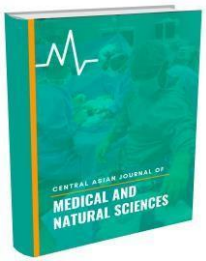

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Article

The Effect Of Prophylactic Intravenous Tranexamic Acid On Blood Loss After Vaginal Delivery In Women At Low Risk Of Postpartum Hemorrhage

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Abstract: To determine the impact of prophylactic tranexamic acid (TA) on both calculated and observed blood loss in women undergoing vaginal delivery who are at low risk of postpartum hemorrhage. This double-blind randomized controlled trial involved 140 women with singleton pregnancies, who were randomly assigned to either receive a placebo or one gram of intravenous tranexamic acid (TA) in combination with 10 IU of oxytocin at the time of fetal delivery. Blood loss was estimated based on hematocrit levels measured before delivery and 12–24 hours postpartum. The blood loss was further quantified by measuring the time elapsed from fetal delivery to placental expulsion and from placental expulsion to the conclusion of the second hour after childbirth. The intervention group experienced significantly lower measured blood loss from placental delivery to two hours postpartum (68 (39) vs. 107 (53) mL, $P < 0.001$) and reduced mean (SD) calculated total blood loss (516 (312) vs. 655 (400) mL, $P = 0.036$) compared to the control group. However, there was no notable difference between the groups in blood loss from fetal delivery to placental expulsion. Additionally, the frequency of estimated blood loss exceeding 1000 mL was lower in the TA group (8% vs. 19%, $P = 0.048$). In conclusion, prophylactic use of tranexamic acid benefits women at low risk of postpartum hemorrhage by effectively reducing blood loss after vaginal delivery. Its preventive use could enhance maternal health and mitigate issues related to excessive blood loss.

Keywords: Tranexamic Acid, Postpartum Hemorrhage, Vaginal Delivery, Low-Risk Women

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1. Introduction

Postpartum hemorrhage (PPH) and its associated complications significantly contribute to maternal mortality and morbidity, responsible for roughly 25% of direct maternal fatalities, particularly in low-resource environments [1,2]. PPH is characterized by excessive bleeding of 500 mL or more within the first 24 hours following childbirth [3]. The primary underlying causes of PPH include uterine atony, trauma to the genital tract, retained placental tissues, and disorders affecting maternal coagulation [4].

Approaches to prevent primary postpartum hemorrhage (PPH) include the use of pharmacological treatments such as uterotonic drugs like oxytocin and ergometrine, alongside non-pharmacological methods like uterine massage [5]. Antifibrinolytic medications have been employed to minimize bleeding in various surgical contexts [6]. Tranexamic acid (TA), an antifibrinolytic drug, functions by inhibiting the lysine-binding sites of plasminogen on fibrin, thereby preventing clot breakdown and mitigating excessive or recurring bleeding [7,8,9]. Additionally, TA may help neutralize the effects of

plasminogen and fibrin degradation products released during the detachment of the placenta [10,11,12].

Tranexamic acid (TA) has been reported to cause potential side effects such as nausea, vomiting, diarrhea, dizziness, seizures, and visual disturbances [14]. Some research has highlighted concerns regarding the increased risk of thrombosis and seizures associated with its use [14]. This study seeks to assess the impact of administering 1 gram of intravenous TA as part of the active management of the third stage of labor. The primary outcome being evaluated is the estimated postpartum blood loss, while secondary outcomes include actual measured blood loss, changes in hemoglobin and hematocrit levels, duration of the third stage of labor, and the need for additional uterotonic medications following vaginal delivery.

2. Materials and Methods

Al Batool institution, a tertiary educational institution in Iraq, hosted this double-blind randomized controlled experiment in 2023. Every participant gave written informed consent, and the study was approved by the ethical committee of Diyala University of Medical College. Midwives, obstetric assistants, and senior obstetricians frequently perform episiotomies, which are performed in over 90% of first vaginal deliveries and 40% of second and third deliveries in hospitals.

The inclusion criteria for the study were women aged 18 to 38 years who planned to deliver vaginally, had a singleton pregnancy with a cephalic presentation between 37 and 42 weeks of gestation, and had normal blood pressure (< 140/90 mmHg). Having five or more pregnancies (grand multiparity), having undergone prolonged oxytocin-induced labor for at least 12 hours, having had a cesarean delivery or any uterine surgery in the past, having uterine fibroids, and having a history of cardiac, liver, kidney, or neurological disorders were among the exclusion criteria chosen for the study.

Additionally, those having a history of blood disorders, diabetes, pre-eclampsia, postpartum hemorrhage in previous pregnancies, coagulation or thromboembolic diseases, or present difficulties such hemorrhage, placental abruption, macrosomia, or polyhydramnios were not included. Another criterion for exclusion was instrumental delivery. Two 500 mg/5 mL ampules of the drug TA, obtained from a pharmaceutical company in Diyala, were used in the trial, whereas two ampules of distilled water (5 mL each) served as the placebo.

The participating ladies gave their informed agreement before being split into two groups using block randomization: the control group and the intervention group. Using block sizes of 4 and 6, this procedure was stratified according to the number of prior births (either first-time mothers or those who had had two or more), with a 1:1 allocation ratio. Prior to delivery and again 12–24 hours after delivery, hemoglobin and hematocrit levels were measured.

