Use of Tranexamic Acid for prevention of Postpartum hemorrhage after Cesarean section in high risk patients: A Randomized Controlled Trial

Aboubakr Mohamed Elnashar[1], Ahmed Walid Anwar Morad[1], Shaymaa Ezzat Abdelfattah [2]* Ehab Elsayed Barakat1
[1]Obstetrics and Gynecology, Faculty of Medicine, Benha University
[2]Resident of Obstetrics and Gynecology, Nasr City Police Hospital

Abstract

Background: Postpartum hemorrhage (PPH) is an obstetric emergency. It is one of the leading five etiologies of maternal deaths worldwide, although the absolute risk of death from PPH is much higher in low-resource countries. It accounts for at least 100,000 deaths each year worldwide and contributes up to 28% of maternal deaths. Timely diagnosis and proper management are essential for preventing PPH-related maternal deaths,

Aim and objectives: to assess the efficacy of administration of Tranexamic Acid in Prevention of postpartum hemorrhage in high risk women for PPH undergoing cesarean section,

Subjects and methods: Our study was conducted at Obstetrics and Gynecology department, in Benha University & Nasr City police Hospitals. A comprehensive sample was taken including all women who are at medium and high risk for PPH after cesarean section birth. Cases were divided into two groups: a study group and a control group. (25 cases in each group),

Result: There was high significant difference between the two studied groups according to blood loss (150cc/pack) and blood transfusion after using tranexamic acid,

Conclusion: Tranexamic Acid is effective in Prevention of postpartum hemorrhage in high risk women for PPH undergoing cesarean section,

Keywords: Postpartum hemorrhage (PPH) and Tranexamic Acid (TXA).

Introduction

Postpartum hemorrhage (PPH) is an obstetric emergency. It is one of the leading five etiologies of maternal deaths worldwide, although the absolute risk of death from PPH is much higher in low-resource countries. It accounts for at least 100,000 deaths each year worldwide and contributes up to 28% of maternal deaths. Timely diagnosis and proper management are essential for pre-

Corresponding author:
Shaymaa Ezzat Abdelfattah
dr.shemo90@gmail.com
mobile: 01009023289

venting PPH-related maternal deaths (1). Postpartum hemorrhage (PPH) is classically defined as "Blood loss from the genital tract either from placental or extraplacental sites greater than or equal to 500 mL following a vaginal delivery, or greater than or equal to 1000 mL following Cesarean Section". It can also be defined as "Cumulative blood loss which is greater than or equal to 1000 mL or accompanied by a state of hypovolemia within 24 h after the birth process regardless of the route of delivery" (2), or "Any blood loss sufficient to compromise hemodynamic status after delivery". More recent evidence suggests fibrinolysis may also play a role (3). According to the recent Confidential Enquiries into Maternal and Child health (CEMACH) Report, obstetric hemorrhage occurs in around 3.7 per 1000 births with uterine atony being the commonest cause (4), but it is often accompanied by a coagulopathy that may be consumptive in nature (5). Tranexamic Acid (TXA); Trans-4-aminoethyl cyclohexanecarboxylic acid is a synthetic derivative of the amino acid lysine. It is a competitive inhibitor of plasminogen activation. It binds to plasminogen and exerts its antifibrinolytic effect through the reversible blockade of the lysine binding sites on plasminogen molecules, blocking activation to plasmin which is the leading accelerator of fibrinolysis and fibrinogenolysis. This study aimed to assess the efficacy of administration of Tranexamic Acid in Prevention of postpartum hemorrhage in high-risk women for PPH undergoing cesarean section.

Patients and Methods

This was an interventional randomized control trial (RCT) for prevention of postpartum hemorrhage after cesarean section conducted on a comprehensive sample of all women who were at medium and high risk for PPH after cesarean section birth at Obstetrics and Gynecology department, in Benha University & Nasr City police Hospitals. Randomization was performed by using closed envelope technique for selection of the cases.

Sample technique: Systematic random sample.

Sample size: as TXA reduces the risk of blood transfusion in postpartum hemorrhage by a percent of 39 % (6) so sample was 44 cases which was divided into two groups: a study group and a control group. (22 cases in each group), sample was calculated using open EPI program with confidence level 95 % and power 80 %. The dropout incidence was expected to be 10%; therefore 3 participants were added to each group. Finally, each group included 25 women.

