrated significant reductions in perioperative blood loss when TXA was administered before skin incision (12, 13). However, the overall evidence remains heterogeneous. A recent Cochrane review found little or no difference in the incidence of EBL ≥ 1000 mL and suggested that prophylactic TXA probably has little or no effect on transfusion requirements (14). In contrast, several contemporary meta-analyses have reported reductions in PPH, perioperative blood loss, transfusion requirements, and additional uterotonic use (15–20).

Importantly, the magnitude of benefit reported in these analyses varies considerably according to study characteristics, patient risk profile, methodological quality, and timing of TXA administration (15–20). Evidence specifically addressing high-risk women remains heterogeneous, and data evaluating the effect of TXA according to anesthesia technique are limited.

Therefore, the present study aimed to evaluate the effect of 1 g intravenous TXA administered after umbilical cord clamping on EBL, the incidence of PPH, and transfusion requirements in women at high risk of PPH undergoing elective cesarean delivery under spinal or general anesthesia. Secondary outcomes included perioperative changes in hemoglobin and hematocrit, additional uterotonic requirements, adverse events, and thromboembolic events during follow-up.

MATERIALS AND METHODS

Study Design and Participants

This prospective randomized study was conducted in the operating rooms of Pamukkale University Hospital between January 2022 and November 2022, following approval by the Pamukkale University Non-Interventional Clinical Research Ethics Committee at its meeting dated August 11, 2020 (meeting no. 15; approval no. 60116787-020/48516). Written informed consent was obtained from all participants before enrollment. This study was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Women aged 18–45 years, with American Society of Anesthesiologists (ASA) physical status II, a gestational age of 37–42 weeks, and at least one risk factor for postpartum hemorrhage (PPH), who were scheduled for elective cesarean delivery under spinal or general anesthesia, were eligible for inclusion. Risk factors for PPH were defined as multiple gestation, previous cesarean delivery, pregnancy-induced hypertension, fetal macrosomia, previous PPH, anemia (hemoglobin < 10 g/dL), placenta previa, and placental invasion abnormalities.

Exclusion criteria were age < 18 or > 45 years, refusal to participate in study-related procedures or assessments, a history of cardiovascular, cerebrovascular, or thromboembolic disease, coagulopathy, known allergy to any study medication, and use of low-molecular-weight heparin or antiplatelet therapy within one week before delivery.

Group Allocation

The choice of anesthesia technique was not randomized and was determined before treatment allocation according to the patient's preference, obstetric and clinical considerations, and the attending anesthesiologist's judgment. Participants were then stratified according to the selected anesthesia technique as spinal or general anesthesia. Within each anesthesia stratum, participants were randomized to receive either tranexamic acid (TXA) or no TXA, resulting in four study groups: Group 1, spinal anesthesia with TXA; Group 2, spinal anesthesia without TXA; Group 3, general anesthesia with TXA; and Group 4, general anesthesia without TXA. A total of 84 women were enrolled, with 21 participants initially allocated to each group.

This stratified design allowed the effect of TXA to be evaluated separately within the spinal and general anesthesia strata. However, because the anesthesia technique itself was not randomized, potential baseline differences between the two anesthesia strata could not be completely excluded. In addition, the relatively small number of participants in each group may have limited the statistical power to detect modest between-group differences.

Trial Registration

This study was not registered in a public clinical trial registry.

Randomization and Blinding

Within each anesthesia stratum, participants were randomized in a 1:1 ratio to either the tranexamic acid (TXA) or control group. The randomization sequence was generated using the RAND function in Microsoft Excel by an independent individual who was not involved in the study. Participants were assigned random numbers and ranked accordingly to establish the allocation sequence. To ensure allocation concealment, sequentially numbered, opaque, sealed envelopes containing the treatment assignments were prepared by the same independent individual before participant enrollment.

Following enrollment and confirmation of the anesthesia technique, the attending anesthesiologist opened the envelopes sequentially within the corresponding anesthesia stratum and assigned participants to the TXA or control group according to the concealed allocation sequence. The attending anesthesiologist was aware of treatment allocation and administered the assigned intervention.

