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Assessment the role of tranexamic acid in prevention of postpartum hemorrhage

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Abstract

Background: Postpartum hemorrhage (PPH) is one of the leading causes of maternal mortality and morbidity worldwide. It is believed that hemostatic imbalance secondary to release of tissue plasminogen activator (tPA) and subsequent hyperfibrinolysis plays a major role in PPH pathogenesis. Antifibrinolytic drugs such as tranexamic acid (TXA) are widely used in hemorrhagic conditions associated with hyperfibrinolysis. TXA reduced maternal death due to PPH and its use as a part of PPH treatment is recommended, and in recent years, a number of trials have investigated the efficacy of prophylactic use of TXA in reducing the incidence and the severity of PPH.
The study is aiming to assess the efficacy of tranexamic acid in reducing blood loss throughout and after the lower segment cesarean section and reducing the risk of postpartum hemorrhage.

Results: The amount of blood loss was significantly lower in the study group than the control group (416.12±89.95 and 688.68±134.77 respectively). Also the 24-h postoperative hemoglobin was significantly higher in the study group (11.66±0.79 mg/dl) compared to the control group (10.53±1.07mg/dl), and the 24-h postoperative hematocrit value was significantly higher in the study group (34.99±2.40) compared to control (31.62±3.22).

Conclusion: Prophylactic administration of tranexamic acid reduces intraoperative and postoperative bleeding in cesarean section and the incidence of postpartum hemorrhage.

Keywords: Antifibrinolytic, Cesarean section, Hyperfibrinolysis, Postpartum hemorrhage, Tranexamic acid

Background

Postpartum hemorrhage (PPH) is one of the leading causes of maternal morbidity and mortality. PPH is responsible for around 25% of maternal death worldwide, 143 000 deaths each year, and reaching as high as 60% in some developing countries (Alam et al. 2017; Sentilhes et al. 2020).

Traditionally, PPH was defined as blood loss more than 500 mL after a vaginal delivery and more than 1000 mL after a cesarean delivery; however, an updated and efficient definition has been suggested by American College of Obstetrics and Gynecology which stated PPH as cumulative blood loss more than or equal to 1000 mL or blood loss accompanied by signs or symptoms of hypovolemia throughout the first 24 h after delivery regardless the delivery route (Committee on Practice Bulletins-Obstetrics 2017).

PPH also contributes significantly to maternal morbidity with the probability for intensive care admission, shock, acute renal failure, disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (ARDS), hysterectomy, and loss of fertility (Committee on Practice Bulletins-Obstetrics 2017; Solomon et al. 2012).

Antifibrinolytic drugs such as tranexamic acid (TXA) are widely used in hemorrhagic conditions associated with increased fibrinolytic activity or hyperfibrinolysis (HF) like PPH (Pacheco et al. 2017).

TXA is a synthetic lysine analogue that competitively inhibits the conversion of plasminogen to plasmin

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preventing the proteolytic action of plasmin on fibrin threads resulting in inhibition of fibrinolysis and stabilizing existing blood clots, thus reducing the risk of hemorrhage (Pabinger et al. 2017).

TXA has been found to reduce intra- and postoperative bleeding like open-heart surgeries, scoliosis correction surgery, liver transplantation, prostatectomy, arthroplasty, and urinary tract surgeries (Pabinger et al. 2017).

The use of TXA has been proven beneficial in trauma patients reducing the risk of hemorrhage and the need for blood transfusion when used within 3 h of injury (Roberts et al. 2013).

Detailed guidelines have suggested the use of uterotonic drugs in obstetric interventions. In contrast, hemostatic drugs are not routinely used as a first-line intervention in PPH (Neb et al. 2017).

Our study target was to assess tranexamic acid efficacy in reducing blood loss during and after lower segment cesarean section and reducing the risk of postpartum hemorrhage.

