Tranexamic Acid Administration for the Prevention of Blood Loss After Vaginal Delivery in a High-Risk Pregnancy: A Double-blind Randomized Controlled Trial

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Research Article

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Abstract

Purpose: The purpose of this study was to examine the effectiveness of tranexamic acid administration for the prevention of postpartum hemorrhage in women with high-risk pregnancies. Tranexamic acid, with the recommended oxytocin, was administered in the third stage of labor to reduce vaginal blood loss and prevent 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) with oxytocin immediately after fetal delivery in the third stage of labor. We measured vaginal blood loss from fetal to placental delivery and the time from fetal to placental delivery.

Results: The mean blood loss in the oxytocin alone group (group 1) was significantly higher than that in the tranexamic and oxytocin group (group 2). The incidence of postpartum hemorrhage (blood loss of ≥500 mL) and blood loss of ≥250 mL was significantly higher in group I than in group 2. The length of the third stage of labor was significantly longer in group 1 than in group 2.

Conclusions: In the women who delivered vaginally and had risk factors of postpartum hemorrhage, the incidence rates of the primary outcome of postpartum hemorrhage and blood loss of <250 mL, and the time to placental delivery were significantly lower in the women who received tranexamic acid with active management of third stage labor than in those who received placebo.

Trial registration number: ClinicalTrials.gov ID: NCT04201951, December 17, 2019

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].

The prevalence rate of PPH in the published literature varies widely from 3–15% of vaginal and cesarean deliveries [3, 4]. The World Health Organization's recommendations for active management of the third stage of labor (AMTSL), 2012, recommends 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]. PPH can be prevented by identifying women with the highest risk of PPH, allowing for measures to be taken for 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 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 prior to 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 CS [8, 9]. A Cochrane systematic review also concluded that TA reduces blood loss after vaginal and cesarean deliveries [10].

Evidence shows that management of 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 500 mL in healthy women after vaginal delivery does not lead to negative maternal consequences; however, uncontrolled blood loss of > 500 mL can be fatal [12].

The use of TA as a prophylactic in the third stage of labor results in a reduction of blood loss. However, 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].

Studies on the use of TA in the third stage of labor combined with AMTSL to decrease blood loss and prevent PPH are controversial in their methodology, as some were conducted in women with low risk of PPH [14, 15] and differed in their time of TA application in relation to delivery and the mode of receiving oxytocin [15, 16], or the studies included both participants who delivered by CS and those who had vaginal deliveries [17, 18].

This study was conducted in women with significant risk factors of PPH. TA was administered early during the third stage of labor with the recommended oxytocin as components of AMTSL for reducing vaginal blood loss and preventing PPH. Furthermore, we propose that adding TA as a component of AMTSL could decrease the time to placental delivery.

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 a 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 who had a singleton pregnancy at ≥ 35 weeks of gestation, grand multiparity, a twin pregnancy, polyhydramnios, a previous history of PPH, a previous history of cesarean section, suspected macrocosmic fetus, prolonged labor, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, been receiving low-molecular-weight heparin and aspirin during pregnancy, an intention to deliver vaginally, 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, placenta previa, and 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 g 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 a 30-cc syringes labeled as bag A (experimental group), containing 1 g/10 mL tranexamic acid diluted with 20 mL 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 g of TA or normal saline) 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). The placebo group received 30 mL of glucose water 5% [Glucose (B Braun) 50 mg/mL] and oxytocin (5 IU/mL, 2 mL; Gland Pharma Limited).

Trial procedure

The intravenous trial regimen was administered slowly (over a period of 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 injection of both medications (oxytocin + TA and oxytocin + glucose water) 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. Blood loss was measured during two periods, 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 of Gai et al. [14] as follows: quantity of blood (mL) = (weight of used materials − weight of materials before use)/1.05.

Maternal observations were recorded every 15 minutes 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 computer program. The information entered in the program was based on the results of a pilot study involving 15 women in each study group (oxytocin vs. oxytocin + TA). 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, at 95%. Accordingly, the estimated sample size for the clinical trial was 100 in each group.

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 regressions were used where the dependent variables were the amount of blood loss and the duration of the third stage of labor. A p value of ≤ 0.05 was considered 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 and 99 were allocated to the placebo group (Fig. 1).

The sample included 196 women. Their mean (± SD) age was 32.0 ± 6.6 years, with a median of 32.0 years and range of 19 to 47 years. Around half (45.9%) of the women were aged 25 to 34 years (Table 1). The gestational age was > 38 weeks in 53.1% of the women, and only 4.6% were nulliparous (Table 1).