The investigator responsible for outcome assessment remained blinded to treatment allocation throughout the assessment process. To maintain blinding, treatment assignment information was removed from the outcome assessment forms, and the investigator had no access to the randomization list or treatment allocation records.

Anesthesia Protocol

Anesthesia Protocol
Spinal anesthesia was performed under standard monitoring with the patient in the sitting position. After aseptic preparation, the subarachnoid space was accessed at the L3–L4 or L4–L5 interspace, and 10 mg hyperbaric bupivacaine combined with 10 μg fentanyl was administered intrathecally. Surgery was initiated after achievement of an adequate sensory block level up to T4. Hemodynamic disturbances were treated with intravenous fluids and vasoactive medications as clinically indicated.

For general anesthesia, patients were preoxygenated and underwent rapid-sequence induction with propofol 2 mg/kg and rocuronium 1.0 mg/kg intravenously, followed by endotracheal intubation. Anesthesia was maintained with sevoflurane in an oxygen–air mixture. Mechanical ventilation was

adjusted to maintain adequate maternal oxygenation and normocapnia, with end-tidal carbon dioxide maintained within the normal physiologic range. Opioid analgesia was administered after umbilical cord clamping.

Perioperative Management

After admission to the operating room, preoperative fasting status was confirmed. Patients were positioned supine with a 15° left lateral tilt and underwent standard monitoring including noninvasive arterial blood pressure, heart rate, electrocardiography, peripheral oxygen saturation (SpO_2), and respiratory rate. Supplemental oxygen at 3–4 L/min via nasal cannula was administered when SpO_2 was < 95%. An 18-gauge intravenous cannula was inserted in the antecubital region, and preoperative hemoglobin and hematocrit values were recorded. Intravenous crystalloid solution was administered at 15 mL/kg, corresponding to approximately 1 L in most patients.

After umbilical cord clamping, all patients received 3 IU of oxytocin by slow intravenous injection over > 30 seconds, followed by an oxytocin infusion at 10 IU/h. In the TXA groups, 1 g intravenous TXA was administered slowly after umbilical cord clamping, concomitantly with oxytocin. If adequate uterine tone was not achieved, an additional 3-IU dose of oxytocin was administered after 2 minutes. When this regimen was insufficient, second-line uterotonic therapy consisted of methylergometrine 0.2 mg intramuscularly or, when clinically indicated, by slow intravenous administration.

Estimation of Blood Loss

EBL was calculated using perioperative hematocrit values according to the following formula:

EBL = Estimated blood volume × (preoperative hematocrit − postoperative hematocrit) / preoperative hematocrit

Estimated blood volume was calculated as:

Body weight (kg) × 85 mL/kg

Postoperative hematocrit was measured at the fourth postoperative hour.

Study Outcomes

The primary outcome was EBL (mL), calculated using preoperative and postoperative hematocrit values.

Secondary outcomes included the incidence of EBL > 500 mL and > 1000 mL, blood transfusion requirement, perioperative changes in hemoglobin and hematocrit, the need for additional uterotonic agents, adverse events potentially associated with TXA, and thromboembolic events during the 3-month follow-up period.

Potential TXA-related adverse events included headache, fatigue, abdominal pain, nausea, vomiting, diarrhea, seizures, anaphylaxis, visual disturbances, myocardial infarction, and cerebrovascular events. Patients were contacted three months after surgery and questioned regarding thromboembolic events.

Sample Size Estimation

The sample size was calculated based on the findings of Naeiji et al. (9). Assuming an effect size of d = 0.9, a two-sided alpha level of 0.05, and a statistical power of 80%, at least 21 participants were required per group. As the effect of TXA was evaluated separately under spinal and general anesthesia, 42 participants were planned for each anesthesia stratum, resulting in a total target sample size of 84 patients.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (minimum–maximum), as appropriate, and categorical variables as numbers and percentages. Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Within-group preoperative and postoperative hemoglobin and hematocrit values were compared using the paired-samples t test. Comparisons of continuous variables among the four groups were performed using one-way analysis of variance (ANOVA) for normally distributed data and the Kruskal–Wallis test for non-normally distributed data. When a significant difference was detected by ANOVA, Tukey's post hoc test was used for pairwise comparisons. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Statistical analyses were performed using IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA). A two-sided P value < 0.05 was considered statistically significant. Additional unadjusted comparisons of estimated blood loss between the TXA and control groups within each anesthesia stratum were performed using summary statistics. Mean differences and corresponding 95% confidence intervals were calculated using Welch's method.