Methods

After institutional ethical approval, number FMASU M D 95/2018, this randomized prospective controlled study was carried out in [Ain Shams University Educational Hospitals] during the period from March 2018 till March 2019 and was conducted on total 100 pregnant women with one previous cesarean section (para1-CS) who were randomly assigned into two groups 50 pregnant women each and subjected to elective cesarean section under spinal anesthesia.

The study group included 50 pregnant women who received 2 g of tranexamic acid (TXA) with the induction of spinal anesthesia plus 10 I.U. oxytocin with the delivery of the baby; the control group received only 10 I.U. oxytocin. Both groups were compared regarding amount of blood loss which was calculated mathematically.

Inclusion criteria

Singleton pregnancy, P1-CS (previous one section after failed consent for trial of labor after CS), age from 18 to 39 years old at time of consent, term ≥ 37 weeks of gestation, elective CS, spinal anesthesia, and written informed consent.

Exclusion criteria

Failed spinal anesthesia (more than 2 attempts), multiple pregnancy, grand multipara, placenta previa, abruptio placentae, polyhydraminos, fever, rupture of membranes, patients on anticoagulants or antiplatelets, eclampsia or pre-eclampsia in current pregnancy, history of cardiovascular diseases as ischemic heart disease or myocardial infarction, repaired or unrepaired congenital heart disease, unstable arrhythmia or congestive heart failure, or the patient had a contraindication to TXA administration as history of venous thromboembolism, active thromboembolic disease, thrombophilia (e.g., protein C deficiency), allergy to TXA, pre-existing hematuria, or history of renal insufficiency.

Thorough history was taken from all patients with meticulous examination (general and obstetric) and full preoperative investigations (Rh typing, complete blood count, activated partial thromboplastin time, prothrombin time and concentration, liver and kidney function tests) done

All patients were kept fasting 8 h preoperative, in induction room, a wide bore IV cannula G18 was inserted and monitors were attached "pulse oximetry, electrocardiogram, and non-invasive arterial blood pressure". All patients were continuously monitored all through the cesarean section. Routine preoperative fluid preload was given in the form of 1 l of ringer solution over 30 min.

In case of failed spinal anesthesia and general anesthesia was used instead, the patient was excluded from the study.

- *Group A* (study group) included (50) pregnant women who received 2 g of tranexamic acid (20 ml in volume) that was diluted in 50 ml normal saline solution 0.9% (70 ml volume) as slow iv infusion with induction of spinal anesthesia. 10 I.U. of oxytocin were given immediately after delivery of the baby.
- *Group B* (control group) included (50) pregnant women who received 20 ml of saline solution 0.9% that was diluted in 50 ml normal saline 0.9% (70 ml volume) with induction of spinal anesthesia and 10 I.U. of oxytocin immediately after delivery of the baby.

The primary outcome of our study is the amount of blood loss during and after CS, which was estimated by calculating the blood loss using standard equations by using preoperative and 24-h postoperative hematocrit value as follows (Butterworth et al. 2013):

1. Estimate blood volume for women 65 ml/kg.
2. Estimate the red blood cell volume (RBCV) at the preoperative hematocrit (RBCVpreop).
3. Estimate RBCV at the postoperative hematocrit (RBCVpostop), assuming normal blood volume is maintained.
4. Calculate the RBCV lost: RBCVlost = RBCVpreop – RBCVpostop

5. Blood loss = RBCV lost × 3.

The secondary outcome measures were vital signs (heart rate, blood pressure, respiratory rate) in preoperative period and at 2, 6, and 24 h postoperatively. Any complications that could be reported such as nausea, vomiting, and hypotension were recorded.

Randomization

Randomization was generated using a computer-generated, random sequence; 100 syringes 20 ml in volume were formed and numbered from 1 to 100 containing either the drug (TXA) or placebo by third operator. All syringes were identically labeled, with the study number being the only discriminating feature between them. This guaranteed the woman's safety and the blinding of all participants, including obstetric staff.