Inclusion criteria: Scheduled or unscheduled cesarean delivery, singleton or twin gestation. Women at high risk for PPH after cesarean section (ACOG, 2017): Placenta previa, accreta, increta or percreta, HCT < 30, bleeding at admission, history of Postpartum hemorrhage and Abnormal vital signs (hypotension or tachycardia). Women at Medium Risk for PPH after cesarean section (ACOG, 2017): Previous Cesarean or uterine surgery, more than four previous deliveries, multiple Gestation, Large Uterine fibroids, chorioamnionitis, magnesium sulphate use and prolonged use of oxytocin. Exclusion criteria: Age less than 18 years, women who are not at high risk for PPH, women attending for normal vaginal delivery and recent diagnosis or history of venous thromboembolism or arterial thrombosis because TXA is a risk factor for thromboembolism, its use is contraindicated, need for therapeutic dose of anticoagulation before delivery, because the risk of thrombosis may be increased with TXA, hypersensitivity to TXA or any of its ingredients. Transfusion or planned transfusion of any blood products during the current admission because the primary outcome is already pre-determined and the need for transfusion will be unrelated to perioperative hemorrhage, seizure disorder (including eclampsia) because TXA is a GABA receptor antagonist, and its use has

been associated with postoperative seizures and if there is no hemoglobin and hematocrit result available from the last 4 weeks since it is necessary to measure the post-operative change in hemoglobin and hematocrit.

Operational Design: All patients were subjected to: An informed consent was taken from every patient. Complete history taking: Personal history, any complaint, obstetric history, menstrual history, past medical and past surgical history and family history, complete physical examination. General examination: Vital signs (Blood pressure, Temperature, Heart rate, Respiratory rate). Patient monitoring included non-invasive blood pressure measurement, electrocardiography, and pulse oximetry. Anesthesia was administered according to the anesthesiologist's instructions. Any hypotension likely to be due to the anesthetic agents was treated by intravenous ephedrine as required. All women underwent cesarean section according to this technique: TXA Administration: Participants were divided into two groups: a study group & a control group. In addition to the standard management, the study group was given TXA 1 gm (100 mg/ml) slowly intravenous infusion during delivery after clamping of the cord (administered over 10 minutes at 1 ml/minute). Second dose of TXA 1 g Intravenous was given if: Bleeding continued after 30 minutes and bleeding restarted within 24 hours of completing the first dose While the control group was not given TXA, and we compared the results in both groups (amount of blood loss during operation to assess efficacy of TXA in prevention of PPH and reduction of intra and postoperative blood loss and to assess its safety and benefit in reduction of incidence of hysterectomy or blood transfusion requirements). Following placental delivery by controlled cord traction, the uterus was exteriorized and massaged. Estimation of blood loss was done by Cochrane Database Syst Rev. (7): Counting or weighing: Counting the number of saturated pads, or by weighing all towel and material used to absorb blood (gauze, pads, sheets, etc.)

Blood Loss = (Weight of materials used - weight of material before use) + volume included in the suction container. In direct blood collection, all blood lost during the third stage of labor (except for the placenta and membranes) was contained in a disposable, funneled, plastic collector bag, which was attached to a plastic sheet, and placed under the woman's buttocks. When the bleeding stopped, there were two options: the bag was weighed (gravimetric technique), or the bag was calibrated, allowing for a direct measurement. Taking in consideration the volume of irrigation fluids, subtracting this volume from the measured blood loss to estimate the final blood loss.

Outcomes:

Primary Outcome: Volume of blood loss.

Secondary outcomes: Transfusion requirements: transfusion of 1 or more units of packed red blood cells or other blood products such as fresh frozen plasma, cryoprecipitate, or platelets or any factor concentrates [Time Frame: within 7 days postpartum].Additional medical intervention through use of uterotonics other than oxytocin such as prostaglandins or methergine, [Time Frame: within 48 hours postpartum]. Additional surgical or radiological interventions to control bleeding and related complications such as: laparotomy, hysterectomy, evacuation of hematoma, uterine packing, intrauterine balloon tamponade, interventional radiology [Time Frame: within 7 days postpartum]. Change in maternal hemoglobin and hematocrit concentration. [Time Frame: from 4 weeks before delivery to 48 hours postpartum]. TXA side effects (nausea, vomiting, dizziness, headache, seizures) or skin reactions) [Time Frame: within 24 hours postpartum]. Thromboembolic events (venous or arterial) [Time Frame: within 7 days postpartum]. Maternal death [Time Frame: within 7 days postpartum]. Administrative Design: The protocol was ap-

plied for approval of Research Ethics Committee. Written consent was taken from all participants before including them in the study and they had the right to refuse without effect on their management.