The final statistical analysis was conducted using a complete-case approach, including 83 of the 84 randomized participants with complete study data. One participant in the general anesthesia–TXA group was excluded because of incomplete data. No imputation methods were applied for missing data.

RESULTS

Patient Flow

A total of 84 patients were enrolled and allocated to the four study groups. One patient in the general anesthesia–TXA group with placenta accreta experienced exceptionally high blood loss, which resulted in incomplete collection of the required study data. This patient was therefore excluded from the final analysis, leaving 83 patients for analysis.

Baseline Characteristics

The four groups were comparable with respect to age and body mass index (BMI) (both $P > 0.05$). However, significant differences were observed in body weight and height among the groups ($P = 0.030$ and $P = 0.020$, respectively). Post hoc analysis showed that patients in the spinal anesthesia control group had significantly higher body weight and height than those in the general anesthesia control group, whereas no significant differences were observed between the remaining groups (Table 1).

Table 1
Baseline characteristics of the study groups

Variable	Spinal + TXA (n = 21)	Spinal control (n = 21)	General + TXA (n = 20)	General control (n = 21)	P value
Age, years	32.52 ± 4.79	31.62 ± 5.01	31.65 ± 4.88	29.33 ± 5.53	0.216
Body weight, kg	78.33 ± 11.19	86.76 ± 17.30	76.45 ± 9.40	75.57 ± 13.46	**0.030**
Height, cm	162.05 ± 6.28	163.57 ± 4.21	158.90 ± 5.12	158.90 ± 5.10	**0.020**
BMI, kg/m²	30.00 ± 5.26	32.37 ± 6.08	28.75 ± 3.83	29.91 ± 5.05	0.154

Data are presented as mean ± standard deviation. BMI, body mass index; TXA, tranexamic acid. P values were calculated using one-way analysis of variance or the Kruskal–Wallis test, as appropriate. Post hoc analysis showed significantly greater body weight and height in the spinal control group than in the general anesthesia control group.

Estimated Blood Loss

Mean EBL was 511.38 ± 310.91 mL in the spinal anesthesia–TXA group, 590.15 ± 400.99 mL in the spinal anesthesia control group, 579.67 ± 379.17 mL in the general anesthesia–TXA group, and 617.26 ± 288.28 mL in the general anesthesia control group. EBL did not differ significantly among the groups ($P = 0.649$) (Table 2).

Table 2
Estimated blood loss and hemorrhage-related outcomes

Outcome	Spinal + TXA (n = 21)	Spinal control (n = 21)	General + TXA (n = 20)	General control (n = 21)	P value
Estimated blood loss, mL	511.38 ± 310.91	590.15 ± 400.99	579.67 ± 379.17	617.26 ± 288.28	0.649
Body weight-adjusted estimated blood loss, mL	517.68	530.83	604.51	649.86	0.685
Blood loss > 500 mL, n (%)	9 (42.9)	13 (61.9)	9 (47.6)	12 (57.1)	0.543
Blood loss > 1000 mL, n (%)	1 (4.8)	2 (9.5)	3 (19.0)	1 (4.8)	0.597
Blood transfusion, n (%)	0 (0)	0 (0)	2 (10.0)	0 (0)	0.091
Additional uterotonic use, n (%)	6 (28.6)	9 (42.9)	8 (40.0)	11 (52.4)	0.475

Continuous data are presented as mean ± standard deviation and categorical data as n (%). TXA, tranexamic acid. P values for categorical outcomes were calculated using the chi-square or Fisher's exact test, as appropriate. One patient with placenta accreta in the general anesthesia–TXA group was excluded from the final analysis.

Because body weight differed significantly among the groups, EBL was additionally adjusted for body weight. The adjusted EBL values were 517.68 mL, 530.83 mL, 604.51 mL, and 649.86 mL in Groups 1–4, respectively, with no significant difference among groups ($P = 0.685$).