Statistical analysis

Data were collected, revised, coded, and entered to Med-Calc software (ver. 19.1.0; MedCalc Software, Ostend, Belgium), and the statistical package for social sciences, version 25.0 (SPSS Inc., Chicago, IL, USA). The quantitative data were presented as mean, standard deviations, and ranges. Also, qualitative variables were presented as number and percentages.

The following tests were done:

- Independent-samples *t*-test of significance was used when comparing between two means.
- Chi-square (χ^2) test of significance was used in order to compare proportions between qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p*-value was considered significant as the following:
- Probability (*P*-value)
- *P*-value ≤0.05 was considered significant.
- *P*-value ≤0.001 was considered as highly significant.
- *P*-value >0.05 was considered insignificant.

Sample size

Using PASS program version 15, setting alpha error at 5% and power at 90%, result from previous study by Salem et al. ***(*Salem et al.** 2016***)*** showed that the incidence of postpartum hemorrhage among tranexamic group was 24.9% and among placebo group 59%; based on this, the needed sample is 100 pregnant women each group is 50 participants.

Results

There is no statistically significant difference between the two groups regarding demographic data.

There was a statistically significant difference as regards blood loss between the two groups (*p*-value < 0.00)1; the blood loss in study group (TXA) was less than the control group (416.12±89.95 and 688.68±134.77 respectively).

The mean drop in 24-h postoperative hematocrit and hemoglobin levels were significantly lower in the TXA group than in the control group. The 24-h postoperative hemoglobin was significantly higher in the study group (11.66±0.79 mg/dl) compared to the control group (10.53±1.07mg/dl), and the 24-h postoperative hematocrit value was significantly higher in the study group (34.99±2.40) compared to control (31.62±3.22).

The postoperative vital data including heart rate, blood pressure, and respiratory rate were more stable in study group than the control group.

And there was no statistically significant difference between groups regarding the incidence of complications

The results of the present study are demonstrated in Tables 1, 2, 3, 4, 5, 6, 7, 8, and 9.

Table 1 shows no statistically significant difference between the two groups regarding demographic data.

Table 2 shows a statistically significant reduction in postoperative hemoglobin and hematocrit values of the control group compared to the study group.

Table 3 shows a statistically significant reduction in RBCV of control group compared to study group.

Table 4 shows a significantly lower blood loss in the study group compared to the control group and more lost RBCV in the control group compared to the study group.

Table 5 shows a significantly lower HR values in study group compared to control group 2 h till 24h postoperative.

Table 6 shows a significantly higher SBP values in the study group compared to the control group 2h till 24h postoperative.

Table 7 shows a significantly higher DBP values in the study group compared to the control group 2h till 24h postoperative.

Table 8 shows no statistically significant difference between groups regarding respiratory rate.

Table 9 shows no statistically significant difference between groups regarding the incidence of complications.

Discussion

TXA is a potent antifibrinolytic agent that prevents binding of plasminogen and plasmin to fibrin molecules. TXA has been used for various medical and surgical situations to decrease bleeding and the need for blood transfusion (Pabinger et al. 2017).

The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial which enrolled around 20,000 patients with acute traumatic bleeding has shown that the early administration of TXA within 3

Table 1 Personal characteristics

Demographic data	Study group "TXA" (*n*=50)	Control group "placebo" (*n*=50)	*P*
Age (years)			
Mean ± SD	27.60±4.03	26.88±4.55	0.404
Weight (kg)			
Mean ± SD	71.28±6.15	71.76±6.02	0.694

h of injury significantly reduces mortality due to bleeding (Roberts et al. 2013).

The World Maternal Antifibrinolytic (WOMAN) trial, which was conducted in patients with established PPH, showed similar results as (CRASH-2) trial in obstetrics context; they found that administration of TXA within 3 h of PPH for treatment purpose of hyperfibrinolysis decreases blood loss and mortality among bleeding patients (Shakur et al. 2017).

