https://doi.org/10.15218/zjms.2022.024

Tranexamic acid for the prevention of postpartum hemorrhage and decreasing blood loss after vaginal delivery in high-risky parturient: A double-blind randomized controlled trial

Received: 02/12/2021 Accepted: 02/03/2022

Chro Sharef Hasan [1] Shahla Kareem Alalaf [2]* Sazgar Abdulla Khoshnaw [1]

Abstract

Background and objective: The purpose of this study was to examine the effectiveness of Tranexamic acid administered in the third stage of labor to reduce vaginal blood loss and prevent postpartum hemorrhage in women with high-risk factors for postpartum Hemorrhage.

Methods: A double-blind randomized placebo-controlled trial with two parallel groups was conducted in women scheduled to undergo vaginal delivery at the Maternity Teaching Hospital, Erbil city, Kurdistan Region, Iraq. The women were randomly assigned to receive tranexamic acid (97 women) or placebo (99 women) immediately after fetal delivery in the third stage of labor. The vaginal blood loss and the time from fetal to placental delivery were measured.

Results: The mean blood loss in the placebo group (Group 1) was 354.5 gram, which was considerably greater than the mean blood loss in the tranexamic group (Group 2), which was 284.4 gram. The incidence of postpartum hemorrhage (blood loss of ≥500 ml.) and (blood loss of ≥250 ml.) was significantly higher in G1 than G2. The length of the third stage of labor lasted 10.28 minutes in G1, which was longer than in G2, which lasted 7.82 minutes. Oxytocin was given to both groups as an active management of the third stage of labor.

Conclusion: In this single-center study, women with risk factors for postpartum hemorrhage who received tranexamic acid had lower postpartum blood loss and a shorter time for placental delivery than those women who received placebo. Larger multicenter randomized clinical trials are needed to generalize these findings.

Keywords: High-risk pregnancy; Oxytocin; Postpartum hemorrhage; Third stage labor; Tranexamic acid.

Introduction

Postpartum hemorrhage (PPH) and its complications are the main causes of maternal mortality and morbidity, predominantly in developing countries, which results in direct maternal death in up to 25% of cases.[1,2] Prevalence rate of PPH in the published literature varies widely from 3% to 15% of vaginal and cesarean deliveries.[3,4] The World Health Organization's recommendations for active management of the third stage of labor (AMTSL), 2012,recommend the use of uterotonics preferably oxytocin, for the prevention of PPH during the third stage of labor in all deliveries, including any women with risk factors of PPH.[5] It can be prevented by identifying women with its highest risk factors. Allowing for measures to be taken in AMTSL, the presence of experienced clinicians, and immediate access to resources such as oxytocin infusion and tranexamic acid (TA).

Numerous studies have identified the individual risk factors of PPH.[6] TA is a synthetic derivative of the amino acid

[1] Department of Obstetrics and Gynecology, Maternity Teaching Hospital, Erbil, Iraq.
[2] Department of Obstetrics and Gynecology, College of Medicine, Hawler Medical University, Erbil, Iraq.
Correspondence: shahla.kareem@hmu.edu.krd

https://doi.org/10.15218/zjms.2022.024

lysine, which exerts its antifibrinolytic effect and can improve the hemostatic mechanism in patients with bleeding.[7] An updated systematic review and meta-analysis to evaluate the safety and effectiveness of TA before cesarean delivery supported the evidence of a beneficial effect of TA in reducing blood loss and the need for blood transfusion in pregnant women undergoing cesarean section.[8] Regarding the effect of TA as a management medication for PPH, the currently available information suggests that the use of TA in patients with PPH would reduce the use of blood products, the need for surgical intervention, and possibly, blood loss from PPH after vaginal delivery and Caesarian Section.[8,9]