In an additional unadjusted comparison within each anesthesia stratum, the mean difference in estimated blood loss between the TXA and control groups was − 78.77 mL (95% CI: −302.99 to 145.45 mL) under spinal anesthesia and − 37.59 mL (95% CI: −251.82 to 176.64 mL) under general anesthesia. These confidence intervals were calculated using Welch's method and included zero in both strata.

Transfusion Requirements

Blood transfusion requirements did not differ significantly among the groups ($P = 0.091$) (Table 2). In the final analyzed cohort, transfusion was required only in the general anesthesia–TXA group, in 2 of 20 patients (10%); no transfusions were required in the other groups. Both patients who required transfusion had placenta previa. A third patient with placenta accreta also required transfusion but was excluded from the final analysis because of incomplete study data associated with exceptionally high blood loss.

Incidence of Postpartum Hemorrhage

The incidence of EBL > 500 mL was 42.9% (9/21) in the spinal anesthesia–TXA group, 61.9% (13/21) in the spinal anesthesia control group, 47.6% (9/20) in the general anesthesia–TXA group, and 57.1% (12/21) in the general anesthesia control group. No significant difference was observed among the groups ($P = 0.543$) (Table 2).

Similarly, the incidence of EBL > 1000 mL was 4.8% (1/21), 9.5% (2/21), 19.0% (3/20), and 4.8% (1/21) in Groups 1–4, respectively, with no significant between-group difference ($P = 0.597$) (Table 2).

Hemoglobin and Hematocrit Changes

Postoperative hemoglobin levels were significantly lower than preoperative values within all four groups (all $P < 0.001$). However, preoperative and postoperative hemoglobin values were comparable among the groups ($P = 0.679$ and $P = 0.575$, respectively). Mean reductions in hemoglobin were 1.06 ± 0.79 g/dL, 1.06 ± 0.73 g/dL, 1.12 ± 0.61 g/dL, and 1.11 ± 0.53 g/dL in Groups 1–4, respectively, with no significant difference among groups ($P = 0.985$).

Postoperative hematocrit values were likewise significantly lower than preoperative values within all groups (all $P < 0.001$). Preoperative and postoperative hematocrit values did not differ significantly among the four groups ($P = 0.541$ and $P = 0.447$, respectively). Mean reductions in hematocrit were 2.80 ± 1.83%, 3.09 ± 2.38%, 3.03 ± 1.61%, and 3.95 ± 1.67%, respectively, with no significant between-group difference ($P = 0.799$) (Table 3).

Table 3
Perioperative hemoglobin and hematocrit values

Variable	Spinal + TXA (n = 21)	Spinal control (n = 21)	General + TXA (n = 20)	General control (n = 21)	Between-group P value
Preoperative Hb, g/dL	11.77 ± 1.36	11.92 ± 1.75	11.76 ± 1.27	11.39 ± 1.39	0.679
Postoperative Hb, g/dL	10.71 ± 1.27	10.86 ± 1.59	10.63 ± 1.40	10.27 ± 1.29	0.575
Decrease in Hb, g/dL	−1.06 ± 0.79	−1.06 ± 0.73	−1.12 ± 0.61	−1.11 ± 0.53	0.985
Preoperative Hct, %	35.07 ± 3.35	36.40 ± 4.87	35.09 ± 3.32	34.82 ± 3.16	0.541
Postoperative Hct, %	32.26 ± 3.18	33.30 ± 4.47	32.06 ± 3.79	31.43 ± 3.44	0.447
Decrease in Hct, %	−2.80 ± 1.83	−3.09 ± 2.38	−3.03 ± 1.61	−3.95 ± 1.67	0.799

Data are presented as mean ± standard deviation. Hb, hemoglobin; Hct, hematocrit; TXA, tranexamic acid. Between-group comparisons were performed using one-way analysis of variance or the Kruskal–Wallis test, as appropriate. Within-group preoperative and postoperative Hb and Hct values were compared using the paired-samples t test. Postoperative Hb and Hct values were significantly lower than the corresponding preoperative values in all groups (all P < 0.001).

Additional Uterotonic Requirement

Additional uterotonic agents were required in 6 of 21 patients (28.6%) in the spinal anesthesia–TXA group, 9 of 21 (42.9%) in the spinal anesthesia control group, 8 of 20 (40.0%) in the general anesthesia–TXA group, and 11 of 21 (52.4%) in the general anesthesia control group. The difference among groups was not statistically significant ($P = 0.475$) (Table 2).

