Tranexamic acid administration; which is effective preoperative versus intraoperative in reducing blood loss during cesarean section

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Abstract

Background: Cesarean section (CS) is frequently performed in Egypt. However, it may be associated with significant blood loss, which carries a substantial risk for perioperative morbidity and mortality. Tranexamic acid is known for its hemostatic effects in multiple gynecological and obstetric procedures, including CS. That drug inhibits the conversion of plasminogen into plasmin. Nonetheless, the proper timing of its administration is not clearly elucidated.

Objectives: We compared preoperative (PrO) versus intraoperative (IO) administration of tranexamic acid regarding blood loss during CS.

Patients and methods: We included 106 pregnant ladies in our prospective randomized trial, who were divided into two equal groups. Intraoperative blood loss was calculated, along with changes in hemodynamics, hemoglobin, and the hematocrit value.

Results: Intraoperative blood loss showed a significant decline ($p < 0.001$) in the PrO group (596.23 mL, compared to 674.53 mL in the IO group). Both study groups expressed no significant difference regarding their preoperative hemoglobin and hematocrit values. However, postoperative laboratory assessment revealed a significant reduction ($p < 0.001$) of both parameters in the IO group (hemoglobin decreased from 11.9 to 10.68 gm/dl whereas hematocrit decreased from 36.05% to 32.02%). The same group expressed a significant increase in heart rate and a significant decline in mean arterial pressure 30 minutes after the procedure, and these changes persisted till the end of the recordings ($p < 0.001$).

Conclusion: The preoperative tranexamic acid administration is superior to its intraoperative administration, as it leads to less blood loss, hemoglobin changes, and a relatively better hemodynamic profile.

Keywords: Cesarean section; Tranexamic acid; Administration time.

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Introduction

In Egypt, the rates of cesarean sections (CS) increased significantly in the 21st century, as more than 50% of deliveries were achieved via CS **(Elnakib et al, 2019)**. Egypt has ranked third after Brazil and the Dominican Republic in CS rates **(Betrán et al, 2016)**. Although CS could be life-saving for both the mother and her baby **(Waniala et al, 2020)**, it is associated with more morbidity compared to normal delivery, especially obstetric hemorrhage **(Shahid & Khan 2013)**. It is crucial for both obstetricians and anesthesiologists to seek methods to decrease obstetric hemorrhage to decrease post-CS morbidity and mortality **(Gari et al, 2022)**.

Tranexamic acid is a lysine analogue that has hemostatic actions by reversible binding to the lysine receptor on plasminogen, preventing its conversion to plasmin. This in turn leads to fibrin matrix stability **(Ockerman et al, 2021; Ramirez et al, 2017; Wang et al, 2022)**.

Its administration has been associated with a significant reduction in blood loss during multiple surgical procedures, including orthopedic, cardiopulmonary, prostatic, dental, maxillofacial, and hepatic procedures **(Ockerman et al, 2021; Balik et al, 2022; Prudovsky et al, 2022)**. Its benefits have been described in the field of obstetrics and gynecology. Its efficacy in decreasing blood loss has been reported in patients with menorrhagia **(Oehler & Rees, 2003)**. Additionally, it decreases intraoperative blood loss and blood transfusion requirements in hysterectomy and myomectomy procedures **(Zakhari et al, 2020)**.

The efficacy of tranexamic acid has been reported in ladies undergoing CS **(Shahid & Khan 2013; Yehia et al, 2014)**. Still, it has not been decided whether it should be given before or during surgery. In the current study, we compared preoperative versus intraoperative administration of tranexamic acid regarding blood loss reduction during CS in the Egyptian setting.

Patients and methods

This randomized prospective trial was conducted at Benha University Hospitals (Anesthesiology in collaboration with Obstetrics and Gynecology Departments). Our trial was designed for pregnant women aged between 18 and 40 years, having a singleton full-term pregnancy, and scheduled for elective CS under spinal anesthesia.

