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Alaa M Ismail, Ahmed M Abbas*, Mohamed A Shahat and Mohammed K Ali

Department of Obstetrics and Gynecology, Faculty of Medicine, Assiut University, Egypt

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***Corresponding author:** Ahmed M Abbas, Department of Obstetrics and Gynecology, Faculty of Medicine, Assiut University, Egypt, Tel: +20 88 2414616; E-mail: bmr90@hotmail.com

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Research Article

Evaluation of Subendometrial and Intramyometrial Blood Flow after Intravenous Tranexamic Acid for Prevention of Postpartum Hemorrhage in Vaginal Delivery: A Randomized Controlled Study

Abstract

Objective: The study aims to test the effect of tranexamic acid (TA) on uterine vasculature and blood loss after vaginal delivery.

Materials and methods: A randomized, double-blind, placebo-controlled trial, conducted in Assiut Woman's Health Hospital, Egypt between the 1st of October 2015 and the 31st of March 2016 included pregnant women (37-42 weeks) with a single living cephalic fetus. The eligible women were randomized to receive TA or placebo after vaginal delivery. Doppler indices were measured for the subendometrial, intramyometrial and uterine blood vessels two hours after delivery. The main study outcome was the effect of TA on subendometrial and intramyometrial blood flow.

Results: Two hundred women were enrolled (n=100 in each group). There was a significant increase in the Doppler indices of subendometrial and intramyometrial blood vessels with no difference in indices in uterine arteries between both groups. The mean of estimated blood loss decreased significantly in TA group ($p<0.001$). The haematocrit and hemoglobin levels were higher in TA group than the placebo group after delivery ($p<0.001$).

Conclusions: The use of intravenous TA after vaginal delivery increases the resistance in the subendometrial and intramyometrial blood vessels and reduces postpartum hemorrhage.

Introduction

Postpartum hemorrhage (PPH) is considered the leading cause of maternal mortality and morbidity in the developing countries [1]. It is contributing to about 25% of direct maternal deaths [2]. The incidence of PPH is about 1.2% [3]. Conservative treatment of PPH includes uterine massage, uterotonics, uterine packing, pelvic vessel ligation, uterine compression suture and uterine artery embolization [4].

Tranexamic acid (TA) is widely used to prevent hemorrhage that is implicated in many medical and surgical situations [5]. A recent systematic review suggested that TA reduces the amount of blood loss after delivery and reduces the requirement for blood transfusion [6]. A Cochrane systematic review also concluded that TA decreases blood loss after vaginal and cesarean delivery [7].

TA is inexpensive and treatment would be considered highly cost effective in low income countries [8]. TA is a synthetic derivative of the amino acid lysine blocks lysine-binding sites on plasminogen molecules, thereby inhibiting the interaction of plasminogen and the heavy chain of plasmin with lysine residues on the surface of fibrin [9]. Through this mechanism, TA exerts its antifibrinolytic effect, but other possible mechanisms such as an effect on uterine vascular flow have not been investigated before in prevention of PPH [10].

Previous study examined the effect of TA on uterine blood flow in women with menorrhagia. Their results demonstrated a reduced impedance to blood flow in the uterine arteries on

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Doppler examination; however they reported no explanation for this surprising effect [11].

Our hypothesis that TA may affect the resistance of uterine blood flow due to its known antifibrinolytic action, thus reduce blood loss and PPH. So, the current study aims to investigate the effect of TA on uterine vasculature after vaginal delivery. To our knowledge; no study has been registered or conducted to evaluate the effect of TA on uterine blood flow after vaginal delivery.

Materials and methods

The current study was a single-center, prospective, registered (Clinical Trials.Gov; NCT02678208), randomized, double-blind, placebo-controlled trial, conducted in Assiut Woman's Health Hospital, Egypt between the 1st of October 2015 and the 31st of March 2016. The Assiut University Medical Ethical Review Board approved the study.

All Women in labor who admitted to our Labor Ward were invited to participate. Informed consent was obtained for participation after discussing the nature of the study including the possible side effects of TA at admission. The recruited women were entered the screening phase of the study included history taking as regard parity, gestational age and risks factors for PPH [12]. Clinical examination was done included body mass index (BMI), blood pressure measurement and cervical examination to assess Bishop Score and the presenting part of the fetus.