Adverse Events and Thromboembolic Outcomes

The frequencies of recorded adverse events, including headache, fatigue, abdominal pain, and nausea, were not significantly different among the four groups (all $P > 0.05$) (Table 4). No seizures were observed in any patient. Because several of these symptoms may also occur as a consequence of surgery or anesthesia, attribution specifically to TXA was limited. During the 3-month follow-up period, no thromboembolic events were identified in any of the 83 patients included in the final analysis.

Table 4
Adverse events observed among the study groups

Adverse event	Spinal + TXA (n = 21)	Spinal control (n = 21)	General + TXA (n = 20)	General control (n = 21)	P value
Headache					**0.823**
No	18 (85.7)	18 (85.7)	16 (80.0)	19 (90.5)	
Yes	3 (14.3)	3 (14.3)	4 (20.0)	2 (9.5)	
Fatigue					**0.232**
No	19 (90.5)	14 (66.7)	16 (80.0)	18 (85.7)	
Yes	2 (9.5)	7 (33.3)	4 (20.0)	3 (14.3)	
Abdominal pain					**0.569**
No	**16 (76.2)**	16 (76.2)	18 (90.0)	18 (85.7)	
Yes	**5 (23.8)**	5 (23.8)	2 (10.0)	3 (14.3)	
Nausea					**0.331**
No	19 (90.5)	21 (100)	17 (85.0)	18 (85.7)	
Yes	2 (9.5)	0 (0)	3 (15.0)	3 (14.3)	
Seizure					–
No	21 (100)	21 (100)	20 (100)	21 (100)	
Yes	0 (0)	0 (0)	0 (0)	0 (0)	

Data are presented as n (%). TXA, tranexamic acid. P values were calculated using the chi-square test or Fisher's exact test, as appropriate. No statistically significant differences in recorded adverse events were observed among the groups.

DISCUSSION

The principal finding of the present study was that administration of 1 g intravenous TXA after umbilical cord clamping was not associated with a statistically significant reduction in EBL in women at high risk of postpartum hemorrhage undergoing elective cesarean delivery. No significant differences were observed among the study groups in the incidence of EBL > 500 mL or > 1000 mL, transfusion requirements, perioperative decreases in hemoglobin and hematocrit, or the need for additional uterotonic agents. These findings were consistent across the spinal and general anesthesia strata. Adverse-event rates were comparable among groups, and no thromboembolic events were identified during the 3-month follow-up period. Given the relatively small sample size, these findings should be

interpreted as showing no statistically significant benefit in this cohort rather than as evidence that prophylactic TXA is ineffective.

Our findings should first be considered in the context of the large TRAAP2 trial. Sentilhes et al. randomized more than 4400 women undergoing cesarean delivery to receive 1 g TXA or placebo in addition to prophylactic uterotonic therapy (10). The primary composite outcome of calculated EBL > 1000 mL or red-cell transfusion occurred significantly less frequently in the TXA group (10). However, no significant differences were observed in mean gravimetrically EBL provider-assessed clinically significant PPH, additional uterotonic use, or postpartum blood transfusion (10). These findings are partially consistent with our results and suggest that statistically significant differences in calculated blood loss do not necessarily translate into reductions in clinically relevant hemorrhage-related interventions.

One of the most important factors that may explain the absence of a significant benefit in our study is the timing of TXA administration. In the present study, TXA was administered after umbilical cord clamping. Cheema et al., in an updated systematic review and meta-analysis of randomized controlled trials, reported that administration before skin incision was associated with a greater reduction in blood loss, whereas administration after umbilical cord clamping did not demonstrate the same magnitude of benefit (11). This distinction may be clinically relevant because administration before incision allows antifibrinolytic activity to be established before surgical tissue injury and placental separation, whereas administration after cord clamping occurs after bleeding has already begun.