A Cochrane systematic review also concluded that TA reduces blood loss after vaginal and cesarean deliveries.[10] Evidence shows that management of the third stage of labor can directly affect important maternal outcomes such as blood loss, the need for manual removal of the placenta, and postpartum bleeding.[11] Blood loss of up to 500ml. in healthy women after vaginal delivery does not lead to negative maternal consequences; however, uncontrolled blood loss of >500ml. can be fatal.[12] The use of TA as a prophylactic in the third stage of labor results in a reduction of blood loss. Moreover, the significant differences in blood loss might not always convey a parallel clinical significance; for instance, in women with severe anemia or cardiovascular diseases, blood loss of as little as 200 ml. during delivery might be life-threatening. To lower the incidence rate of major morbidities and mortality due to PPH, it is vital to reduce blood loss in vaginal deliveries.[13] According to the authors' best knowledge, there is the scarceness of published articles on the use of TA in the third stage of labor combined with AMTSL to decrease blood loss, further more, these studies had major methodological shortcoming including the selection of participants.[14,15] The French TA for preventing PPH following a vaginal delivery (TRAAP) trial was a large multicenter double-blind randomized controlled trial conducted on 3891 women who underwent vaginal delivery. However, the inclusion criteria were women at a term with a singleton live fetus and did not concentrate on a risky group of women for PPH.[16] This study was conducted in women with significant risk factors of PPH to investigate whether the prophylactic administration of TA as a component of AMTSL would decrease the incidence of PPH and blood loss vaginally. Furthermore, we proposed that adding TA could decrease the time to placental delivery following decreased blood loss vaginally.

Methods

Design and Study Setting

A double-blind randomized placebo-controlled trial with two parallel groups was conducted in women scheduled to undergo a vaginal delivery at the Maternity Teaching Hospital, Erbil city, Kurdistan Region, Iraq, between February 1, 2020, and October 10, 2020. The women were randomly assigned to receive TA or placebo immediately, along with the administration of the uterotonic agent, after fetal delivery in the third stage of labor, and their data were collected. Blood loss was measured during two periods, from fetal to placental delivery and from placental delivery to 2 hours after.

Participants

Eligible participants were women aged ≥18 years, all women intend to deliver vaginally, who had a singleton pregnancy at ≥37 weeks of gestation, having a risk factor for PPH: Grand multiparity defined as having ≥ 5 deliveries more than 20 weeks gestation,[17] a twin pregnancy, polyhydramnios, a previous history of PPH, a previous history of cesarean section, suspected macrocosmic fetus (defined as birth weight greater than 4000gm.),[18] prolonged labor (defined as women in an active stage of labor lasting more than 12 hours,[19] HELLP (hemolysis, elevated liver

https://doi.org/10.15218/zjms.2022.024

enzymes, and low platelets) syndrome, been receiving low-molecular-weight heparin and aspirin during pregnancy, and agreed to participate. Patients with intrauterine fetal death, history of thromboembolic disease, current, or previous history of heart disease, renal and liver disorders, history of seizure or epilepsy, having thrombocytopenia, thrombophilia, placenta previa, placental abruption, or refusal to participate were excluded from the trial. An obstetrician (one of the authors) provided the women with information about the trial during early labor when the obstetrician considered that vaginal delivery was likely (≥4 cm of cervical dilation). The women confirmed participation at the labor ward and provided written informed consent.

Randomization and Procedures

Eligible women were randomly assigned in a 1:1 ratio to receive 1 gm of TA or placebo (glucose water) administered intravenously. A computer-generated randomization code list was created using the program accessible at www.randomization.com. Two blocks of randomly varied sizes were used for the two arms. An independent statistician generated the randomization numbers. TA and placebo were prepared at a single site and by the same person (an independent pharmacist in the labor ward pharmacy). They were numbered and labeled in infusion bags containing 30-cc syringes labeled as bag A (Experimental Group), containing 1gm/10ml. TA diluted with 20ml. of 5% glucose water, and bag B (Placebo Group), containing 30 ml. of 5% glucose water, each with a 30 ml./vial of the trial regimens (1 gm of TA or glucose water) depending on the randomization number. Neither the investigators nor the participants were aware of the trial-group assignments. At the end of the delivery, the randomized number of the bag was applied to the questionnaires containing information about the patient and the details of the procedures. A statistician in the College of Medicine of Hawler Medical University independently analyzed the data until the trial was completed and the database was closed. All the participating women, researchers, and data handlers were blinded to the individual allocations throughout the study.

Interventional Drug and Grouping

The participants in the interventional group received two ampules of 5 ml. TA added to 20 ml. of 5% glucose water (TRENAXA 500 mg, Macleod Pharmaceuticals Ltd., India) and the placebo group received 30ml. of glucose water 5% [Glucose (B Braun) 50 mg/ml.]