We included pregnant women (37-42 weeks), with a live fetus and cephalic presentation who were passed spontaneously in labor and expected to normal vaginal delivery. Only women with normal progress of labour according to follow-up using modified WHO partograph were included in the study.

We excluded women with any risk factors for postpartum hemorrhage; such as over distended uterus by (multiple gestations, polyhydramnios or macrocosmic baby), grand multipara, women with hypertensive disorders, previous history of PPH, and history of scarred uterus.

A statistician, not otherwise involved in the study, prepared a computer generated randomization tables and placed the allocation data in serially numbered sealed envelopes. Each envelope had a card noting the intervention type inside. The envelopes opened only by the clinician according to the order of delivery of women. After acceptance of eligible women to participate in the study, we assigned them randomly in a 1:1 ratio to receive TA or placebo immediately after vaginal delivery. Once allocation had been done, it could not be changed.

All women received 10 IU oxytocin intramuscular after delivery of the fetus (the standard protocol of management of third stage of labor) [13]. Then participants were allocated to one of two groups; group I (tranexamic acid group) received TA (Kapron®, Amoun, Egypt) containing 1 g/10 ml. TA diluted with 20 ml of 5% glucose and given over a 5 minute period. Group II (placebo group) received 30 ml of 5% glucose over the same period of time. A single pharmacist was responsible for the packaging of both preparations, so neither the clinicians nor the patient knew the type of the preparation (double-blind study). A trained labor ward nurse opened the envelopes immediately after delivery and start IV infusion of the labeled bottle according to the intervention card.

The uterine arteries, subendometrial and intramyometrial blood flow were assessed by Doppler ultrasound two hours after delivery in both groups by level II sonographer who was blinded by the patient's intervention group. All scans were performed by the same sonographer.

Doppler signals obtained from the uterine arteries in the region of the lower uterine segment. The uterine artery was demonstrated by color Doppler technique with real time spectral analysis (Sonoline G60 S Ultrasound imaging system, Siemens, Germany). The high pass filter was set at 125 Hz and the uterine artery was obtained immediately after the crossing of the hypogastric artery. For examining the uterine arteries, the gate of the Doppler was positioned when good color signal were identified on the screen. The subendometrial and intramyometrial blood vessels demonstrated by color Doppler technique. The systolic/ diastolic ration (S/D), resistance index (RI) and pulsatility index (PI) of uterine arteries, subendometrial and intramyometrial blood vessels were calculated when three similar consecutive waves were obtained. The average value of the result of each index was calculated.

The primary outcome of this study was the effect of TA on Doppler indices of subendometrial and intramyometrial blood flow two hours after administration. The secondary outcomes included the Doppler changes in the main uterine artery, the volume of blood loss, the need for blood transfusion, need for additional uterotonics (methylergometrine or misoprostol), and lastly; the changes in hemoglobin and hematocrit values after delivery.

All study participants were followed up for 24 hours at Postpartum Ward. Blood loss volume (ml) was assessed after 2 hours of delivery by measuring the collected blood in the calibrated plastic drape which put under the patient during the third stage of labor. Doppler blood flow assessment of uterine arteries, subendometrial and intramyometrial blood vessels was done at the end of the second hour. The hemoglobin and hematocrit values were measured 24 hours after delivery.

The sample size calculation was based on the secondary outcome (volume of blood loss) during third stage of labor in vaginal delivery. Previous study estimated blood loss with use of placebo in third stage of labor was 350 ml and after use of TA was 260 ml with mean difference about 90 ml [14]. Using a two-sided chi-square (χ 2) test with an α of 0.05, a total sample size was calculated to be at least 190 patients in the 2 groups (95 in each arm) with 95% power to detect a 25% difference in the both groups. We increased the sample size to 100 women in each group to account for possible drop-out cases (Epi-info™, CDC, USA. 2016).

All data were analyzed using SPSS software Chicago, IL, USA, version 21. Comparison between categorical variables in both groups was done by Chi-square test and continuous variables were compared using Student T-test. We considered P value < 0.05 as a significant value.

