Original Article

Role of prophylactic tranexamic acid in reducing blood loss during cesarean section: A double-blind placebo-controlled randomized controlled trial

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Abstract

Background: Postpartum hemorrhage (PPH) is defined by the World Health Organization as blood loss of ≥500 mL within 24 h of delivery. Globally, hemorrhage accounts for 27.1% of maternal deaths, making it the leading direct cause of maternal death. PPH has been identified in more than two-thirds of reported hemorrhage-related deaths, causing 38% of maternal deaths in India. Tranexamic acid, an antifibrinolytic, has been used to control bleeding after PPH is identified. **Materials and Methods:** Antenatal women admitted for elective cesarean section were randomized into two arms: the case group (received one gram of tranexamic acid 20 min prior to skin incision) and the control group (received a placebo), each group consisting of 36 participants. Clinical Trials Registry – India (CTRI) registration number – CTRI/2021/02/031579. **Results:** The mean (±standard deviation [SD]) intraoperative blood loss in the case group was 241.25 (±67.83) mL, and in the control group, it was 344.92 (±146.67) mL (P = 0.001), while postoperative blood loss did not differ significantly between the groups (P = 0.1470). In terms of the difference in hemoglobin, there was a significant difference between the two groups (P = 0.001). No significant maternal or neonatal side effects were found. **Conclusion:** Preoperative tranexamic acid, when given in elective cesarean section, significantly reduces intraoperative blood loss.

Keywords: Antifibrinolytics, maternal morbidity, maternal mortality, obstetric hemorrhage, postpartum hemorrhage, tranexamic acid

Introduction

The World Health Organization (WHO) defines postpartum hemorrhage (PPH) as a blood loss of 500 mL or more within 24 h of delivery; severe PPH is defined as a blood loss of 1000 mL or more during the same timeframe.[1] Every year, some 530,000 women die during pregnancy and childbirth; South Asia accounts for almost one-third of these deaths.[2] Hemorrhage is the primary direct cause of maternal death worldwide, accounting for 27.1% of all maternal deaths. PPH is responsible for 38% of maternal mortality in India and has been linked to more than two-thirds of reported hemorrhage-related deaths.[3,4]

Worldwide rates of cesarean sections (CS) have increased; in India, the rate is 17.2%. This has resulted in high morbidity from significant loss of blood.[5] A solution needs to be devised in order to effectively limit blood loss and morbidity in patients undergoing CS.

A lysine analog called tranexamic acid (TXA) inhibits the activation of plasmin and fibrinolysis. Consequently, the mechanism of action of this medication is the stabilization of pre-existing clots

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rather than the promotion of the development of new ones. This drug is reasonably priced and widely accessible. It also has a 3-year shelf life and can be kept at room temperature. Its half-life is 80 min, and its effects begin to take action 5 to 15 min after administration. Furthermore, breastfeeding is safe because breast milk contains very little (1/100) of this medication.[6] As a result, it is thought to be extremely valuable in areas like Southern Asia that have few resources. Researchers from a variety of specializations participated in the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2 (CRASH-2) trial, which increased interest in and knowledge about TXA.[7]

The WHO recommends that if PPH is diagnosed within 3 h of birth, administration of TXA is commenced immediately. For PPH treatment, 1 g of TXA is given intravenously over 10 min within 3 h of vaginal or cesarean delivery.[8] There is little evidence to support TXA's use in preventing PPH, despite the World Maternal Antifibrinolytic (WOMAN) trial providing evidence for its efficacy in treating PPH that has already been diagnosed.[9] Preventive use of TXA may reduce postpartum hemorrhage and the need for blood transfusions, according to reviews and meta-analyses of numerous trials. The Royal College of Obstetricians and Gynecologists currently recommends considering the use of prophylactic TXA only in women at high risk for PPH undergoing CS.[10] But, even for low-risk women, larger sufficiently powered multicenter randomized controlled studies are required before prophylactic TXA use for PPH prophylaxis would be recommended.