Recent randomized controlled trials specifically involving women at high risk of PPH also support the potential importance of administration timing. Neumann et al. randomized 212 women at increased risk of PPH to receive 1 g TXA or placebo at least 10 minutes before skin incision and reported significantly lower calculated and gravimetrically measured blood loss in the TXA group (12). Similarly, Ortuanya et al. administered 1 g TXA at least 10 minutes before surgery in 200 high-risk women and reported lower mean blood loss, higher postoperative hemoglobin levels, a lower incidence of PPH, and less frequent additional uterotonic use in the TXA group (13). The differences between these findings and those of the present study may therefore be related, at least in part, to pre-incision versus post-cord-clamping administration.

Nevertheless, the overall evidence regarding prophylactic TXA during cesarean delivery remains heterogeneous. A recent Cochrane review by Rohwer et al. found little or no difference in EBL ≥ 1000 mL and probably little or no difference in transfusion requirements following prophylactic TXA administration (14). Importantly, much of the highest-certainty evidence included women at relatively low risk of PPH, which may limit its applicability to women with a higher baseline hemorrhagic risk (14).

In contrast, several recent meta-analyses have reported more favorable effects of prophylactic TXA. Provinciatto et al. analyzed 38 randomized controlled trials involving 22,940 parturients and reported reductions in PPH, blood transfusion, and additional uterotonic requirements with prophylactic TXA (15). However, substantial methodological heterogeneity among the included studies remains an important

concern (15). Al Naimi et al., in a meta-analysis of 24 trials including 19,584 participants, also reported an overall reduction in blood loss, but noted substantial heterogeneity and smaller treatment effects in studies conducted in high-income countries and in trials at lower risk of bias (16). These findings suggest that the magnitude of the reported benefit may vary considerably according to study design, methodological quality, and population characteristics (16).

Guinness et al. similarly reported reductions in PPH > 1 L, estimated mean blood loss, hemoglobin decline, and additional uterotonic requirements with prophylactic TXA (17). However, greater treatment effects were observed in smaller studies and studies conducted in developing economies, raising uncertainty regarding the clinical benefit of universal prophylactic administration (17). The authors also suggested that women at higher risk of PPH may represent a population in whom prophylactic TXA could have greater clinical relevance (17).

More recent meta-analyses focusing specifically on high-risk women have generally reported more favorable findings. Daghmouri et al. included 11 randomized controlled trials involving 1627 high-risk women and found that prophylactic TXA significantly reduced intraoperative blood loss, PPH, and transfusion requirements (18). Sandoval López et al. analyzed nine randomized controlled trials involving 1776 women at high risk of PPH and reported reductions in total blood loss, intraoperative blood loss, blood loss > 1000 mL, additional uterotonic use, transfusion requirements, and complementary surgical interventions (19). Their subgroup analysis also suggested that the benefit was greater when TXA was administered 15–20 minutes before skin incision (19). Gao et al. similarly reported reductions in blood loss, PPH, blood loss > 1000 mL, transfusion requirements, and additional uterotonic use in a meta-analysis focusing on high-risk women, although substantial heterogeneity was observed for several continuous outcomes (20).

Accordingly, the absence of a statistically significant benefit in our study does not necessarily conflict with the emerging evidence supporting prophylactic TXA in selected high-risk women. Differences in administration timing, baseline hemorrhagic risk, sample size, outcome definitions, and methods used to estimate blood loss may contribute to the differences between studies (11–20). In particular, administration after umbilical cord clamping in our study may have reduced the opportunity for TXA to exert its antifibrinolytic effect during the earliest phases of surgical bleeding.

No significant difference in transfusion requirements was observed among the groups in the present study. In the final analyzed cohort, only two patients required postoperative blood transfusion, both of whom had placenta previa; an additional patient with placenta accreta who required transfusion was excluded from the final analysis because of incomplete study data associated with exceptionally high blood loss. Because transfusion was an infrequent event, the present study had limited statistical power to detect differences in this outcome. TRAAP2 likewise did not demonstrate a significant reduction in blood transfusion when transfusion was evaluated as an individual secondary outcome (10). The Cochrane review also concluded that prophylactic TXA probably results in little or no difference in transfusion requirements (14). Conversely, several meta-analyses have reported significantly lower

transfusion rates with prophylactic TXA (15, 18–20). Differences in baseline hemorrhage risk, transfusion thresholds, administration timing, and the frequency of severe hemorrhage may partly explain these discrepant findings.