Table 1
Basic characteristics of the study sample

	n	(%)
Age (years)		
< 25	32	(16.3)
25–34	90	(45.9)
≥ 35	74	(37.8)
Mean (± SD)	32.0	(± 6.6)
Gestational age (weeks)		
35–38	92	(46.9)
> 38	104	(53.1)
Parity		
Nulliparous	9	(4.6)
Multiparous 1–4	112	(57.1)
Grand multiparous ≥ 5	75	(38.3)
Total	196	(100.0)

The patients in group 1 (n = 99) were given oxytocin alone, while those in group 2 (n = 97) were given TA in addition to oxytocin. The mean blood loss in group 1 (354.5 mL) was significantly ($p < 0.001$) higher than that in group 2 (284.4 mL), as shown in Table 2. The mean blood loss did not differ significantly among the following factors: previous history of PPH ($p = 0.222$), macrosomic fetus ($p = 0.450$), and previous history of cesarean section ($p = 0.358$), while the amount of blood loss was significantly higher in those with grand multiparity ($p = 0.010$) and no polyhydramnios ($p = 0.005$; Table 2).

Table 2
Differences in mean blood loss among the studied factors

	n	Mean blood loss (g)	(± SD)	p
Intervention				
Oxytocin	99	354.5	(± 97.9)	< 0.001
TA + oxytocin	97	284.4	(± 105.1)	
Pervious 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)	
Multiparous				
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 fetus				
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)	
TA: Tranexamic acid, PPH: Postpartum hemorrhage, CS: Cesarean section				

The length of the third stage of labor was significantly ($p < 0.001$) long in group 1 (10.28 minutes) as compared with that in group 2 (7.82 minutes). It was significantly ($p = 0.001$) longer in those with grand multiparity (9.61 minutes) than in those with no grand multiparity (8.73 minutes). Table 3 shows no significant association between the length of the third stage of labor with the following variables:

previous history of PPH (p = 0.570), polyhydramnios (p = 0.137), macrosomic fetus (p = 0.771), and previous history of cesarean section (p = 0.438).

Table 3
Differences in the mean length of the third stage of labor among the studied factors

	n	Mean length of the third stage (min)	(± SD)	p
Intervention				
Oxytocin	99	10.28	(± 1.33)	< 0.001
TA + oxytocin	97	7.82	(± 1.54)	
Pervious 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 fetus				
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)	
TA: Tranexamic acid, PPH: Postpartum hemorrhage, CS: Cesarean section				

The incidence of PPH was significantly (p = 0.025) higher (13.1%) in the oxytocin group (group 1) than in the TA group (4.1%; group 2; Fig. 2). A same pattern can be observed in Fig. 3 where the incidence of

blood loss of > 250 mL was 90.9% in group 1 and 51.5% in group 2 (p < 0.001).

Table 4 shows that the women in the TA group and those with polyhydramnios had significantly less amount of blood loss (p < 0.001 and p = 0.0.048, respectively) irrespective of the other factors. The regression coefficient (*B*) was − 62.33 for the TA group and − 47.27 for the women with polyhydramnios.

Table 4
Multiple regression analysis with amount of blood loss (grams) as dependent variable

	Unstandardized Coefficients		Standardized Coefficient			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 tranexamic acid	−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

Regarding the duration of the third stage of labor, Table 5 shows that when TA was administered, the duration of the third stage of labor significantly decreased (p < 0.001; *B* = − 2.39).

Table 5
Multiple regression analysis with duration of the third stage of labor (minutes) as dependent variable

	Unstandardized Coefficients		Standardized Coefficient	*t*	p	95% Confidence Interval for *B*	
	B	Standard Error	Beta			Lower Bound	Upper Bound
(Constant)	10.152	0.182		55.820	< 0.001	9.793	10.510
Intervention tranexamic acid	−2.394	0.212	−0.634	−11.268	< 0.001	−2.813	−1.975
Grand multiparity	0.260	0.219	0.067	1.188	0.236	−0.171	0.691

Discussion

In this clinical trial involving women who delivered vaginally and were at risk of PPH, all those who received prophylactic oxytocin and TA with oxytocin had significantly lower incidence rates of 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 the TA group.

Many previous studies used TA to prevent PPH and confirmed the same finding as in the present study that TA is a complementary component of the management of the third stage of labor for preventing PPH [18–20].

This trial was restricted to pregnant women who had high-risk factors of PPH; we did not include women with lower risks in the routine management of the third stage of labor. Most other previous studies with the same objectives included generally women who delivered, some of whom having risk factors [4, 5, 10, 15–17]. We assumed that women with high-risk factors are more prone to PPH.