Statistical Analysis: Data were checked, entered and analyzed using SPSS version 23 for data processing. The following statistical methods were used for analysis of results of the present study. I- **The student "t"** test for comparison of means of two independent groups. **II-Mann Whitney test** was used to calculate difference between quantitative variables in not normally distributed data in two groups. **III- Chi- square test (X2):** Used to find the association between row and column variables.

Results

Table (1): Comparison between the two studied groups according to age (years) and BMI

	Study (n = 30)		Control (n = 30)		t	P
Age (years)						
Min. – Max.	21.0 – 39.0		22.0 – 42.0		1.585	0.119
Mean ± SD.	30.23 ± 5.02		32.20 ± 4.58			
Median (IQR)	30.0 (26.0–34.0)		32.0 (30.0–36.0)			
BMI (kg/m²)	**No.**	**%**	**No.**	**%**		
<18.5	0	0.0	0	0.0	χ^2=1.071	^{MC}p=0.612
18.5 – 24.9	3	10.0	1	3.3		
>25	27	90.0	29	96.7		
Min. – Max.	24.0 – 35.0		25.0 – 33.0		t=1.315	0.194
Mean ± SD.	28.40 ± 2.58		29.13 ± 1.63			
Median (IQR)	28.0 (27.0–30.0)		29.50 (28.0–30.0)			

tχ^2: Chi square test MC: Monte Carlo test , t: Student t – test
p: p value for comparing between the two studied groups
*: Statistically significant at p ≤ 0.05
There was no significant difference among the two studied groups as regards age (years) and BMI (kg/m²).

Table (2): Comparison between the two studied groups according to Hemoglobin & HCT before and after using tranexamic acid

Hemoglobin	Study (n=30)	Control (n=30)	t	p
Hemoglobin Before TXA				
Min. – Max.	7.70 – 12.60	7.70 – 11.10	1.989	0.051
Mean ± SD.	10.60 ± 1.23	10.04 ± 0.94		
Median (IQR)	10.50 (10.0–11.20)	0.30 (9.70–10.60)		
After TXA				
Min. – Max.	7.0 – 12.30	7.0 – 9.90		
Mean ± SD.	10.33 ± 1.20	8.90 ± 0.76	5.507*	<0.001*
Median (IQR)	10.30 (9.80–11.0)	9.10 (8.90–9.30)		
p_1	<0.001*	<0.001*		

HCT				
Before TXA				
Min. – Max.	28.0– 37.50	27.60 – 34.10		
Mean ± SD.	33.15 ± 2.07	32.16 ± 1.74		
Median (IQR)	33.40 (32.0–34.0)	32.65 (31.90–33.20)		
After TXA				
Min. – Max.	28.0 – 35.60	28.0 – 32.0		
Mean ± SD.	32.91 ± 1.90	30.50 ± 1.16		
Median (IQR)	33.05 (32.10–34.0)	31.0 (29.80–31.10)		
p_1	0.049*	<0.001*		

t: Student t-test
p: p value for comparing between the two studied groups
p1: p value for Paired t-test for comparing between Before and After in each group
*: Statistically significant at $p \leq 0.05$

There was no significant difference between the two studied groups before administration of TXA. There was high significant difference between the two studied groups after administration of TXA. In the control group there was high significant difference between Hemoglobin before administration of TXA and Hemoglobin after administration of TXA. In the study group there was high significant difference between HCT before administration of TXA and HCT after administration of TXA.