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Results

Out of 267 eligible women delivered at our Labor ward, 200 women were consented to participate in the study. Consenting women were randomized into two groups: TA group and placebo group. Twelve women were excluded from the final analysis due to occurrence of severe PPH required surgical interventions either conservative measures or hysterectomy. The causes of exclusion as well as the study flowchart were shown in Figure 1.

Both groups were comparable regarding the baseline criteria (Table 1). As regard the primary outcome; we found a significant increase in the S/D, RI and PI in the subendometrial and intramyometrial blood vessels of the TA group more than placebo group (p=0.001). No significant differences between S/D, RI and PI of the uterine arteries between both groups (p=0.34, p=0.48 and p=0.25; respectively) after 2 hours of TA use (Table 2).

The mean estimated blood loss from the third stage of labor till two hours postpartum was significantly lower in the TA group than that in the placebo group (337.4±100.6 versus 436. 9±106.3 mL, respectively; p<0.001). More women in the placebo group (7.5%) than in the TA group (4.2%) required additional uterotonics but without statistically significant difference (p=0.37). There was no significant difference in the requirement for blood transfusion between the two groups (7.4% versus 10.7%, p=0.46) (Table 3).

As regard the haematocrit and hemoglobin levels before delivery; both groups were similar, however; after 24 hours of