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. This raises the concern whether TA can be used for this purpose besides decreasing vaginal blood loss after delivery. More 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 [18].

We did not examine the side effects of TA. 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 [19, 20]. We also did not examine the risk factor of venous thromboembolism (VTE) associated with the use of TA, as the authors of a double-blind randomized placebo-controlled trial conducted in 20000 women who had delivered and received either TA or placebo with a clinical diagnosis of PPH concluded that adverse events, including VTE, did not differ significantly between the groups [6].

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 using the same protocol.

Although we estimated the sample size into two groups of participants according to a pilot study using TA and placebo, still the sample size was small. 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

Another limitation is that we included all risk groups of PPH as one group, while the grand multiparous women and those with polyhydramnios were the two at risk groups that would benefit more from TA administration than the other risk groups. We assumed that if a trial could be conducted in the future with a larger sample size and with each risk group included separately, important data on the effect of TA in each risk group may be obtained.

In conclusion, the women with vaginal delivery and risk factors of PPH who received TA at the time of AMTSL had significantly decreased incidence rates of PPH and blood loss of > 250 mL and time to placental delivery than those who received placebo.

Declarations

Funding

This study received no funding support.

Conflicts of interest

The authors declare that they have no conflict of interest.

Availability of data and materials

The information provided in this article, including all raw data, are available from the corresponding author on reasonable request to any scientist wishing to use them for non-commercial reasons at a condition that participant

Code availability

Not applicable

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 in accordance with 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)

Authors' contribution

CS Hasan: Data collection, Manuscript writing and editing

SK Alalaf: Project development, Manuscript writing

SA Khoshnaw: Manuscript writing and editing, Project development

Consent to participate

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.