Table (3): Comparison between the two studied groups according to Outcome after using of TXA

Outcome	Study (n=30)		Control (n=30)		Test of seg	p
	No.	%	No.	%		
Blood loss 150cc/pack						
Min. – Max.	5.0 – 8.0		8.0 – 18.0		U=1.500*	<0.001*
Mean ± SD.	6.30 ± 0.65		10.70 ± 2.78			
Median (IQR)	6.0 (6.0–7.0)		10.0 (9.0–12.0)			
Complications						
Blood transfusion	3	10.0	29	96.7	χ^2=45.268*	<0.001*
Hysterectomy	0	0.0	3	10.0	χ^2=3.158	^{FE}p=0.237
Death	0	0.0	0	0.0	–	–

U: Mann Whitney test χ^2: Chi square test FE: Fisher Exact
p: p value for comparing between the two studied groups
*: Statistically significant at $p \leq 0.05$

This table shows that there was high significant difference between the two studied groups according to blood loss (150cc/pack) and blood transfusion after using tranexamic acid.

Discussion

Our study was conducted at Obstetrics and Gynecology department, in Benha University & Nasr City police Hospitals. Comprehensive samples were taken including all women who are at medium and high risk for PPH after cesarean section birth. Cases were divided into two groups: a study group and a control group. (25 cases in each group).

This study demonstrated that there was no significant difference among the two studied groups as regards age (years) and BMI (kg/m2). Jianjun et al. (8) performed a randomized, double-blind, case-controlled study conducted on 174 primipara undergoing CS. 88 of them given 10 mg/kg TXA immediately before CS were compared with 86 others to whom TXA was not given. In agreement with our results, there was no significant difference among the two studied groups as regards age (years) and weight (kg).

Previous study by Ononge et al. (9) suggest that maternal age, number of maternal births, and child size are risk factors for postpartum hemorrhage. In Yang et al. (2021) study, their univariate analysis found that maternal age, number of maternal births, and fetal macrosomia were significantly associated with PPH. Although these factors have not been shown to be independently related to PPH in multivariate logistic regression analysis, they still have a suggestive role in the occurrence of postpartum hemorrhage.

In clinical practice, cesarean delivery for older women, multigravida and large fetuses still require close attention. The number of cesarean sections and fetal position are independent risk factors for PPH (10). Sentilhes et al. (11) enrolled 4551 eligible participants and randomly assigned them to receive tranexamic acid (2276 women) or placebo (2275); 112 women were excluded because they withdrew consent or were found to be ineligible after randomization. In agreement with our results, the baseline characteristics of the women, protocol adherence, and other aspects of management of the third stage of labor were similar in the two groups.Abdel-Fatah et al. (12) showed that the mean age of tranexamic acid intervention group was 28.62 ± 6 years (ranging from 20-40 years) and mean age of control group was 27.38 ± 7.1 years and ranged from (20-48). The difference was statistically non-significant.

In agreement with our results, Perveen et al. (13) found that mean age of tranexamic acid intervention group was 28.80 ± 3.72 years with no significant difference between the studied groups. Average gestational age was 38.94 ± 0.814 weeks in TXA group and 39.02 ± 0.864 weeks in control group with no statistical difference.

Yehia et al. (14) reported 28.4 ± 4.9 years mean age in women with postpartum hemorrhage. Xu et al. (15) also reported that mean age was 26.7 ± 3.7 years. Besides, Goswami et al. (16) reported 23.6 ± 2.5 years mean age in women having PPH.

This study illustrated that there was no significant difference among the two studied groups as regards gravidity, parity, abortion and number of CS. In agreement with our results, Abd El-Gaber et al. (17) illustrated that no statistically significant difference regarding the baseline criteria; parity and gestational age of both groups.

This study reported that there was no significant difference in hemoglobin between the two studied groups before administration of TXA. There was high significant difference in hemoglobin between the two studied groups after administration of TXA. In the study group there was high significant difference in hemoglobin before and after using of tranexamic acid.

In agreement with our results, Jianjun et al. (8) reported that there was no significant difference in hemoglobin between the two studied groups before administration of TXA. After admission in TXA group Hemoglobin declined by 1.1 ± 0.3. Decrease was significantly ($P<0.01$) less than Control group as

hemoglobin declined by 1.6 ± 0.6 in control group.

According to Bekassy et al. (18) the incidence of thrombosis during pregnancy and puerperium is five to six times higher than that in the general population, so it is interesting to observe that no significant difference was found in the incidence of thrombosis in these two groups. In another 100 women, including 50 pregnant women given TXA to prevent blood loss during and after cesarean delivery, thrombotic complications were absent (19).