The sample size was estimated via the PASS software program, using the data obtained from a pilot study conducted at our hospitals. The findings of that pilot study revealed a mean blood loss of 558.33 + 97.54 mL with preoperative tranexamic acid administration, versus 616.66 + 74.54 mL with intraoperative administration. Based on the previous data, 48 ladies were required in each group in order to achieve 90% power and a 5% significance level. For an expected 10% non-response rate, five patients were added to each group. Thus, 53 ladies were required in each group (total number = 106).

Before CS, all ladies received the standard preprocedural evaluation, including history taking (focusing on gravidity, parity, and date since the last menstrual period), general examination (focusing on patient body mass index BMI), a detailed obstetric examination (including obstetric ultrasound), and routine laboratory investigations (including hemoglobin level, hematocrit value, and coagulation profile). All ladies were classified according to the “American Society of Anesthesiologists” (ASA), and only ladies with classes II or III were enrolled in our study. We excluded ladies with morbid obesity, bleeding diathesis, twin pregnancies, preeclampsia, polyhydramnios, oligohydramnios, a history of thromboembolic disease, or a known allergy to tranexamic acid. Ladies

presenting with obstetric emergencies, scheduled for upper segment CS, or having the procedure under general anesthesia were also excluded.

Our participants were randomly assigned into two groups: the PrO group received IV tranexamic acid 1 gm (Kapron, Amoun Pharmaceuticals, Obour City, Egypt) 15 minutes prior to the operation, and the IO group received the same tranexamic acid dose 10 minutes after the skin incision. The randomization was done via the "sealed envelope method". Tranexamic acid was diluted in 20 ml of dextrose 10% in both groups and given by IV infusion over 10 minutes. All participants signed an informed consent form explaining the technique and possible complications of each intervention.

All the ladies received a preload of saline or ringer lactate solutions (10 ml/kg) one hour before the procedure. They received the standard hemodynamic monitoring on arrival to the operative room. Baseline heart rate (HR) and mean arterial blood pressure (MAP) were recorded. All operations were performed by the same obstetric team under spinal anesthesia. The anesthetic technique was done when the lady was sitting, by the injection of 1.5 – 2 mL hyperbaric bupivacaine into the subarachnoid space (L 3 – 4 interspace). After baby delivery, all patients received 10 IU of oxytocin (Syntocinon, Novartis Pharmaceuticals, Egypt) over three minutes. During the procedure, HR and MAP were recorded every 10 minutes till the procedure ended.

After the operation, the amount of intraoperative blood loss was estimated by adding the amount of blood in the suction jar to the blood lost in towels. The amount of blood loss in towels was estimated by calculating the difference between postoperative and preoperative weight, and 1 gm of weight difference was taken as 1 mL of blood loss **(Gari et al, 2022; Ambardekar et al, 2014)**. The need for intraoperative blood transfusion was also recorded.

All ladies were transferred to PACU, where HR and MAP were recorded, and then they were transferred to the inward where close monitoring was done. The same hemodynamic parameters (HR and MAP) were assessed every 10 minutes for the first hour after the procedure. In addition, the hemoglobin level and the hematocrit value were repeated 12 hours after the operation. The percent of change in relation to the corresponding baseline value was also estimated in both groups. The incidence of postoperative complications, including postpartum hemorrhage and deep venous thrombosis (DVT), was recorded.

The main outcome of our study was the amount of intraoperative blood loss, while secondary objectives included changes in hemoglobin levels, hematocrit values, and hemodynamic parameters, in addition to the incidence of postoperative complications.

Ethical approvals

The study protocol was presented for departmental approval and then approved by the faculty ethical committee. The protocol was discussed with the patients before enrolment and those accepted were asked to sign the written consent. After the completion of case collection, the final approval of the outcomes was obtained [RC: 16-3-2023].

