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Tranexamic Acid Versus Etamsylate in Reducing Blood Loss During Normal Vaginal Delivery in Patients with High Risk of Postpartum Hemorrhage: Randomized Controlled Trial

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ABSTRACT

Patients and methods: This was a prospective double-blinded multi-center randomized controlled trial conducted from April 2022 till September 2022 involving one hundred eighty women categorized into three categories, each involving 60 females who received either tranexamic acid, etamsylate or placebo just after birth of the baby. **Results:** Loss of blood in tranexamic acid was the same as the blood loss in etamsylate and both were lower than the placebo group. The difference in hemoglobin after delivery in tranexamic acid individuals was the same as etamsylate group and both of them were lower than placebo group. The occurrence of postpartum hemorrhage and blood transfusion in tranexamic acid category and etamsylate category were significantly less than placebo. **Conclusions:** Etamsylate is an efficiently alternative agent for tranexamic acid in decreasing blood loss with lower side effects, therefore, it can be used instead of tranexamic acid in women with contraindications or anticipated to be have higher risk to develop tranexamic acid side effects. **Trial registration number**: PACTR202205750416982

Keywords: Blood loss; Normal vaginal delivery; Etamsylate; Tranexamic acid.

INTRODUCTION

The conventional definition of primary postpartum bleeding is blood loss of 500 ml or more from the genital tract within 24 hours of baby birth[(1)].

Postpartum hemorrhage can be major (>1000 ml) or minor (500–1000 ml). The first can be further subcategorized into moderate (1001–2000 ml) and severe (more than 2000 ml). Lower body mass females (<60 kg), blood loss of a lower level may be clinically potential[(2)]. Secondary postpartum hemorrhage is an excessive or abnormal bleeding from the birth duct between 24 hours and 12 weeks postpartum[(3)]. Tranexamic acid is an antifibrinolytic that reduces loss of blood by the blockage of lysine-binding locations on plasminogen molecules[(4)]. It reduces bleeding in elective operation and death among trauma patients, with side-effects including vomiting, nausea, headache, diarrhea, or more severe complications such as myocardial infarction and pulmonary embolism[(5)]. Its onset of action: within 5 min, half-life: 120 min and peak plasma concentration 6–8 min. Etamsylate is a synthetic hemostatic agent referred in capillary bleeding cases. Its action is exerted through improving adhesion of platelets and restoring resistance of capillary. It reduces the time of bleeding and promotes aggregation of platelets when platelets are adequate. The agent exerts antihyaluronidase action. It suppresses the synthesis of PGI-2 and correct abnormal function of platelet. Adverse impacts involve fall in blood pressure only in case of intravenous administration, blood and lymphatic system disorder as agranulocytosis, neutropenia, skin rash and headache [(6)]. Its onset of action is 5 minutes after the injection, peak plasma concentration: 4 hours after the injection [(7)]

Aim: To assess if etamsylate can be an alternative to tranexamic acid for reducing loss of blood during vaginal birth.

PATIENTS AND METHODS

This is a parallel prospective double-blinded multi-center randomized controlled trial done in October 6 Hospital and Ain Shams Maternity Hospital comparing the impact of tranexamic acid, etamsylate and placebo in decreasing loss of blood in patient with high risk for postpartum hemorrhage.

Population of the study included all women underwent a vaginal delivery from April 2022 through September 2022, with gestational age 37-40 weeks, and were counselled about the pros and cons of the medications after having history, general, local and ultrasound examination and lab tests with high risk of postpartum hemorrhage as history of previous postpartum hemorrhage, except those known for hypersensitivity or have contraindications to any of the drugs used and those complaining coagulation diseases. The study setting was in October 6 University Hospital and Ain Shams University Hospital.

Inclusion criteria: Pregnant women who gave birth vaginally, full term of gestation age, susceptible for postpartum hemorrhage as multipara, history of pervious postpartum hemorrhage, precipitate labor, instrumental delivery or prolonged induction of labor, anemic (hemoglobin between 8-10 mg/dl), diabetic and macrosomic baby. Exclusion criteria: Women with thrombophilia, coagulopathy or liver, kidney or cardiovascular diseases, or drug contraindication as allergy to tranexamic acid or its excipients. The study involved 180 patients categorized into three groups (Figure 1):

- **Group 1:** included 60 females who received 1g of tranexamic acid.
- **Group 2:** included 60 females who received 1g of etamsylate.
- **Group 3:** included 60 females who received 10 mL of normal saline.