Also, in Jianjun et al. (2013) study no significant abnormal vital signs occurred after TXA administration as BP, HR, RR, hemoglobin, platelet count, postoperative PT and PPT did not change very much in the TXA group compared with the control group.This has been validated by other studies. Abd El-Gaber et al. (17) demonstrated that as regard to change in hemoglobin level and hematocrit value pre and 24 hours postoperative were highly statistically significant differences between the two groups.

Jianjun et al. (8) demonstrated that there was no significant difference in postoperative PT ($p = 0.23$), PTT ($p = 0.40$), serum hemoglobin concentration ($p = 0.14$) and platelet count ($p = 0.75$) 24 h after surgery. In addition, serum hemoglobin concentration and platelet count show a decline in the control group than in the TXA group. Though the decline in hemoglobin was significantly different between these two groups, no statistical difference in platelet count could be found as bleeding in control group was not high enough to perform a significant change in blood components or criteria other than hemoglobin level.

Jianjun et al. (8) demonstrated that it is evident that the risk of postpartum hemorrhage increases in the control group than the TXA group ($p = 0.04$) from placental delivery to the end of CS, whereas rarely patients suffer PPH from the end of CS to 2 h postpartum in both TXA and control groups. Moreover, more patients in the control group (n = 19) had PRBCs infused than in the TXA group. Abd El-Gaber et al. (17) showed that as regard to changes in hemoglobin level and hematocrit value 24 hours postoperative in their study, the changes were significantly high in placebo group than tranexamic group. Also the need for additional uterotonic drugs, additional surgical interventions or blood transfusion were significantly less in tranexamic group. These results were agreed with many previous studies as what had been reported by the meta-analysis by Simonazzi G et al. (20) of the 9 RCTs for evaluation the efficacy of prophylactic tranexamic acid in decrease postpartum hemorrhage at cesarean delivery. Tranexamic acid was associated with a significant reducing postpartum blood loss (low incidence and low severity), a significantly lower hemoglobin level drop postoperative and less need for additional uterotonic drugs.

This study showed that there was high significant difference between the two studied groups according to blood loss 150cc/pack and blood transfusion after using tranexamic acid. In agreement with our results, Abdel-Fatah et al. (12) showed that the mean blood loss during CS of tranexamic acid intervention group was 484 cc and mean blood loss during C/S of control group was 705 cc, where the difference highly statistically significant ($p=0.000$). According to the study by Gungorduk et al. (21) a reduction in postoperative bleeding of around 17 % at 2 h was found in the intervention participants who received 1 g of TXA regardless of their weight.

A multi-center, randomized trial was conducted by Gai et al. (22) suggesting that approximately 18 % reduction of blood loss was found in the experimental group.

Two meta-analyses by Peitsidis et al. (23) and Novikova et al. (24) reported that the TXA effect compared with placebo showed 32.5 and 75.1ml reduction in blood loss, respectively.

In agreement with our results, Abd El-Gaber et al. (17) showed that amounts of blood loss had a highly statistically significant difference between the two groups (less in group A). Another study by Campbell et al. (25) reported that in Egypt the main causes for avoidable deaths were suboptimal care, delay in the recognition of the case, improper antenatal care and finally lack of supplies include blood and its derivatives e.g. fresh frozen plasma and platelets. Many medications have been tried in prevention of postpartum hemorrhage, authors used tranexemic acid in their study because it has affordable price, easily administered and has rare side effects.

CONCLUSION

TXA, with its antifibrinolytic properties, is increasingly being used worldwide to treat PPH. Tranexamic Acid is effective in Prevention of postpartum hemorrhage in high-risk women for PPH undergoing cesarean section.