Statistical analysis

Our data were analyzed using the SPSS software program for MacOS (Version 26). While numerical data were expressed in means and standard deviations, categorical data were expressed in numbers and percentages. To compare the two groups, we used the student t-test for the former type of data, while the Chi-square or Fisher Exact tests were used for the latter. If the obtained p-value was less than 0.05, it was considered significant.

Results

The included ladies had a mean age of 25.84 years in the PrO group, compared to a mean of 26.7 years in the IO group. The mean values of their BMI were 24.97

and 25.83 kg/m2 in the two groups, respectively. The majority of our participants had ASA class II (98.1% and 94.3% of ladies in the same groups, respectively), whereas the remaining ladies had class III. All class III ladies had gestational diabetes mellitus.

As regards their obstetric history, the mean gestational age was 28.53 weeks in the PrO group, compared to 38.72 weeks in the IO group. Their gravidity had mean values of 2.85 and 3.11, while their parity had mean values of 1.36 and 1.62 in the same groups, respectively. As shown in (**Table.1**), no significant statistical difference was noted between our two groups regarding the previously mentioned parameters.

Table 1. Demographic criteria, ASA physical status, and obstetric history of the included ladies

Variables		PrO group (n= 53)	IO group (n= 53)	95% CI	P
Age (years)		25.87 ± 4.612	26.70 ± 4.909	-2.66, 1.00	0.372
BMI (kg/m2)		24.97 ± 2.341	25.83 ± 2.270	-1.75, 0.03	0.058
ASA	**II**	52 (98.1%)	50 (94.3%)	-	0.308
	III	1 (1.9%)	3 (5.7%)		
Gestational age (weeks)		38.53 ± 1.170	38.72 ± 1.063	-0.62, 0.24	0.387
Gravidity		2.85 ± 1.081	3.11 ± 1.281	-0.72, 0.19	0.254
Parity		1.36 ± 1.111	1.62 ± 1.130	-0.70, 0.17	0.228

Although operative time was statistically comparable between the two groups (46.04 and 45.28 minutes in the PrO and IO groups, respectively – p = 0.709), intraoperative blood loss showed a significant decline in the PrO group (p < 0.001). The ladies in the PrO group had a mean blood loss of 596.23 mL, compared to 674.53 mL in the IO group.

Both study groups expressed no significant difference regarding their preoperative hemoglobin and hematocrit values (p = 0.209 and 0.57, respectively). Nonetheless, postoperative laboratory assessment revealed a significant reduction of both parameters in the IO group, compared to the PrO group (p = 0.004). Additionally, the percent of change between the preoperative and postoperative values significantly declined in the PrO group. (**Table.2**) illustrates the previous data.

Table 2. Operative time, intraoperative blood loss, and changes in hemoglobin and hematocrit in the two groups

Variables		PrO group (n= 53)	IO group (n= 53)	95% CI	P
Operative time (minutes)		46.04 ± 9.872	45.28 ± 10.849	-3.2, 4.75	0.709
Intraoperative blood loss (ml)		596.23 ± 101.834	674.53 ± 85.835	-114, -42	**< 0.001**
Hemoglobin (gm/dl)	**Baseline**	12.12 ± 0.908	11.90 ± 0.920	-0.1, 0.58	0.209
	Postoperative	11.28 ± 1.007	10.68 ± 1.063	0.19, 0.99	**0.004**
	Change (%)	-7.15 ± 2.032	-10.28 ± 3.554	2.02, 4.25	**< 0.001**
Hematocrit (%)	**Baseline**	36.38 ± 2.925	36.05 ± 2.943	-0.8, 1.45	0.570
	Postoperative	33.94 ± 3.354	32.02 ± 3.330	0.63, 3.20	**0.004**
	Change (%)	-6.77 ± 4.577	-11.23 ± 4.331	2.74, 6.17	**< 0.001**

No ladies required intraoperative blood transfusion. Also, no participants developed postoperative DVT in our study. We encountered only one patient with postoperative hemorrhage in the PrO group (1.9%). The incidence of postoperative No significant difference was noted between our groups regarding the incidence of postoperative complications (p > 0.05) (**Table. 3**).