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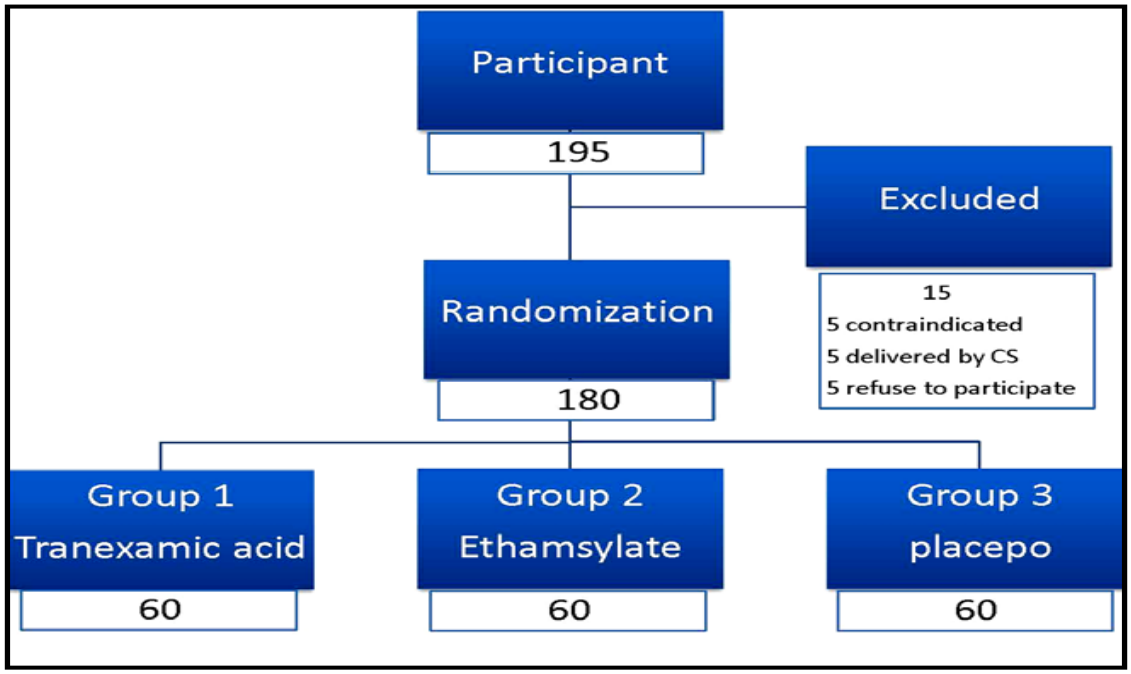

Fig. (1): Consort study flow chart

All patients in the three groups received 10 IU of oxytocin infusionwithin 2 minutes after birth of the baby.

The sample randomization sequence was produced using the software Research Randomizer®. Each group had 60 patients were randomly generated from a pool of 180. Each patient was allocated to her group prior to their delivery according to that number. Sequentially numbered opaque sealed envelopes were used for concealment**.**

Brown envelopes with these numbers (1 to 180) written on them were then filled with the appropriate medication and sealed, along with a sheet of paper bearing the words "tranexamic acid", "etamsylate" or "placebo." A statistician and an obstetrician carried out the randomization, while a hospital pharmacist carried out the concealment without sharing the findings with the researchers. All of the study team members had access to a locker where the envelopes were kept[(8)].

The designated sealed envelope was delivered by the researchers or one of the research assistants, who then gave it to the labor ward officer who administered the medicine or the placebo within two minutes of the baby's delivery. The investigators received the used envelope and its resealed contents. Until un-blinding was completed at the conclusion of the study, the investigators stored all used envelopes and packs in a separate locker.

All used pads and towels that were saturated in blood were placed on a digital scale between the birth of the baby and the placenta, the repair of any genital lacerations or episiotomies, and the completion of all third stage labor activities were recorded. The notion of the fourth stage of labor, in which uterine contractility and hemodynamic status (vital signs) were monitored for 1-2 hours postpartum while the mother was still in the labor and delivery unit, served as the foundation for the measurement of blood loss through the weighing of sanitary pads within 2 hours of delivery. The lady that was most at risk for developing primary PPH at this time, was necessitating careful monitoring and evaluation [(9)].

There were 15 patients took epidural anesthesia, 3 patients took general anesthesia and 1 patient needed insertion of intrauterine balloon as there was significant postpartum hemorrhage and they needed to beexamined to detect the cause of bleeding.

Blood loss estimation was ascertained by evaluating the weights ofthe pads before and after 2 h of birth. Total loss of blood (ml)= [weight of Pad after 2 h (gm) – weight of Pad before use (gm)], converted to ml; considering that 1g difference in pad weight=1ml of blood [(10)].

Blood loss >500ml was be considered as excessive bleeding (postpartum hemorrhage).