Materials and Methods

Patient Recruitment

This study was a single-center, double-blind, placebo-controlled randomized controlled trial (RCT) with one case arm (group A) and one control arm (group B). It was conducted over a period of 18 months after obtaining ethical clearance (Institutional Ethics Committee [IEC] Proposal number: AIIMSRPR/IEC/2020/676) and Clinical Trials Registry – India {CTRI) registration (CTRI registration number – CTRI/2021/02/031579). All prenatal women scheduled for elective CSs had to meet the following criteria to be included: single pregnancy, age 18–35 years, gestational age 37–42 weeks, live fetus, hemoglobin level more than 9 g/dL within the previous 6 weeks of lower segment cesarean section (LSCS), and LSCS performed under spinal anesthesia. Pregnancy-related complications, such as severe preeclampsia, multiple pregnancies, polyhydramnios, babies weighing >4 kg, placenta previa, placenta accreta spectrum, as well as two or more prior CSs, intrauterine death, anticoagulation within a week before LSCS, history of seizures, and allergy to TXA, were the exclusion criteria. Potential participants were recruited at the time of admission for their CS. Detailed history, examination, and investigations were noted in the Case Record Form for the women giving informed written consent.

Blinding and randomization

Participants were allotted to either of the two groups by block randomization using opaque sealed envelopes, that is, by offering patients opaque sealed envelopes inside which the case or control group was mentioned. Sealed opaque envelopes were opened in the preoperative area by an independent on-duty nursing officer who is not part of the study and gave relevant intervention to the patient according to the group allotted. This ensured the blinding of the patient and the investigator. At the time of intravenous cannula insertion, 2 mL of blood was collected for hemoglobin estimation. Hemoglobin estimation was done in the pathology lab of AIIMS Raipur by an automated analyzer – SYSMEX XN 1000. An independent nursing officer administered one gram of TXA in 100 mL Normal saline (NS) as an intravenous infusion over 15 min at least 20 min prior to skin incision to women in Group A (case group) and 100 mL NS intravenous infusion over 15 min as a placebo 20 min prior to skin incision to women in Group B (control group).

Blood Loss Estimation

Blood loss was assessed using the gravimetric method. Surgical mops, the operation table's perineal sheet, and pads used for vaginal toileting during surgery were weighed before and after the procedure using an electronic scale. The blood collected in the suction machine's bottle (from placental delivery to the end of vaginal toileting) was measured to represent suctioned blood loss, contributing to the total blood loss calculation. Intraoperative blood loss was determined by adding: Blood absorbed by soaked surgical mops (wet weight – dry weight) + Blood absorbed by perineal sheets, surgical drapes, and pads during vaginal toileting (wet weight – dry weight) + Blood collected in the suction container. In addition, uterotonics administered for uterine atony were recorded. In addition, any occurrences of nausea, vomiting, or diarrhea after drug administration were noted. Postoperative blood loss was measured from the end of vaginal toileting up to 3 h postpartum using the gravimetric method. A weight of 1 mg was considered equivalent to 1 mL of blood. Hemoglobin levels were estimated to be 48 h after surgery. Participants were monitored for 48 h to detect the development of venous thromboembolism. Unblinding was conducted after assessing all participants for subsequent data analysis.

Statistical Analysis

The sample size was calculated based on an RCT conducted by Sahu *et al.*[11] n (sample size) = $\{2 \times SD2 \times (Z\alpha 2 + Z\beta 2)2\} \div \{M2 - M1\}2$, where SD = mean standard deviation of study and control groups = 103.23, $Z\alpha = 2.58$ (99% confidence interval), $Z\beta = 1.28$ (90% power), M2 (mean blood loss in the control group) = 422.5 mL, M1 (mean blood loss in the study group) = 350.5 mL. After calculation, the sample size (n) came out to be 30 for each group. Taking into account a potential 20% loss to follow-up, the sample size was increased to 36 participants per group. Data was collected, tabulated, and statistically analyzed using the Statistical Program for Social Sciences (SPSS, version 26, Chicago: SPSS Inc.) software. Numerical variables were presented as mean and standard deviation (SD), while categorical variables were presented as a number and percentage. A t-test was used

to find the significance between the two groups with regard to the continuous variables. Wilcoxon–Mann–Whitney U test, Chi-square test, and Fisher exact test were used for comparison between groups as regard qualitative variables. The probability value $P \leq 0.01$ was taken as the level of significance.

Results

Out of the 104 pregnant women, 72 women scheduled for elective CS who met the inclusion and exclusion criteria and provided consent to participate were included in the study [Figure 1].

There were no differences between the two groups in terms of demographic parameters, body mass index (BMI), and period of gestation (POG), as shown in Table 1.

Previous CS due to cephalopelvic disproportion, present in 47.2% of both groups, emerged as the most common indication, as illustrated in Figure 2. Regarding the distribution of indications, no significant difference was observed between the two groups ($\chi^2 = 4.944$, $P = 0.899$).