Trial Procedure

The intravenous trial regimen in both groups was administered slowly (over 60 seconds) immediately after fetal delivery, coinciding with the routine prophylactic intravenous injection of oxytocin and clamping of the umbilical cord. All the other aspects of the management of the third stage of labor were the same in the two groups. The duration of the third stage was measured and recorded in minutes starting from the injection of both groups and placental delivery. During the fetal delivery, a sterile disposable pad of known weight was placed beneath the patient's buttocks to collect blood loss and then weighed. The estimated blood loss is combined blood loss from the two periods during which postpartum bleeding was measured, from fetal to placental delivery and from placental delivery to 2 hours after childbirth. Blood soaked gauzes, gowns, sheets, and tampons were all weighed before and after use (when blood-soaked), and blood loss was estimated using the formula as follows:[20]

Quantity of blood (ml.) = (weight of used materials − weight of materials before use)/1.05.

Postpartum Hemorrhage was defined as the loss of 500 ml or more of blood from the genital tract within 24 hours of the birth of the newborn, minor PPH is defined as vaginal blood loss of 500–1000 ml., while major postpartum hemorrhage is defined as blood loss of more than 1000 ml.[21,22] The study is randomized, and

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both groups get the same care. Maternal observations were recorded every 15 min. in the first hour and every 30 min. in the second hour after delivery, and these data were recorded.

Sample Size Estimation

The sample size was estimated using the openEpi.com, Version 3, open-source calculator computer program. The information entered in the program was based on the results of a pilot study involving 15 women in each study group [placebo (Group 1) and TA (Group 2)]. The mean (±SD) blood loss in group 1 was 176.467 ± 39.169 mL, and that in Group 2 was 162.4 ± 13.081 ml. The power was set at 90%, and the confidence interval (2-sided) at 95%. Accordingly, the estimated sample size for the clinical trial was 100 in each group.

Ethical Standards

The experimental protocol of this study was approved by the ethics committee of the Kurdistan Board of Medical Specialty Research Ethics (No. 1398; October 1, 2019). This study was conducted following the ethical standards of the institutional review committee of the Maternity Teaching Hospital (Document no. 1/9B; October 22, 2019) and the Code of Ethics of the World Medical Association (Declaration of Helsinki 2013; ClinicalTrials.gov ID: NCT04201951.

All participants were assured that confidentiality would be maintained and that information obtained from them would be used for research purposes only. All study subjects agreed to participate in the trial voluntarily and provided written informed consent which included also approval to publish the data in a journal.

Statistical Analysis

Data were analyzed using the statistical package for social sciences (version 25). The Student *t*-test for two independent samples was used to compare two means. Multiple regression analysis was used for the prediction of the amount of blood loss (or the prediction of the time of the third stage of labor) as dependent variables and for adjustment for other factors that affect the dependent variables. Factors found to be significantly associated with blood loss were entered in the regression model. The *P* value of ≤ 0.05 was considered as statistically significant.

Results

A total of 234 women in labor were evaluated for eligibility, of which 38 were excluded because of either not meeting the inclusion criteria or declining to participate in the trial. A total of 196 women were randomized 1:1 into two groups, of whom 97 were allocated to the TA group (Group2) and 99 were allocated to the placebo group (Group 1) as in Figure 1. All randomized participants received the allocated treatment and no woman was lost to follow up.