The primary outcome was: “The blood loss quantity estimated by the difference between pre weighted pads and weight of pads soaked with blood, towels were weighed 2 h postpartum” [(7)]. Two digital scale, one placed in October 6th University Hospital and the other one placed in Ain Shams Maternity Hospital.

Secondary outcomes were: “Complete blood picture hemoglobin pre and postoperative and clinical data including blood pressure, pulse. The proportion of cases experienced postpartum bleeding, blood transfusion requirement and the need for more interventions to combat postpartum bleeding”.

Sample size calculation:

PASS® version 11 software was used for sample size calculation, at 0.05, the type-1 error (α) was set and the power (1-β) at 80%.

Results from an earlier study showed that the mean blood loss in group 1 (tranexamic), 2 (etamsylate) and controls was 591.55 ±162.08, 630.72±145.8 and 678.37±171.49 respectively [(11)]**.** Based on such values revealed a minimal sample size of 59 subjects in each group. The study would include 65 cases per group to take in account for 10% dropout rate.

Ethical Approval:

Institutional approval was obtained from The Research Ethics Committee of October 6 University No. PMC-Me-2202013. Every patient signed informed consent form. The attending obstetrician who recruited patients was responsible for obtaining informed consent. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Method

Data analysis was performed using SPSS (IBM corporation Armonk NY) V 27 software. Differences were considered significant at $p<0.05$, otherwise is non-significant. Continuous variables as age and parity were expressed as means and standard deviations (Mean±SD).

RESULT

The demographic data included age and parity with any risk factor. The mean of age in all groups was 29 ± 7 and the mean of parity was 1.93 ± 1.82. The loss of blood in tranexamic acid was the same as the blood loss in etamsylate and both were highly significantly lower than the placebo group **(Table 1).**

Table (1): Shows the blood loss in all groups.

	Mean	SD	Min	Max	P-value
Tranexamic acid	333.55	307.627	100	1900	0.001
Etamsylate	324.77	183.448	110	980	
Placebo	638.25	200.284	398	1210	
Total	430.45	276.870	100	1900	

The difference in hemoglobin after delivery in tranexamic acid group was the same as etamsylate group and both of them lower than placebo group **(Table 2).** Postpartum hemorrhage and blood transfusion in tranexamic acid group and etamsylate group were highly significantly less frequent than placebo **(Table 3).**

Table (2): Comparing HB after delivery in each group with the other one.

	Mean	SD	P-value
Tranexamic acid	9.07	± 1.3	< 0.001
Etamsylate	8.37	± 1.3	
Placebo	6.74	± 1.2	

Table (3): Shows postpartum hemorrhage and blood transfusion in all groups.

		Group						Chi square	P value
		Tranexamic acid		Etamsylate		Placebo			
		No	%	No	%	No	%		
Postpartum hemorrhage	**Yes**	6	10.0%	6	9.8%	31	52.5%	39.6	<0.001
	No	54	90.0%	55	90.2%	28	47.5%		
Blood Transfusion	**Yes**	6	10.0%	6	9.8%	35	59.3%	50.176	<0.001
	No	54	90.0%	55	90.2%	24	40.7%		

DISCUSSION

Postpartum hemorrhage is an obstetric emergency and its anticipated prophylactic measures are crucial in conducting modern obstetrics practice. This randomized trial showed that the blood loss, PPHge and blood transfusion, are reduced significantly in tranexamic acid and etamsylate individuals than placebo. Hemoglobin (Hb) after delivery was highly significantly more in the two studied groups than placebo.

Postpartum blood loss was determined objectively since it was evaluated by two strategies: The first by comparing the weight of pre-weighted towels to that of blood-soaked towels and the other is comparison between pre surgical Hb and postoperative Hb after 12 h of the procedure rather than being visually estimated. Several studies have shown visual estimation to be an unreliable method [12-14].

The current results were supported by the research of **Jianjun Xu *et al.*** The study group included 88 females received TXA, whereas the control included 86 females. TXA remarkably reduced the amount of blood from the end of cesarean to 2 hours postpartum: (46.6 ± 42.7 ml) versus (84.7 ± 80.2 ml) in the study and controls groups, respectively ($p < 0.01$). It also remarkably reduced the amount of overall blood from delivery to 2 hours postpartum: (379.2 ± 160.1 ml) in the tranexamic women versus (441.7 ± 189.5 ml) in the controls ($p = 0.02$) [15].

The current results were supported in both (blood loss and effect onhemoglobin after delivery) by **Sekhavat *et al.*** Each of the study and control group involved 45 females who received TXA and those who didn't, respectively. TXA considerably reduced the blood amount from the end of cesarean procedure to 2 hours postpartum: (28.02 ± 5.53 ml) versus (37.12 ± 8.97 ml) in the study and control groups, respectively ($p = 0.001$). Hb 24 hours post cesarean section was considerably greater in the study group compared to the control (12.57 + 1.33 and 11.74 +1.14 respectively, $p = 0.002$) [16].