In both trials, CRASH-2 and WOMAN, the administration of TXA beyond 3 h of trauma or delivery was associated with an increase in mortality compared to placebo (Lier et al. 2019).

Activation of fibrinolytic system has been demonstrated during the process of labor. Elevated levels of tissue plasminogen activator (tPA) and D-dimer are indicators of fibrinolysis activation (Ducloy-Bouthors et al. 2018).

With placenta separation, there is a rapid reduction in fibrinogen level with fibrin threads production leading to decrease plasminogen level which in turn stimulates the fibrinolytic system (Ducloy-Bouthors et al. 2018).

The endothelium produces more tPA and expresses more thrombomodulin receptors which interact with thrombin that results from the activated coagulation system resulting in protein C activation (Pacheco et al. 2019).

Protein C activation leads to inhibition of plasminogen activator inhibitor 1 (PAI-1) with unrestricted activity of tPA. The result is augmented fibrinolysis with rapid degradation of established fibrin clots. Therefore, the use of TXA seems to reduce the blood loss (Pacheco et al. 2019).

In the event of severe PPH, shock-related tissue hypoxia, hypoperfusion, and acidosis can lead to the excessive release of tissue factor from damaged cells, which cause an imbalance between the coagulation and fibrinolytic systems and lead to a worse state of hyperfibrinolysis. Inhibition of hyperfibrinolysis by TXA restores the balance of the hemostatic system (Pabinger et al. 2017).

Table 2 Hemoglobin (Hb) and hematocrit (HCT) level

	Study group "TXA" (*n*=50)	Control group "placebo" (*n*=50)	*P*
Hb.			
Preoperative			
Range	10.1–13.7	10.1–13.9	0.466
Mean±SD	12.63±0.82	12.18±1.08	
Postoperative			
Range	9.5–12.8	8.3–12.1	0.024*
Mean±SD	11.66±0.79	10.53±1.07	
Reduction			
Mean±SD	0.97±0.27	1.65±0.46	<0.001**
HCT			
Preoperative			
Range	29.9–41.3	30.1–41.9	0.215
Mean±SD	37.96±2.55	36.49±3.22	
Postoperative			
Range	28.5–38.5	25–36.4	<0.001**
Mean±SD	34.99±2.40	31.62±3.22	
Reduction			
Mean±SD	2.97±0.83	4.87±1.36	<0.001**

*p-value <0.05 S; **p-value <0.001 HS

Table 3 Red blood cell volume (RBCV)

RBCV	Study group "TXA" (*n*=50)	Control group "placebo" (*n*=50)	*P*
Preoperative			
Range	1391–2120	1311–2095	0.152
Mean±SD	1764.08±189.62	1703.48±232.51	
Postoperative			
Range	1308–1976	1073–1900	0.005*
Mean±SD	1624.88±184.75	1478.40±223.51	
Reduction			
Mean±SD	139.20±38.98	225.08±63.02	<0.001**

*p-value <0.05 S; **p-value <0.001 HS

Our study was conducted on 100 pregnant females enrolled for elective CS randomly divided into two groups; one group received a prophylactic 2 g of TXA with induction of anesthesia and 10 units of oxytocin after delivery of the baby while the control group received placebo and 10 units of oxytocin.

There was a statistically significant difference as regards blood loss between the two groups (p-value < 0.00)1; the blood loss in study group (TXA) was less than the control group (416.12±89.95 and 688.68±134.77 respectively). The mean drop in 24-h postoperative hematocrit and hemoglobin levels was significantly lower in the TXA group than in the control group. The 24-h postoperative hemoglobin was significantly higher in the study group (11.66±0.79 mg/dl) compared to the control group (10.53±1.07mg/dl), and the 24-h postoperative hematocrit value was significantly higher in the study group (34.99±2.40) compared to control (31.62±3.22). Thus, TXA reduces intraoperative and postoperative bleeding.