The mean (± SD) duration of the operation was 62.42 (±6.53) min in the case group and 60.89 (±7.33) min in the control group, which did not exhibit statistical significance (W = 704.500, $P = 0.527$).

As presented in Table 2, within the case group, the mean (± SD) intraoperative blood loss measured 241.25 (±67.83) mL, whereas in the control group, it totaled 344.92 (±146.67) mL. Intra-operative blood loss demonstrated a substantial difference between the two groups (W = 267.500, $P = 0.001$), whereas postoperative blood loss did not reach significance (t = -1.468, $P = 0.147$). In the case group, the mean (± SD) postoperative loss was 42.69 (±11.42) mL, and in the control group, it was 46.44 (±10.23) mL. The mean preoperative hemoglobin level in the case group was 11.217 (±1.089) g/dL, and in the control group, it was 11.664 (±1.439) g/dL; the difference was not statistically significant ($P = 0.1415$). Moreover, the mean postoperative hemoglobin level was 10.857 (±1.317) g/dL in the case group and 10.653 (±±1.807) g/dL in the control group; again, the difference was not statistically significant ($P = 0.5887$).

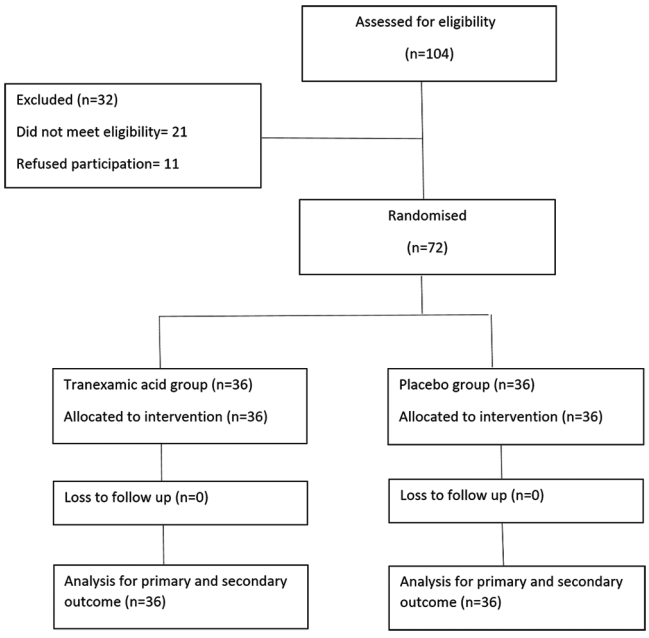

Figure 1: Participant randomization and treatment

Regarding the decrease in hemoglobin level, there was a significant difference between the two groups (W = 367.500, $P = 0.001$). The mean (± SD) change in hemoglobin level was 0.48 (±0.62) g/dL in the case group and 1.29 (±1.24) g/dL in the control group.

Table 1: Demographic profile

Parameters	Group		*P*
	Case (*n*=36)	Control (*n*=36)	
Age (Years)	29.42±2.81	29.44±3.71	0.755[1]
Age Group			0.095[2]
21–25 Years	2 (5.6%)	5 (13.9%)	
26–30 Years	23 (63.9%)	14 (38.9%)	
31–35 Years	11 (30.6%)	17 (47.2%)	
Parity			0.384[3]
Primigravida	6 (16.7%)	9 (25.0%)	
Multigravida	30 (83.3%)	27 (75.0%)	
Occupation			0.781[3]
Professional	8 (22.2%)	9 (25.0%)	
Housewife	28 (77.8%)	27 (75.0%)	
Region			1.000[3]
Rural	6 (16.7%)	6 (16.7%)	
Urban	30 (83.3%)	30 (83.3%)	
Education***			0.037[3]
Primary	1 (2.8%)	0 (0.0%)	
Secondary	2 (5.6%)	9 (25.0%)	
Higher Secondary	9 (25.0%)	2 (5.6%)	
Graduate	18 (50.0%)	17 (47.2%)	
Post Graduate	6 (16.7%)	8 (22.2%)	
Socio-Economic Status			0.952[2]
Upper Class	4 (11.1%)	3 (8.3%)	
Upper Middle	17 (47.2%)	15 (41.7%)	
Middle	10 (27.8%)	12 (33.3%)	
Lower Middle	4 (11.1%)	5 (13.9%)	
Lower Class	1 (2.8%)	1 (2.8%)	
BMI (Kg/m²)	26.44±3.56	25.21±1.40	0.176[1]
BMI			0.467[2]
18.5–22.9 Kg/m²	2 (5.6%)	2 (5.6%)	
23.0–24.9 Kg/m²	10 (27.8%)	11 (30.6%)	
25.0–29.9 Kg/m²	20 (55.6%)	23 (63.9%)	
30.0–34.9 Kg/m²	2 (5.6%)	0 (0.0%)	
35.0–39.9 Kg/m²	2 (5.6%)	0 (0.0%)	
POG (Weeks)	39.22±0.83	39.14±1.03	0.734[4]
POG***			0.029[3]
37–40 Weeks	31 (86.1%)	23 (63.9%)	
40–42 Weeks	5 (13.9%)	13 (36.1%)	