The safety findings of the present study should also be interpreted cautiously. No thromboembolic events occurred during the 3-month follow-up period, and there were no significant differences in recorded minor adverse events among the groups. Contemporary meta-analyses have generally not demonstrated a significant increase in thromboembolic complications associated with prophylactic TXA (11, 15). However, thromboembolic events are uncommon, and even large trials have limited precision for detecting small differences in such rare outcomes. In the TRAAP2 trial, thromboembolic events occurred in 0.4% of women receiving TXA and 0.1% of those receiving placebo, although the difference was not statistically significant (10). Therefore, the absence of thromboembolic events in our cohort should not be interpreted as definitive evidence regarding the safety of prophylactic TXA with respect to rare thrombotic complications.

Several limitations of the present study should be acknowledged. First, this was a single-center study with a relatively small sample size, limiting statistical power, particularly for infrequent outcomes such as severe PPH, blood transfusion, and thromboembolic events. Second, the high-risk population included women with different obstetric risk factors, including anemia, multiple gestation, hypertensive disorders of pregnancy, macrosomia, previous PPH, placenta previa, and placental invasion abnormalities, resulting in heterogeneity in baseline hemorrhagic risk. Third, TXA was administered after umbilical cord clamping, whereas current evidence suggests that administration before skin incision may be associated with a greater reduction in blood loss (11–13, 19). Fourth, EBL was calculated using perioperative hematocrit values rather than being assessed simultaneously using a gravimetric method. The postoperative hematocrit measurement obtained four hours after surgery may have been influenced by perioperative fluid administration and incomplete equilibration following acute blood loss. Finally, one patient with placenta accreta and exceptionally high blood loss was excluded from the final analysis because complete study data could not be obtained, which should be considered when interpreting the results.

Conclusion

In women at high risk of postpartum hemorrhage undergoing elective cesarean delivery, prophylactic administration of 1 g intravenous TXA after umbilical cord clamping was not associated with a statistically significant reduction in EBL, the incidence of postpartum hemorrhage, transfusion requirements, perioperative hemoglobin or hematocrit decline, or additional uterotonic requirements. Similar findings were observed in both spinal and general anesthesia strata. No thromboembolic events were identified during the 3-month follow-up period. Given the relatively small sample size, these findings should be interpreted cautiously and should not be considered evidence that prophylactic TXA is ineffective. Further adequately powered randomized controlled trials are needed to determine whether administration before skin incision provides greater clinical benefit in high-risk cesarean delivery.

WHAT IS ALREADY KNOWN

1. Tranexamic acid is effective for the treatment of established postpartum hemorrhage and has been increasingly investigated as a prophylactic strategy during cesarean delivery.
2. Previous randomized trials and meta-analyses have reported heterogeneous results regarding the effect of prophylactic TXA on blood loss, transfusion requirements, and additional uterotonic use.
3. The timing of TXA administration may influence its prophylactic efficacy, with several recent studies suggesting greater benefit when TXA is administered before skin incision.

WHAT THIS STUDY ADDS

1. In women at high risk of postpartum hemorrhage, 1 g intravenous TXA administered after umbilical cord clamping was not associated with a statistically significant reduction in EBL or other hemorrhage-related outcomes.
2. Similar findings were observed in both spinal and general anesthesia strata.
3. These findings support the possibility that the timing of TXA administration may be an important determinant of prophylactic efficacy in high-risk cesarean delivery.

Abbreviations

ASA
American Society of Anesthesiologists physical status classification
BMI
Body mass index
ECG
Electrocardiography
EBL
Estimated blood loss
Hb
Hemoglobin
Hct
Hematocrit
IV
Intravenous
IU
International unit
PPH
Postpartum hemorrhage
SpO_2
Peripheral oxygen saturation
TXA

Tranexamic acid

Declarations

Ethics approval and consent to participate

This study was approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee at its meeting held on August 11, 2020 (meeting no. 15; approval no. 60116787-020/48516). Written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

BÖ and MY contributed to the conception and design of the study. AMY and MY contributed to data acquisition. MY and AMY performed the statistical analysis and interpreted the data. BÖ drafted the initial manuscript. All authors critically revised the manuscript, read and approved the final version.

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Not applicable.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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