Table 3. Postoperative complications

Variables	PrO group (n= 53)	IO group (n= 53)	P
Intraoperative blood transfusion	0 (0.0%)	0 (0.0%)	1
Postpartum hemorrhage	1 (1.9%)	0 (0.0%)	0.315
Postoperative DVT	0 (0.0%)	0 (0.0%)	1

Basal, intraoperative, and early postoperative heart rate measurements showed comparable values between the two groups. However, the last three postoperative recordings showed a significant rise in that parameter in the IO group ($p < 0.05$), as shown in (**Table .4**).

Table 4. Heart rate changes in both study groups

Heart rate (bpm)		PrO group (n= 53)	IO group (n= 53)	95% CI	P
Intraoperative	**Baseline**	86.68 ± 8.489	86.25 ± 9.996	-3.14, 4.01	0.810
	10 min	93.83 ± 10.261	93.08 ± 11.984	-3.54, 5.05	0.728
	20 min	92.98 ± 8.863	92.40 ± 9.749	-3.00, 4.17	0.747
	30 min	92.91 ± 9.422	92.45 ± 9.819	-3.25, 4.16	0.809
	40 min	92.83 ± 9.194	92.42 ± 9.947	-3.27, 4.10	0.824
	50 min	92.51 ± 9.316	92.25 ± 9.808	-3.42, 3.95	0.887
	60 min	92.47 ± 9.609	92.40 ± 10.087	-3.72, 3.87	0.969
Postoperative	**PACU**	92.64 ± 9.375	92.66 ± 10.517	-3.86, 3.82	0.992
	10 min	92.40 ± 9.117	93.77 ± 10.655	-5.20, 2.44	0.476
	20 min	92.32 ± 9.446	95.06 ± 10.856	-6.66, 1.18	0.169
	30 min	92.49 ± 9.415	96.21 ± 10.932	-7.65, 0.21	0.064
	40 min	92.49 ± 9.450	97.68 ± 11.123	-9.16, -1.21	**0.011**
	50 min	92.53 ± 9.871	99.15 ± 11.302	-10.71, - 2.54	**0.002**
	60 min	92.77 ± 10.110	100.53 ± 11.361	-11.90, -3.61	**< 0.001**

As regards MAP changes, although baseline and intraoperative recordings showed no significant difference between the two groups, postoperative recordings at 40, 50, and 60 minutes showed a significant statistical decline in MAP in the IO group. Although that difference was statistically significant, it was clinically irrelevant (**Table.5**).

Table 5. MAP changes in both study groups

MAP (mmHg)		PrO group (n= 53)	IO group (n= 53)	95% CI	P
Intraoperative	**Baseline**	95.13 ± 6.114	94.15 ± 6.209	-1.39, 3.35	0.414
	10 min	87.36 ± 8.039	86.91 ± 6.842	-2.42, 3.33	0.755
	20 min	91.09 ± 8.434	91.17 ± 7.876	-3.22, 3.07	0.962
	30 min	91.13 ± 8.528	90.96 ± 7.942	-3.00, 3.34	0.916
	40 min	91.26 ± 8.667	91.13 ± 7.923	-3.07, 3.33	0.935
	50 min	91.68 ± 8.955	90.77 ± 7.982	-2.36, 4.17	0.584
	60 min	91.13 ± 8.727	90.85 ± 8.305	-3.00, 3.56	0.865
Postoperative	**PACU**	90.77 ± 8.911	91.00 ± 8.724	-3.62, 3.17	0.895
	10 min	90.64 ± 8.786	89.74 ± 8.793	-2.48, 4.29	0.597
	20 min	90.62 ± 9.191	88.62 ± 8.889	-1.48, 5.48	0.257
	30 min	90.04 ± 9.150	87.17 ± 8.862	-0.60, 6.34	0.104
	40 min	89.81 ± 9.257	85.74 ± 8.634	0.63, 7.52	**0.021**
	50 min	89.91 ± 9.471	84.47 ± 8.389	1.99, 8.88	**0.002**
	60 min	89.85 ± 9.566	83.36 ± 8.239	3.05, 9.93	**< 0.001**