Traditional methods for assessing blood loss during and after CS are actually not easy and inaccurate because blood is mixed with amniotic fluid in suction container. Estimating blood loss after CS by inspecting vaginal soaked towels or even weighing them is a subjective method; it tends to overestimate or underestimate blood loss (Kandappan and Anand 2016).

Our study estimated the blood loss mathematically using preoperative and 24-h postoperative hematocrit values. We chose this method as a quantitative objective measure for blood loss estimation.

Similar results postoperative of the current study were observed in a prospective randomized study by Kandappan and B. This study demonstrates that a single intravenous dose of TXA (15 mg/kg body weight) when given intraoperative significantly reduces the blood loss both during and after the lower segment cesarean section in multigravida pregnant females and its use was not associated with any serious side effects (Kandappan and Anand 2016). However, this study used subjective methods for blood loss estimation. Blood was collected via a suction catheter, the volume was weighed and soaked gauze and pads were also weighed using an electronic weighing machine.

Another prospective randomized trial supporting the results of our current study was carried by Xu et al. The study was conducted on 174 pregnant females undergoing CS. A dose of 10 mg/kg TXA was given to 88 pregnant females immediately before CS who were compared with 86 others who had placebo. The amount of blood loss from placental separation till 2 h postpartum was significantly reduced in the TXA group than in the control group. But the amount of blood loss was collected subjectively through a suction container, soaked gauze, wet pads, and sanitary towel (Xu et al. 2013).

Abdel-Aleem et al. pointed to similar results in their prospective randomized study comparing preoperative injection of 1 g of TXA in elective cesarean section; the

Table 4 Lost RBCV and blood loss

	Study group "TXA" (*n*=50)	Control group "placebo" (*n*=50)	*P*
Lost RBCV			
Range	83–193	131–325	<0.001**
Mean±SD	138.92±29.73	230.92±45.73	
Blood loss			
Range	250–579	393–975	<0.001**
Mean±SD	416.12±89.95	688.68±134.77	

**p-value <0.001 HS

Table 5 Heart rate in both groups through the procedure

Heart rate	Study group "TXA" (*n*=50)	Control group "placebo" (*n*=50)	*P*
Preoperative	87.55±5.87	86.52±5.05	0.201
2 h postoperative	97.85±6.18	103.52±9.17	0.041*
6 h postoperative	93.73±5.67	101.46±8.45	0.032*
24 h postoperative	90.64±3.30	94.80±6.70	0.010*

p-value>0.05 NS; **p*-value <0.05 S

Table 6 Systolic blood pressure (mmHg) in both groups all through the procedure

Systolic BP (mmHg)	Study group "TXA" (*n*=50)	Control group "placebo" (*n*=50)	*P*
Preoperative	118.45±10.55	116.39±12.42	0.126
2h postoperative	113.30±10.09	101.76±8.03	0.046*
6h postoperative	108.15±6.90	93.28±4.64	0.016*
24h postoperative	119.48±5.20	98.54±4.84	0.015*

p-value >0.05 NS; **p*-value <0.05 S

Table 7 Diastolic blood pressure (mmHg) in both groups all through the procedure

Diastolic BP (mmHg)	Study group "TXA" (*n*=50)	Control group "placebo" (*n*=50)	*P*
Preoperative	81.27±5.34	82.49±4.12	0.229
2h postoperative	77.25±10.82	72.10±4.74	0.015*
6h postoperative	72.10±4.74	67.36±2.37	0.011*
24h postoperative	79.31±2.99	72.72±1.85	0.010*

p-value >0.05 NS; **p*-value <0.05 S

Table 8 Respiratory rate in the two groups all through the procedure

Respiratory rate	Study group "TXA" (*n*=50)	Control group "placebo" (*n*=50)	*P*
Preoperative	16.89±2.04	16.35±2.22	0.144
2h postoperative	16.72±2.02	16.18±2.20	0.156
6h postoperative	16.56±2.00	16.02±2.18	0.180
24h postoperative	15.89±1.92	15.38±2.09	0.216