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Figures

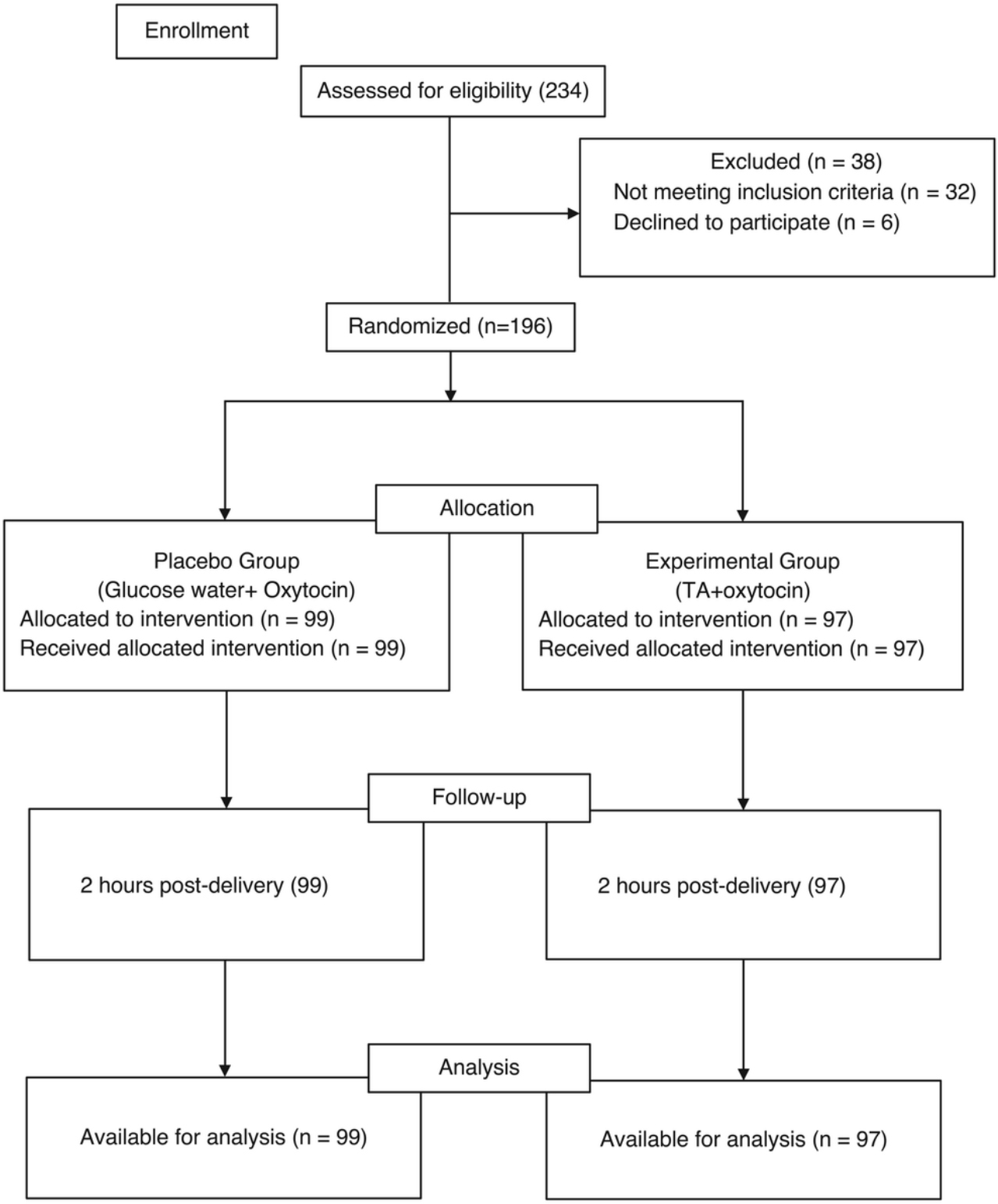

Figure 1

Flowchart of the study

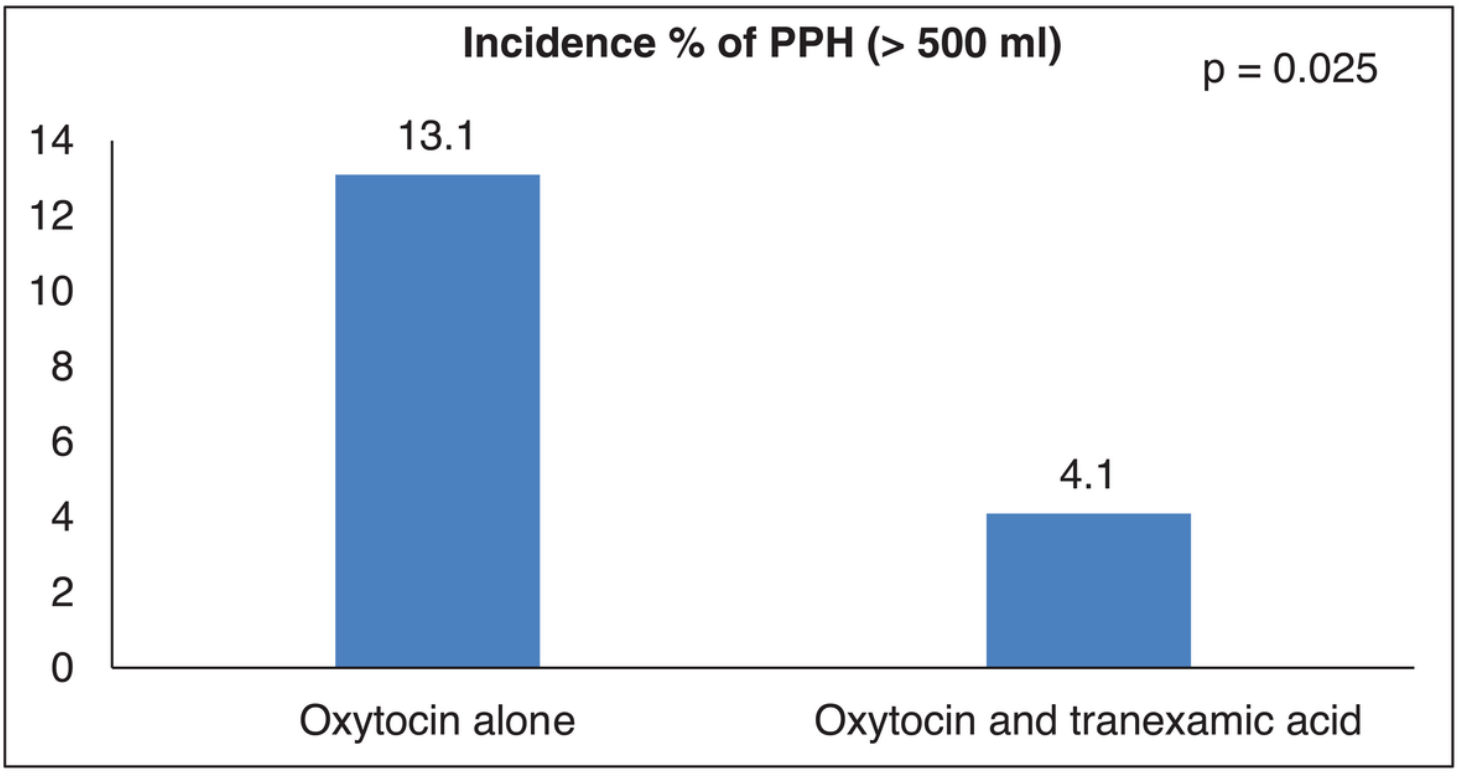