https://doi.org/10.15218/zjms.2022.024

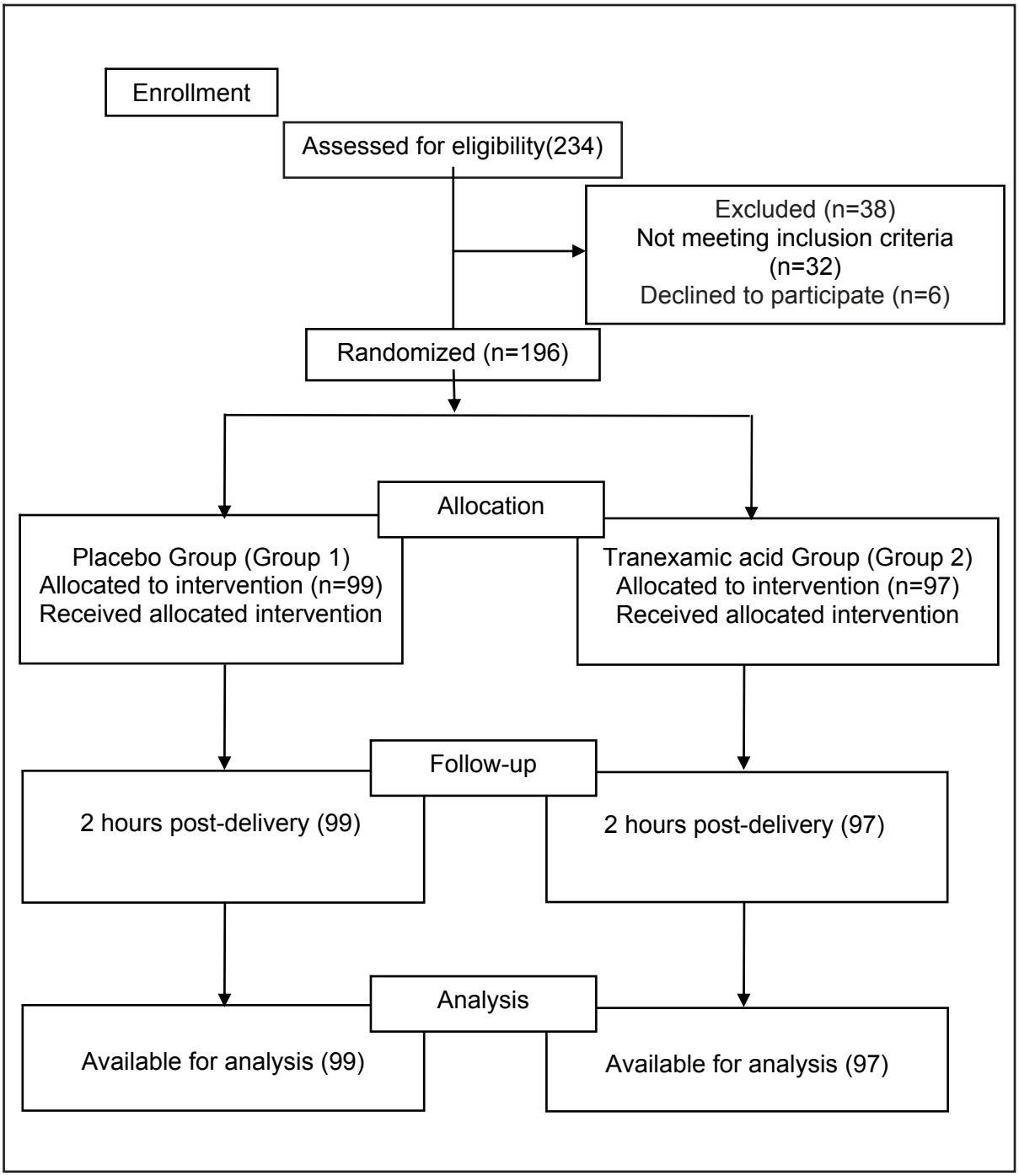

Figure 1 Flowchart of the study

https://doi.org/10.15218/zjms.2022.024

There was no significant difference between the two groups regarding basic characters. Their mean age was 32.0 ± 6.6 years in the Group 1 versus 31.48± 6.7 years in Group 2, the mean gestational age was 38.6±0.9 weeks versus 38.4±0.9 weeks in Group 1 and Group 2 respectively. The same for the mean parity was 4.1±1.9 in Group 1 versus 3.9±1.8 in Group 2. The incidence of mild postpartum hemorrhage was significantly higher (13.1%) in Group1 than in Group 2 (4.6%) (*P* = 0.001). All were a mild form of postpartum hemorrhage and did not require any uterotonics to manage the bleeding. The mean blood loss of Group 1 was significantly (*P* <0.001) higher than that of Group 2, as presented in Table1 and Figure 2.

The mean blood loss didn't differ significantly among the following factors: previous history of post-partum hemorrhage, macrosomic baby, and previous history of Cesarean section, while the mean blood loss was significantly higher among those with grand multiparity, and among those with no polyhydramnios.