p-value >0.05 NS

Table 9 Incidence of complications in the two groups

Complications	Study group "TXA" (*n*=50)	Control group "placebo" (*n*=50)	*P*
Nausea	5 (10%)	2 (4%)	0.433
Vomiting	6 (12%)	3 (6%)	0.486
Hypotension	2 (4%)	1 (2%)	0.786
Hypersensitivity	0 (0%)	0 (0%)	1.000
Bradycardia	4 (8%)	3 (6%)	0.839

p-value >0.05 NS

mean total blood loss was significantly lesser in the TXA group than the control group. However, they also used a subjective methods in collecting blood loss; the weight of dry towels was subtracted from the weight of wet towels, and the weight of blood was changed into volume using the formula considering that the blood is slightly denser than water so, volume of the blood = weigh × 0.9 (Abdel-Aleem et al. 2013).

In addition, another study was carried by Sentürk et al. on 223 pregnant females enrolled for cesarean section; half of them received 1 g of TXA versus the placebo group. Blood loss was determined, using the following formula, by measuring the wet and dry weights of the patient's pads and tampons.

Blood loss volume = wet weight of the pad or tampon − dry weight of the pad or tampon/1.05.

Sentürk et al. found that preoperative administration of TXA reduced the intraoperative and postoperative blood loss with no increase in thromboembolic side effects (Sentürk et al. 2013).

Our study showed only mild side effects of TXA like hypersensitivity, nausea, vomiting, and hypotension which were not statistically significant between the two groups.

Limitations

Our study has some limitations such as using of a fixed dose of tranexamic acid regardless the body weight (2 g TXA to all pregnant females in study group); our calculating method for blood loss did not discriminate between intraoperative and postoperative bleeding; also, it did not have enough power to assess the incidence of severe postpartum bleeding (more than 1000 ml of blood) or the incidence of serious complications as severe thromboembolic events, seizures, or the need for blood transfusion; however, previous studies have shown the safety of this drug for use in both pregnant and non-pregnant patients.

Conclusion

Prophylactic administration of tranexamic acid reduces intraoperative and postoperative bleeding in cesarean section and the incidence of postpartum hemorrhage.

Abbreviations

ARDS: Adult respiratory distress syndrome; ASA: American Society of Anesthesiology Physical Status Classification System; CS: Cesarean section; DBP: Diastolic blood pressure; DIC: Disseminated intravascular coagulation; Hb: Hemoglobin level; HCT: Hematocrit level; HF: Hyperfibrinolysis; PAI: Plasminogen activator inhibitor; PPH: Post-partum hemorrhage; *P*-value: Probability; RBCV: Red blood cell volume; RCT: Randomized controlled trial; SBP: Systolic blood pressure; SD: Standard deviation; SPSS: Statistical package for Social Science; tPA: Tissue plasminogen activator; TXA: Tranexamic acid

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Authors' contributions

NG designed the study, revised the literature, performed the analysis, followed up the patients, measured and calculated the blood loss, and wrote the manuscript. AM designed the study, performed the analysis, and wrote and critically revised the manuscript. FS revised the literature, performed the analysis, and critically reviewed the manuscript. WB revised the literature, followed up the patients, measured and calculated the blood loss, collected the data, performed the analysis, and critically reviewed the manuscript. MI followed up the patients, measured and calculated the blood loss, collected the data, and performed the analysis. All authors approved the final version of the manuscript.

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

After approval of the ethical committee in faculty of medicine, Ain Shams University number FMASU M D 95/2018, this observational prospective study was conducted over 100 pregnant females for 1 year from March 2018 to March 2019. Written informed consent was obtained from patients' legal guardian(s) after explaining of the procedure and its potential complications.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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