The current findings were supported by study of **Torky *et al.*** as both TXA and etamsylate were related to considerably lower average blood loss, requirement for transfusion and interventions to reduce blood loss than placebo and postoperative Hb and hematocrit were remarkably higher in both studied groups as compared to placebo [11].

These results were enhanced by the study of **Mohamed *et al.*** where the blood loss quantity, blood transfusion requirement or further intervention, were minimal in the users of tranexamic acid and etamsylate than in the oxytocin users. Additionally, the values of Hb and hematocrit post-surgically were high in the women who received both tranexamic acid and etamsylate comparing with those received syntocinon [17].

Similar findings were documented by the study of **Alanwar *et al.*** that found that TXA and etamsylate considerably reduced hemorrhage during and after cesarean operation. The overall blood loss of the studied cases (149.22±54.74 ml) was considerably less than that of the control (353.75±115.56 ml) ($p<0.001$). Post-surgical Hb and hematocrit were remarkably higher in the study than the control group ($p<0.001$); the fall in Hb and hematocrit were remarkably less in the study group ($p < 0.001$)[18].

Similar outcomes were documented by **Roy *et al.* and Gungorduk *et al.* who** conducted studies to estimate the efficacy of TXA in reducing bleeding after vaginal birth. A remarkable reduction in bleeding occurred in the TXA compared to the placebo (**8,19**).

Bhatia and Deshpande[20], showed the effectiveness of TXA in reducing bleeding during elective cesarean operation and this is in line with The Royal College of Obstetricians and Gynecologists' recommendations.

A total of 20,060 mothers with postpartum bleeding in 21 low and middle-income countries between 2010 and 2016 were incorporated in a randomized double-blind placebo-controlled trial to receive either 1 g tranexamic acid intravenously (n = 10,051) or placebo (n = 10,009) with standard care. In case of continuous bleeding, a second dose of placebo or 1 g of tranexamic acid could be given. It was reported that tranexamic acid reduced mortality due to hemorrhage [155 (1.5%) vs 191 (1.9%)], especially in females received treatment within 3 hours of delivery [89 (1.2%) vs 127 (1.7%), p = 0.008]. Also, a reduction of bleeding-associated laparotomy was noted [82 (0.8%) vs 127 (1.3%); p = 0.002] following caesarean and vaginal deliveries. It was deduced that tranexamic acid reduced mortality related to bleeding among females with postpartum bleeding without adverse events" [21].

World Health Organization (WHO), advised using TXA for the management of Postpartum hemorrhage, if oxytocin and other uterotonics are ineffective in stopping the bleeding or if it is believed that the bleeding may be partially a result of trauma [22].

Furthermore, early tranexamic acid therapy dramatically lowers mortality in trauma patients with hemorrhage, according to the CRASH-2 experiment. The medication was included to the WHO Model List of Essential Medicines as a consequence of this trial [23].

TXA is most frequently used in the treatment of idiopathic menorrhagia and pregnancy-related bleeding (threatened abortion and placenta previa) in obstetric and gynecologic therapy [24].

There is study about the synergistic impact of TXA and combination with etamsylate on loss of blood in pediatric cardiac surgery, it revealed that the combination of TXA and etamsylate among such patients was more efficient in reducing post-surgical loss of blood and requirement of transfusion in the first postoperative 24 h than the administration of TXA alone; this study matches with our study [25].

However, **Torky *et al.*** study concluded that the effect of TXA appears to be superior to etamsylate in terms of reducing blood loss, the need for transfusion,

and increasing postoperative Hb and hematocrit; however, TXA was linked to a higher risk of side effects, specifically vomiting and nausea, than etamsylate [(11)].

Our findings were inconsistent with **Bonnar and Sheppard *et al.,*** who concluded that when compared to mefenamic acid, etamsylate did not diminish the average amount of menstrual blood lost (mean blood loss was 186 ml prior to therapy and 148 ml during treatment). Additionally, TXA decreased blood loss by 54% (mean blood loss, 164 ml prior to therapy, 75 ml during treatment) [(26)].

The limitations of our study are lochia and liquor contamination of the evaluated blood may not have been fully avoided.

Finally, larger studies including larger size are required to investigate the efficacy of etamsylate. Current study included only a group of 180 females. Various dosage and administration routes to compare the efficiency of each route are also required.

CONCLUSIONS

Our results demonstrated that the etamsylate could be an effective alternative therapy to TXA in reducing loss of blood during vaginal delivery, therefore, it can be used in cases with contraindications or to avoid its side effects.

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