Table 1 Mean blood loss among the studied factors

	No.	Mean blood loss (gm.)	(±SD)	*P*
Intervention				
Group 1 (Placebo)	99	354.5	(±97.9)	< 0.001
Group 2 (TA)	97	284.4	(±105.1)	
Previous history of PPH†				
Yes	27	338.4	(±78.7)	0.222
No	169	316.9	(±110.9)	
Prolonged labor				
Yes	1	250.0	(±0.0)	NA
No	195	320.2	(±107.3)	
Grand multiparity				
Yes	75	344.6	(±104.3)	0.010
No	121	304.5	(±106.5)	
Polyhydramnios				
Yes	22	260.4	(±97.6)	0.005
No	174	327.4	(±106.2)	
Macrosomic baby				
Yes	21	308.4	(±66.6)	0.450
No	175	321.2	(±111.1)	
Previous history of CS‡				
Yes	76	329.3	(±126.9)	0.358
No	120	313.8	(±92.6)	

† PPH: Postpartum Hemorrhage; ‡CS: Cesarean section

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Furthermore, as compared to Group 1 and Group 2 experienced reduced vaginal blood loss (less than 250 ml) in the third stage of labor (*P* <0.001) as shown in Figure 2.

Table 2 shows that women of Group 2 and women with polyhydramnios had significantly less amount of blood loss (*P* <0.001 and *P* = 0.048 respectively) irrespective of the other factors. The regression coefficient (B) was -62.33 for Group 2 and -47.27 for the polyhydramnios.

Table 2 Multiple regression analysis where the dependent variable is vaginal blood loss

	Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
	B	SE	Beta	t	*P*	Lower Bound	Upper Bound
(Constant)	350.143	13.230		26.466	<0.001	324.048	376.238
Intervention TA	-62.336	14.863	-0.292	-4.194	<0.001	-91.652	-33.020
Grand multiparity	15.276	15.785	0.069	0.968	0.334	-15.859	46.410
Polyhydramnios	-47.277	23.715	-0.140	-1.994	0.048	-94.053	-0.502

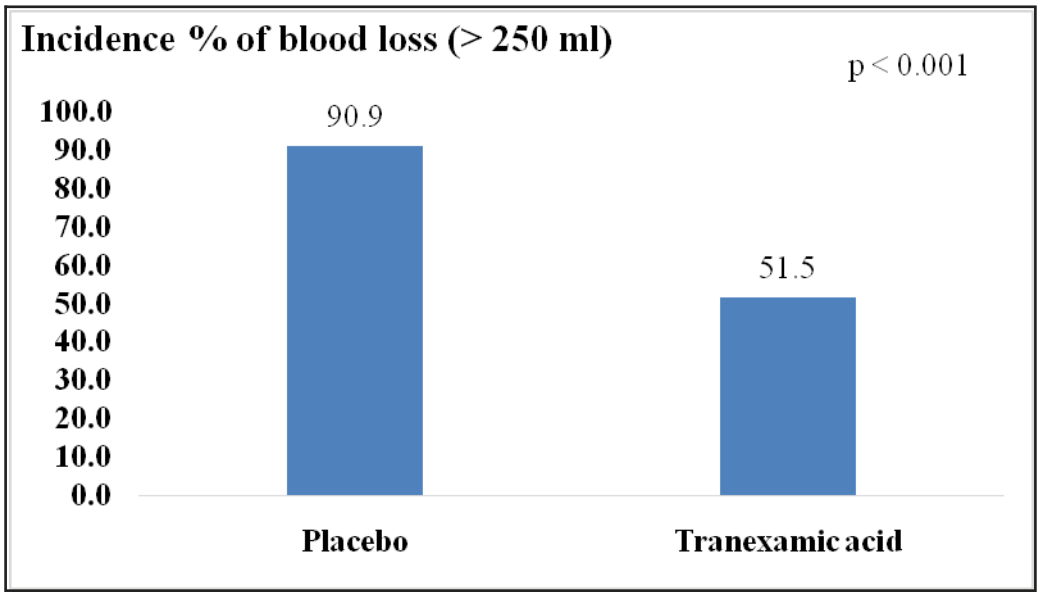

Figure 2 Blood loss (> 250 ml) in the two study groups

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Regarding the meantime of the third stage of labor, it was significantly longer in Group 1 (10.28±1.33 minutes) compared with the Group 2 (7.82±1.54 minutes). It was significantly longer among those with grand multiparity compared with those with less parity as in Table 3.