***Significant at $P<0.05$, [1]: Wilcoxon–Mann–Whitney U test, [2]: Fisher's exact test, [3]: Chi-squared test, [4]: *t*-test

The distribution of additional uterotonics did not exhibit significant differences between the two groups (χ^2 = 1.014, P = 1.000).

Regarding the distribution of blood transfusion requirements, there was no noticeable difference between the two groups (χ^2 = 3.130, P = 0.239). Blood transfusions were not necessary for any participants in the case group, while three participants (8.3%) in the control group required transfusions.

No significant maternal or neonatal side effects were observed, as demonstrated in Tables 3 and 4.

Discussion

This study was conducted from April 2021 to August 2022 and involved 72 low-risk pregnant women planned for elective CS.

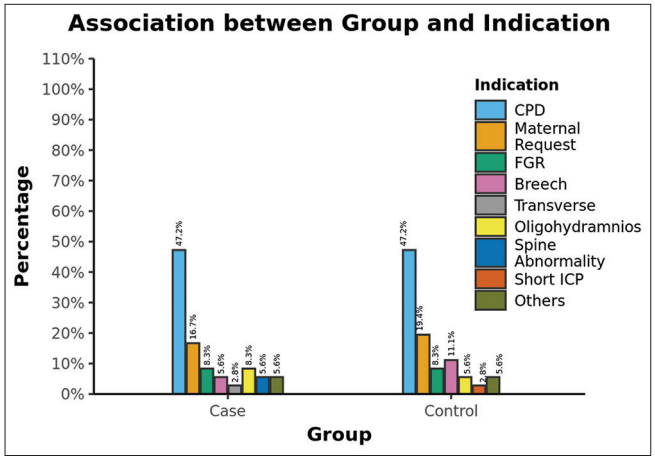

Figure 2: Distribution of women according to indication. CPD = Cephalopelvic Disproportion, FGR = fetal growth restriction, ICP = interconception period

Their gestational age ranged from 37 to 42 weeks, and they were categorized into two groups, with one case group (received one gram of TXA preoperatively) and one control group (received placebo).

In RCTs conducted by Sahu *et al.*,[11] Sekhavat *et al.*,[12] Movafegh *et al.*,[13] Goswami *et al.*,[14] Lakshmi *et al.*,[15] Ray *et al.*,[16] Medhi *et al.*,[17] Oseni *et al.*,[18] Iqbal *et al.*,[19] and Lee *et al.*,[20] both groups were matched for demographic analysis.

Similar to our study, Ali Movafegh *et al.*[13] found no discernible change in the procedure length (P = 0.638) between the two groups. In contrast, substantial differences in the surgery length between the case group and control group were reported in the studies by Goswami *et al.*[14] and Lakshmi *et al.*[15]

In this study, intraoperative blood loss and total blood loss differed significantly between the two groups (W = 267.500, P = 0.001), whereas postoperative blood loss did not show a significant difference (t = −1.468, P = 0.147). Similar results have been reported in other RCTs as well[13,15-18,20] and also corroborated with the Tranexamic Acid for Preventing Postpartum Hemorrhage Following a Cesarean Delivery (TRAAP2) trial results, where 4431 women undergoing elective and emergency CS were randomized to receive prophylactic TXA or placebo.[21] The significance of TXA in reducing intraoperative blood loss in low-risk women undergoing CS was found in a recent systematic review that evaluated 15 RCTs.[22]

None of the participants in the case group and five participants (13.88%) in the control group experienced blood loss greater than 500 mL. Insignificant differences between the two groups were found in terms of intraoperative blood loss in the study conducted by Sahu *et al.*[11]