Figure 2

Incidence of postpartum hemorrhage (>500 mL) in the two study groups

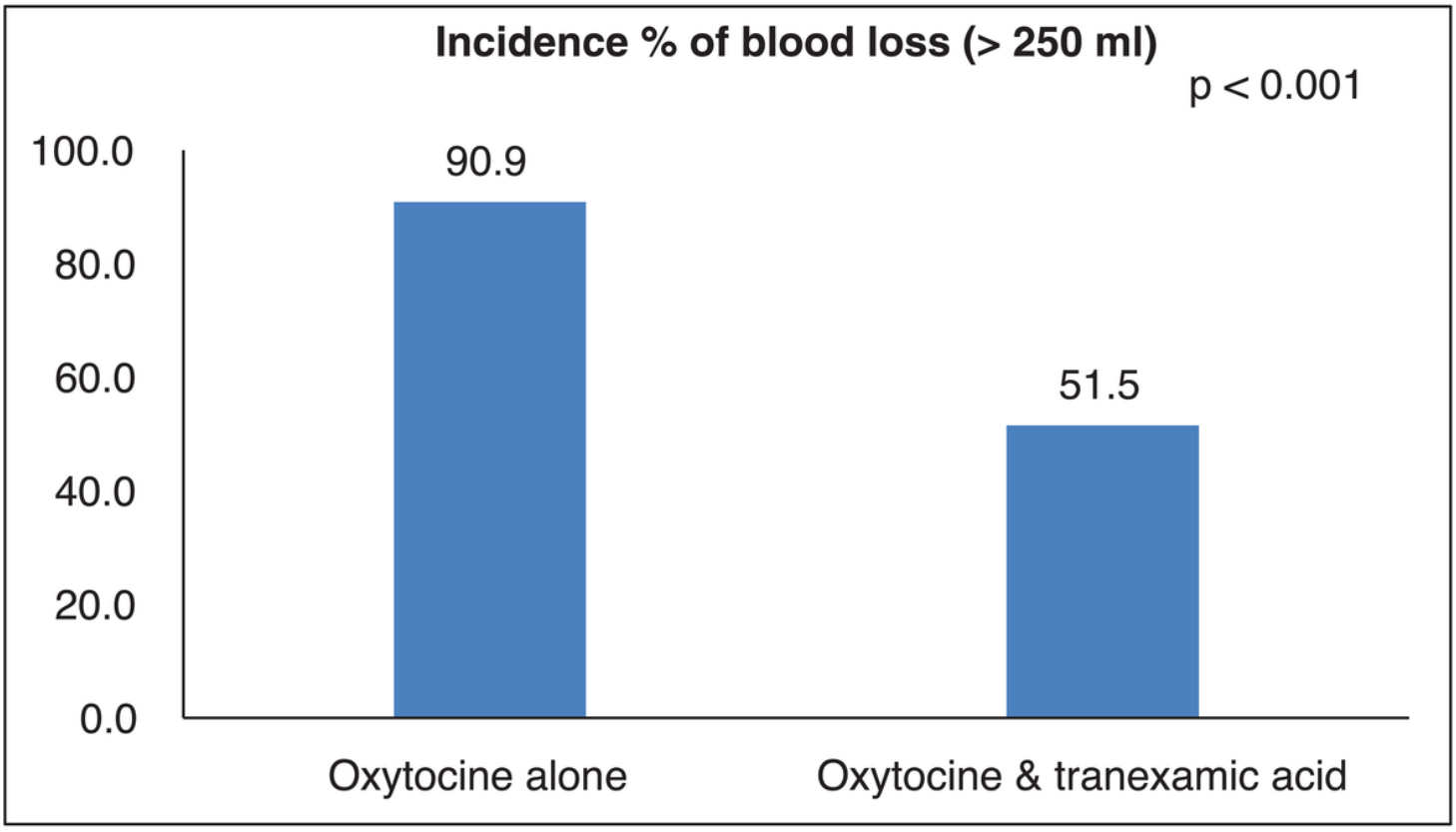

Figure 3

Incidence of blood loss (>250 mL) in the two study groups