Discussion

In this clinical trial involving women who delivered vaginally and were at risk of postpartum hemorrhage, all those who received prophylactic TA combined with ordinary AMTS had significantly lower the incidence rates of primary PPH (≥500 ml.) than those who received placebo (glucose water plus oxytocin). Furthermore, the incidence of vaginal blood loss of >250 ml. in the third stage of labor was significantly lower in Group 2. Many previous studies used TA to prevent PPH and confirmed the same finding as in the present study that TA is a complementary component in the management of the third stage of labor for preventing PPH.[16,23,24] This trial was restricted to pregnant women who had high-risk factors of PPH; The women with lower risks did not include in the routine management of the third stage of labor. Most other previous studies with the same

Table 3 Mean length of the third stage of labor among the studied factors

	No.	Mean length of the third stage (min.)	(±SD)	*P*
Intervention				
Group 1 (Placebo)	99	10.28	(±1.33)	< 0.001
Group 2 (TA)	97	7.82	(±1.54)	
Previous history of PPH†				
Yes	27	9.26	(±1.99)	0.570
No	169	9.04	(±1.88)	
Prolonged labor				
Yes	1	9.00	(±0.0)	NA
No	195	9.07	(±1.90)	
Grand multiparity				
Yes	75	9.61	(±1.90)	0.001
No	121	8.73	(±1.82)	
Polyhydramnios				
Yes	22	8.50	(±1.85)	0.137
No	174	9.14	(±1.89)	
Macrosomic baby				
Yes	21	8.95	(±1.69)	0.771
No	175	9.08	(±1.92)	
Previous history of CS‡				
Yes	76	8.93	(±1.90)	0.438
No	120	9.15	(±1.89)	

† PPH: Postpartum Hemorrhage; ‡CS: Cesarean section

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objectives included generally women who delivered, some of whom had risk factors.[4,5,10,16] Women with high-risk factors are more prone to postpartum hemorrhage. The time of the third stage of labor to successfully deliver the placenta in the TA group was surprisingly significantly shorter than that in the routine group. Larger sample size trials are needed to confirm this property of TA. Postpartum blood loss was determined objectively by estimating the amount of blood loss by weighing all soaked diapers and mattresses and weighing any clots. Quantitative methods of measuring obstetric blood loss using gravimetric methods have been shown to be more accurate than visual estimation methods.[25] However, previous studies found that vomiting or nausea was more frequent in the TA group than in the placebo group, and both features were not reported to be severe.[16,24] The risk factor of venous thromboembolism (VTE) associated with the use of TA was not examined, as published double-blind randomized placebo-controlled trials in multicenter settings were conducted found that adverse events, including VTE, did not differ significantly between the groups.[16,18] This trial has some limitations. It was not a multicenter trial; thus, its results were limited to the current hospital and could not be generalized to other institutions. This also suggests the need for future studies that include many settings but use the same protocol. Although the study sample was estimated into 2 groups of participants according to a pilot study using TA and placebo, still the sample size was small and the randomization may be affected by an inability to produce equal distributions of confounding factors.

However, the basic characters included the gestational age which was already specified to 37 weeks and more and grand multiparity which was a risk factor for postpartum hemorrhage that was difficult to be matched. Thus, to generalize the results, a larger sample size, and multicenter research are required. The trial did not have the power to assess the effect of TA on the incidence rates of severe PPH, although none of the women included lost ≥1000 ml. of blood vaginally after delivery in both groups of participants. The grand multiparous women and those with polyhydramnios were the two at-risk groups that have more responses from TA administration than the other risk groups in losing blood vaginally after delivery. This study suggest that if randomized controlled trials could be conducted in the future with larger sample size and with each risk group included separately, important data on the effect of TA in each risk group may be obtained.

Conclusion

This study concluded the women with risk factors for postpartum hemorrhage who received TA had lower postpartum blood loss and a shorter time for placental delivery than those women who received placebo. A larger multicenter randomized clinical trial is needed to generalize these findings

Funding

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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