Table 2: Distribution of women according to blood loss

Parameter	Group		Wilcoxon–Mann–Whitney *U* Test	
	Case	Control	W	*P*
Mean Intraoperative blood loss (mL) (±SD)	241.25±67.83	344.92±146.67	267.500	<0.001
Mean Total blood loss (mL) (±SD)	284.17±76.83	391.36±153.34	274.000	<0.001
Mean Drop in haemoglobin (g/dL) (±SD)	0.48±0.62	1.29±1.24	367.500	0.001
			t-test	
Mean Postoperative blood loss (±SD)	42.69±11.42	46.44±10.23	−1.468	0.147

SD=Standard deviation

Table 3: Distribution of women according maternal side effects

Side effects	Group			Fisher's exact test	
	Case *n* (%)	Control *n* (%)	Total *n* (%)	χ^2	*P*
None	28 (77.8%)	29 (80.6%)	57 (79.2%)		
Nausea	4 (11.1%)	3 (8.3%)	7 (9.7%)	0.1604	0.9229
Vomiting	4 (11.1%)	4 (11.1%)	8 (11.1%)		
Diarrhea	0 (0%)	0 (0%)	0 (0%)		
Deep venous Thrombosis	0 (0%)	0 (0%)	0 (0%)		
Total	36 (100.0%)	36 (100.0%)	72 (100.0%)		

Table 4: Distribution of women according to neonatal features

Birth Weight (kg)	Group		Wilcoxon–Mann–Whitney *U* Test	
	Case	Control	W	*P*
Mean birth weight (±SD)	2.88±0.44	3.04±0.45	546.000	0.253
Mean APGAR at 1 min	8.36±0.64	8.36±0.83	620.500	0.741
Mean APGAR at 5 min	9.64±0.49	9.61±0.55	654.500	0.936

APGAR=Appearance, pulse, grimace response, activity, and respiration

A blood loss of greater than 500 mL was observed in only two (4%) women in the study group compared to nine (18%) women in the control group, which was statistically significant ($P \leq 0.05$). Postoperative bleeding for 2 h from the end of CS was significantly reduced in the case group.

Regarding the change in hemoglobin level, there was a significant difference between the two groups (W = 367.500, $P = 0.001$). Comparable results have been reported in other studies as well.[11-13,15-19] The minimum postoperative hemoglobin level was 8.1 g/dL in the case group, while it was 6.3 g/dL in the control group.

The distribution of additional uterotonics did not differ significantly between the two groups ($\chi 2 = 1.014$, $P = 1.000$), which is consistent with the results of Iqbal *et al.*[19] and Lee *et al.*[20] However, contradictory results were reported by Lakshmi *et al.*,[15] who found that 20 IU of oxytocin was required in nine participants in the case group and three participants in the control group ($P < 0.05$).

Regarding the distribution of blood transfusion requirement, there was no noticeable difference between the two groups ($\chi 2 = 3.130$, $P = 0.239$). Similar results were observed by Sahu *et al.*,[11] but contradictory results were noted by Medhi *et al.*,[17] Goswami *et al.*,[14] and Iqbal *et al.*[19]

Neither the cases nor the controls exhibited pulmonary embolism, deep vein thrombosis, or diarrhea. In addition, neonates in neither group required any resuscitation, which is consistent with the results of other studies.[11-20]

The strengths of this study include its contribution to the growing body of evidence regarding the role of preoperative TXA in reducing blood loss, even in low-risk patients. We utilized the gravimetric method for assessing blood loss, which is favored by various authors.[23] In addition, we employed postoperative drop in hemoglobin as an outcome marker, a method recommended by some authors.[24]

This study has a few limitations, including the fact that postoperative patient monitoring was conducted only for 3 h; hence, the long-term effects of the drug could not be predicted. Furthermore, neonatal side effects were not studied in the postpartum period. Also, the study is powered only for the detection of estimated blood loss difference between the case and control group, but not for secondary outcomes. This study was only conducted in low-risk women; hence, its effect on women with a high risk of PPH cannot be determined from this study.

Conclusion

When administered preoperatively during elective CS, TXA significantly reduced intraoperative blood loss. However, there was no notable reduction in postoperative blood loss. TXA also demonstrated a significant reduction in the postoperative decrease in hemoglobin levels. Nevertheless, it did not lead to a significant reduction in the requirement for additional uterotonics. TXA was determined to be safe, as there were no significant maternal or neonatal side effects observed.

Considering that tranexamic acid is an affordable and readily available drug, its use can play a vital role in decreasing maternal morbidity and, consequently, alleviate the strain on hospital resources, particularly in settings with limited resources.

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Conflicts of interest

There are no conflicts of interest.

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