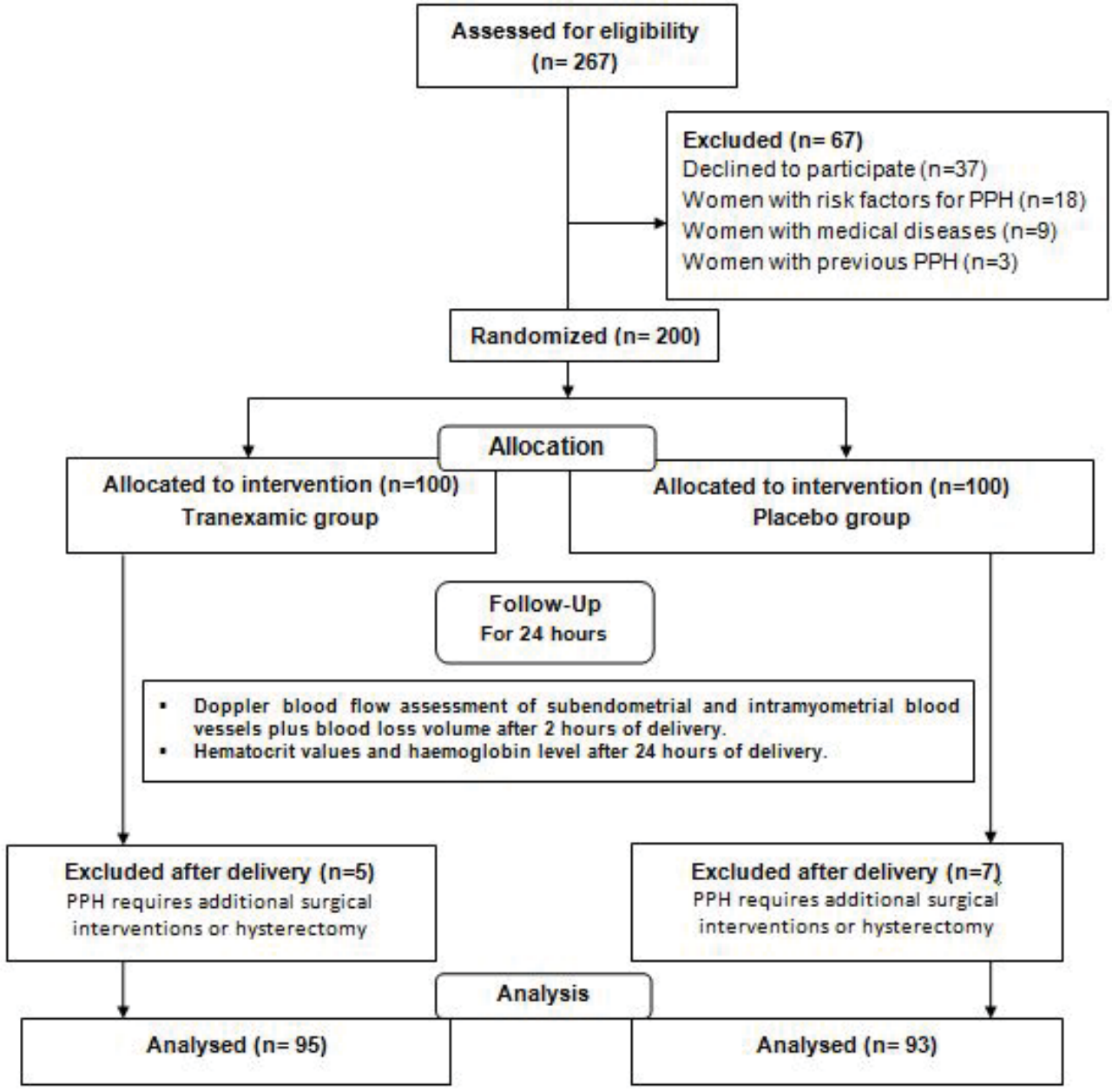

Figure 1: The study flow chart

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delivery both hematocrit and hemoglobin levels were higher in TA group than the placebo group (p<0.001) (Table 3).

Discussion

This is the first reported RCT investigating the effect of TA on uterine blood flow after vaginal delivery. The current study results proved that the use of TA increased blood flow resistance on intramyometrial and subendometrial blood vessels which is associated with decrease in the uterine blood flow and decrease the overall blood loss.

The main mechanism of action of TA is through its antifibrinolytic effect which makes it effective during the third stage of labor [15, 16]. During placental delivery there is an activation of the fibrinolytic system that lasts up to 10 hours postpartum. This leads to rapid degradation of fibrinogen and fibrin and increase in the activation of fibrin degradation products followed by further vaginal bleeding [17].

Although; TA is used profusely in gynecology, studying blood flow after use of TA is scarce in literature and no studies report its effect in uterine vasculature in pregnancy or delivery. An old study reported that TA significantly reduces uterine artery vascular resistance in women with dysfunctional uterine bleeding after 2 month of use [11]. This was a surprising effect and did not matching with the action of tranexamic acid in reducing menstrual blood loss. Small sample size of this study (24 patients) makes the credibility of the results questionable.

Another study may support our hypothesis reported by Ip et al. who found that with use TA, fibroid necrosis may occur. This is due to intralesional thrombosis of the small feeding vessels [18]. This is the same which we hypothesized and found that TA affected the small uterine vessels (intramyometrial and subendometrial blood vessels) but did not affect the main uterine artery.

TA could be used in addition to prophylactic uterotonics in the active management of third stage of labor after vaginal delivery [19]. A Cochrane systemic review (2015) on the use of TA for prevention of PPH concluded from the results of six RCTs that TA is an effective drug for preventing PPH especially in low risk women [7]. The results of our registered study might be included in their next reanalysis.

Three previous randomized controlled studies have shown that TA reduces PPH after vaginal delivery [14, 20, 21]. The same effect observed in our study. The mean blood loss volume was one of our secondary outcomes. There was significant reduction in blood loss volume in women who received TA versus placebo (337.4±100.6 versus 436.9±106.3 mL, respectively; p<0.001). These results were keeping in track with the study of Gungorduk et al. in which blood loss volume in women who received TA versus placebo (261.5±146.8 versus 349.9±188.85 mL, respectively; p<0.001) [14]. Also our results keep with Mirghafourvand et al, who reported blood loss greater than 500 mL was less common in women who received TA [21].

In our study, the volume of blood loss was estimated by measuring the amount of collected blood in the calibrated plastic drape under the patient. In all previous studies, mean blood loss volume was measured by weighing a sheet soaked from the end of the delivery till 2 hours after birth [14, 20, 21]. We think that using the drape is more accurate in estimating the amount of blood loss after delivery.

Although the use of additional uterotonics was less common in the TA group, no significant difference between both groups. Our results agreed with the results of Gungorduk, et al. and Mirghafourvand, et al. [14, 21] in which they reported that the use of uterotonics was less frequently in the women receiving TA versus placebo although they reported a statistical significant difference between both groups in both studies.

Table 1: The baseline characteristics of the study participants.