Discussion

The current study was conducted to evaluate which is better; preoperative or intraoperative administration of tranexamic acid in parturient ladies undergoing CS. After intensive literature research, we did not find any previous studies handling that perspective of ours, and that poses an advantageous point in favor of our research. Although previous studies have confirmed the efficacy of IV tranexamic acid in decreasing blood loss during CS **(Shahid & Khan 2013; Yehia et al, 2014; Shalaby et al, 2022)**, most of these studies are case-control ones in which the control group received a placebo.

For example, Shahid and Khan conducted their study on Pakistani pregnant ladies who were divided into two groups; the first one received tranexamic acid 10 minutes before the skin incision, whereas the other group received a placebo. There was a significant reduction in intraoperative blood loss from the time of placental delivery to the end of the procedure in association with tranexamic acid administration (356.44 vs. 710.22 ml in the placebo group – $p < 0.001$) **(Shahid & Khan 2013)**.

Moreover, in a more recent study, Shalaby et al. conducted a similar study, in which the authors administered the same agent 15 minutes before the procedure. There was a significant reduction in intraoperative blood loss. Additionally, hemoglobin and hematocrit values were significantly lower in the placebo group **(Shalaby et al, 2022)**.

Our findings revealed that preoperative is far better than intraoperative administration regarding intraoperative blood loss, hemoglobin levels, and hematocrit value changes. Both groups received the same drug dose through the IV route, which provides a rapid and effective way for drug delivery **(Jain, 2020)**, as the maximum serum drug concentration (> 10 mg/L for a 1 g IV dose) is reached by the end of infusion **(Grassin-Delyle et al, 2022)**. However, we think that the preoperative establishment of maximum serum concentration may be more effective than achieving it during the operation. The elapsed ten minutes prior to the intraoperative administration as well as the time of infusion itself may delay achieving maximum serum concentrations in the IO group.

Regarding hemodynamic changes in our study, we noticed a significant decline in MAP and a significant increase in HR half an hour after the operation in the IO group. That could be explained by the increased blood loss in the IO group.

No ladies required blood transfusion in our study. Despite the increased blood loss in the IO group, all values were within the normal range of blood loss during CS, which ranges between 500 and 1000 ml **(Vimala et al, 2006; Glover, 2003)**. Even in the ladies in the IO group who had significantly lower MAP and higher HR in the postoperative period, the hemodynamic changes did not reach a critical level (hemodynamic compromise) enough to commence blood transfusion.

We encountered only one case of postpartum hemorrhage (1.9%) in the PrO group, and that coincides with previous reports that stated that the incidence of that complication may reach 10% after CS **(Fawcus & Moodley, 2013)**.

No ladies had DVT or other thromboembolic events in our study groups. Previous studies confirmed our findings, as the administration of IV tranexamic acid was not associated with a significant risk of thromboembolic complications **(Franchini et al, 2018; Taeuber et al, 2021)**.

Although our trial handled a unique research point that is rarely described in the literature, it has some drawbacks manifested in the relatively small sample size collected from one medical institution in addition to the lack of a control group. We recommend conducting more studies

in the upcoming future to overcome the previous drawbacks and to decisively estimate the best time for IV tranexamic acid administration in bloody surgical procedures like CS.

Conclusion

Preoperative tranexamic acid administration is superior to its intraoperative administration, as it is associated with less blood loss, hemoglobin changes, and a relatively better hemodynamic profile in pregnant ladies undergoing CS. The administration of preoperative tranexamic acid is highly recommended to decrease blood loss during CS procedures.

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