References

1. Say L, Chou D, Gemmill A, et al. Global cause of maternal death. Lancet Glob Health. 2014; 2: e323–333.
2. ACOG 2017 Guidelines.
3. Ducloy-Bouthors, AS, Duhamel A, Kipnis E, et al. Postpartum haemorrhage related early increase in D-dimers is inhibited by tranexamic acid: Haemostasis parameters of a randomized controlled open labelled trial. Br J Anaesth. 2016; 116: 641–648.
4. World Health Organization. Maternal mortality fact sheet. Geneva: WHO; 2018. [(accessed February 16, 2018)].
5. Cortet M, Deneux-Tharaux C, Dupont C, et al. Association between fibrinogen level and severity of postpartum haemorrhage: Secondary analysis of a prospective trial. Br J Anaesth. 2012; 108: 984–989.
6. British Journal of Anaesthesia. 2015; 114: 576–587.
7. Cochrane Database Syst Rev. 2018; 9: CD010980.
8. Jianjun Xu, Wei Gao, Yingnan Ju. Tranexamic acid for the prevention of postpartum hemorrhage after cesarean section: a double-blind randomization trial. 2013; 287: 463–468.
9. Ononge S, Mirembe F, Wandabwa J. Incidence and risk factors for postpartum hemorrhage in Uganda. Reprod Health. 2016; 13: 38-44.
10. Yang, Y., He, J., Deng, N. Factors Associated with Primary Postpartum Hemorrhage in Elderly Women Undergoing Repeated Cesarean Deliveries. International journal of women's health. 2021; 13: 1261–1267.
11. Sentilhes, L., Sénat, M. V., Le Lous, M, et al. Tranexamic acid for the prevention of blood loss after cesarean delivery. New England Journal of Medicine. 2021; 384: 1623-1634.
12. Abdel-Fatah, A. T., Ibrahim, S. A. S., Mohammed, S. A. A, et al. Effectiveness of Tranexamic Acid in Preventing Postpartum Hemorrhage in Cesarean Delivery of High-Risk Pregnancy. The Egyptian Journal of Hospital Medicine. 2022; 86: 238-241.
13. Perveen S, Ali R, Mehak R. Efficacy of Tranexamic Acid to Control of Postpartum Hemorrhage. Population. 2017; 7: 11-16.
14. Yehia A, Koleib M, Abdelazim I, et al. Tranexamic acid reduces blood loss during and after cesarean section: A double blinded, randomized, controlled trial. Asian Pacific Journal of Reproduction. 2014; 3: 53-56.
15. Xu J, Gao W, Ju Y. Tranexamic acid for the prevention of postpartum hemorrhage

after cesarean section: a double-blind randomization trial. Arch Gynecol Obstet. 2013; 287: 463-468.

16. Goswami U, Sarangi S, Gupta S, et al. Comparative evaluation of two doses of tranexamic acid used prophylactically in anemic parturients for lower segment cesarean section: A double-blind randomized case control prospective trial. Saudi J Anaesth. 2013; 7: 427-431.
17. Abd El-Gaber A, Ahmed HH, Khodry MM, et al. Effect of tranexamic acid in prevention of postpartum hemorrhage in elective caesarean delivery: a randomized controlled study. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2018; 8: 1-5.
18. Bekassy Z, Astedt B. Treatment with the fibrinolytic inhibitor tranexamic acid—risk for thrombosis? Acta Obstet Gynecol Scand. 1990; 69: 353–354.
19. Movafegh A, Eslamian L, Dorabadi A. Effect of intravenous tranexamic acid administration on blood loss during and after cesarean delivery. Int J Gynaecol Obstet. 2011; 115: 224–226.
20. Simonazzi G, Bisulli M, Saccone G, et al. Tranexamic acid for preventing postpartum blood loss after cesarean delivery: a systematic review and meta-analysis of randomized controlled trials. Acta Obstet Gynecol Scand. 2016; 95: 28-37.
21. Gungorduk K. Efficacy of intravenous tranexamic acid in reducing blood loss after elective cesarean section: a prospective, randomized, double-blind, placebo-controlled study. Am J Perinatol. 2011; 28: 233–240.
22. Gai MY. Clinical observation of blood loss reduced by tranexamic acid during and after caesarian section: a multicenter, randomized trial. Eur J Obstet Gynecol Reprod Biol. 2004; 112: 154–157.
23. Peitsidis P, Kadir RA. Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum. Expert Opin Pharmacother. 2011; 12: 503–516.
24. Novikova N, Hofmeyr GJ. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2010; 7: CD007872.
25. Campbell O, Gipson R, Issa AH, et al. National maternal mortality ratio in Egypt halved between 1992-93 and 2000. Bulletin of the World Health Organization. 2005; 83: 462-471.