Characteristics	Group I TA group (n = 100)	Group II Placebo group (n= 100)	P-value
	Mean ± SD	Mean ± SD	
Age (years)	26.18 ± 5.37	27.18 ± 6.94	0.26
Body mass index (Kg/m^2)	25.6 ± 5.2	25.2 ± 5.5	0.67
Parity	2.17 ± 1.97	2.54 ± 1.98	0.19
Number of abortions	0.19 ± 0.52	0.33 ± 0.84	0.16
Gestational age (weeks)	38.7± 1.58	38.55 ± 1.63	0.48

TA; Tranexamic acid, SD; standard deviation

Table 2: The results of Pulsed-wave Doppler examination in both groups.

Pulsed-wave Doppler		Group I TA group (n = 95)	Group II Placebo group (n= 93)	P value
		Mean ± SD	Mean ± SD	
Subendometrial	S/D	3.40 ± 0.84	3.08 ± 0.82	<0.01*
	RI	0.70± 0.20	0.64 ± 0.16	<0.01*
	PI	1.08 ± 0.14	1.02 ± 0.11	0.001*
Intramyometrial	S/D	4.75 ± 1.09	4.11 ± 0.76	<0.001*
	RI	0.79 ± 0.07	0.72 ± 0.05	<0.001*
	PI	1.79 ± 0.35	1.66 ± 0.39	0.01*
Uterine artery	S/D	4.77 ± 1.49	4.97 ± 1.39	0.34
	RI	0.77 ± 0.12	0.78 ± 0.12	0.48
	PI	1.82 ± 0.55	1.93 ± 0.78	0.25

TA; Tranexamic acid, S/D; systolic/diastolic, RI; resistant index, PI; pulsatility index
* Statistical significant difference (P < 0.05)

Table 3: The secondary outcomes of the study.

		Group I TA group (n = 95)	Group II placebo group (n= 93)	P value
Mean blood Loss (mL) (mean ± SD)		337.4 ±100.6	436.9 ±106.3	<0.001*
Additional uterotonics, n (%)		4 (4.2%)	7 (7.5%)	0.37
Blood transfusion, n (%)		7 (7.4%)	10 (10.7%)	0.46
Haematocrit values (%)[a] (mean±SD)	Before	34.2± 2.5	33.9 ± 2.6	0.40
	After	30.4 ±1.4	27.2±1.6	<0.001*
Hemoglobin level (g/L)[a] (mean±SD)	Before	10.8 ±1.4	10.6± 1.2	0.28
	After	9.7 ±0.7	8.4 ± 0.9	<0.001*

TA; tranexamic acid, SD; standard deviation
* Statistical significant difference (P < 0.05)
[a] Haematocrit values and hemoglobin level from before delivery to 24 hours later on.

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Use of TA for preventing PPH can help in reduction in blood transfusion, which is expensive and may be not available in many settings. In the current study, there is a lower rate of blood transfusion in TA group but with no statistical significant difference. The current study showed higher hemoglobin and hematocrit levels 24 hours after delivery in TA group than the placebo group. Similarly, Gungorduk et al. [14] reported higher post-delivery hemoglobin (9.9±1.4 g/dL and 9.3±0.9 g/dL, P <0.001) and hematocrit levels (30.2±1.2 % and 29.0±1.3%, P < 0.001) in the TA than the placebo group.

The main strengths of our study were its design as a double-blind placebo-controlled randomized trial with standardized dosing and route of administration of TA. Also, the sonographer who performed the Doppler ultrasound examination was unaware of patients' intervention group and this eliminates the risk of bias of Doppler results. In addition, the same sonographer evaluated all study cases so no interobserver variation.

The study had some limitations. First, we lacked sufficient power to detect a difference in our primary outcome, as our sample size was based on an estimation of the secondary outcome (volume of blood loss). A larger sample size studies based on our results will be needed to prove our hypothesis. Second, our study didn't address the adverse effects of TA as it was not one of our study outcomes.

In conclusion, the use of TA with active management of the third stage following vaginal delivery increases the resistance in the intramyometrial and subendometrial blood vessels and reduced postpartum blood loss. This effect may be secondary to its antifibrinloytic action, paving the way to understand the direct action of TA on uterine vasculatures.

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