Hematocrit readings recorded both before and after delivery were used to calculate the quantity of blood loss. The proportion of blood volume lost, which is represented by the difference between the pre-delivery and post-delivery hematocrit values divided by the pre-delivery hematocrit, was multiplied by the total maternal blood volume (0.75 × {[maternal height (in inches) × 50] + [maternal weight (in pounds) × 25]}).

The placenta, gauzes, gowns, sheets, and tampons were all weighed using a digital scale in this study, and the neonates' weights were recorded using ward scales. Following the delivery of the anterior shoulder, the intervention group received one gram of intravenous TA, and the control group received one gram of a placebo mixed with 200 milliliters of normal saline during a ten-minute period. Following delivery, the umbilical chord was clamped and severed. Following confirmation that the placenta had detached, the Brandt-Andrews method—which entailed the mother exerting effort while gently pulling on the umbilical cord—was used to deliver it. Weighing the placenta came next.

The length of the third stage of labor was measured and recorded in minutes. The researcher's role was limited to measuring blood loss, placental weight, and vital signs,

and they did not participate in the delivery process or the subsequent care. Immediately after delivery, a sterile disposable plastic cover with a predetermined weight was positioned under the woman, and a graduated container with a plastic cover was placed beneath the delivery bed to collect any blood loss, which was subsequently weighed. After the placenta was delivered, both groups were administered 10 IU of oxytocin in 500 mL of normal saline over 20 minutes. The dosage of oxytocin given, along with information about other medications administered to both groups, was recorded. Blood loss was assessed at two different time intervals. The first measurement period started from the moment the fetus was delivered until the placenta was delivered, while the second period extended from the delivery of the placenta to the end of the second hour following childbirth. The weights of blood-soaked gauzes, gowns, sheets, and tampons were measured both before and after use, and blood loss was calculated using the method described by Gai et al. [13].

The formula for calculating the quantity of blood (in milliliters) was: (weight of used materials - weight of materials before use) / 1.05. In cases of perineal tears or episiotomies, any gauzes used during these procedures were excluded from the blood loss measurements after inserting a tampon in the vagina, although the weights of the tampons retained in the vagina were included. Maternal observations were documented every 15 minutes during the first hour and every 30 minutes during the second hour after delivery, and this information was systematically recorded.

The normality of the quantitative data was evaluated using the Kolmogorov-Smirnov (K–S) test. An independent t-test was then employed to compare the means of measured blood loss, calculated blood loss, and the duration of the third stage of labor, as well as to assess the mean differences in hemoglobin and hematocrit levels before and after delivery between the groups.

3. Results

A total of 140 pregnant women allocated into the two groups were examined, as illustrated in Figure 1. The groups were comparable regarding socio-demographic characteristics, as well as reproductive and delivery-related factors, along with newborn and placental weights. The demographic profiles of the participating women are displayed in Table 1.

Table 1. Demographic and obstetric features of participants by group

Characteristics	Tranexamic acid n = 80	Placebo n = 80
Age (years)*	25.2 (4.8)	26.1 (4.7)
Ba housewife	50 (85)	54 (87)
Urban resident	36 (60)	37 (62)
Body mass index (kg/m^2)*	26.2 (3.1)	27.9 (4.2)
Getting prenatal care	60 (100)	59 (98)
Multiparous	30 (50)	30 (50)
Oxytocin for labour induction	39 (65)	35 (58)
Birth weight (g)*	3326.7 (380.9)	3339.1 (400.7)
Placental weight (g)*	547.9 (99.1)	552.7 (78.1)
Type of delivery NVD	8 (12)	8 (12)
NVD + episiotomy	52 (87)	52 (87)

Haemoglobin levels before delivery (g/L)*	12.9 (0.9)	13.0 (0.9)
Haematocrit levels before delivery (%)*	38.3 (2.3)	38.8 (2.0)

The majority of deliveries (75%) were unassisted vaginal births with an episiotomy performed. Nearly all participants, except for one, had received prenatal care throughout their pregnancy. Half of the participants had never given birth before, and 64% received oxytocin during the first stage of labor (see Table 1). Prior to randomization, there were no statistically significant differences between the intervention and control groups regarding hemoglobin levels (P = 0.263) and hematocrit levels (P = 0.361). The postpartum drop in hemoglobin did not significantly differ between the two groups (1.3 vs. 1.6, P = 0.114). The average decline in hematocrit for the intervention group was 3.7 (standard deviation of 2.3), while for the control group, it was 4.8 (standard deviation of 3.0).

It was determined that the difference was statistically significant (P = 0.032). On the other hand, the mean blood loss from fetal birth to placental delivery did not differ significantly between the two groups (P = 0.523). Conversely, the intervention group experienced a considerably reduced mean blood loss from placental delivery to two hours postpartum than the control group (P < 0.001).

Additionally, the intervention group's mean estimated blood loss, as determined by hematocrit tests, was considerably lower than that of the control group (mean difference: 140, 95% CI: 9–271, P = 0.035). Compared to the placebo group, the TA group experienced a decreased incidence of postpartum hemorrhage (PPH) surpassing 1000 mL (7% vs. 18%, P = 0.047). Although safety was not the primary goal of this study, any adverse effects were noted as a secondary outcome. No one in the placebo group and two (3.2%) in the intervention group reported feeling lightheaded or nauseous (Table 2).

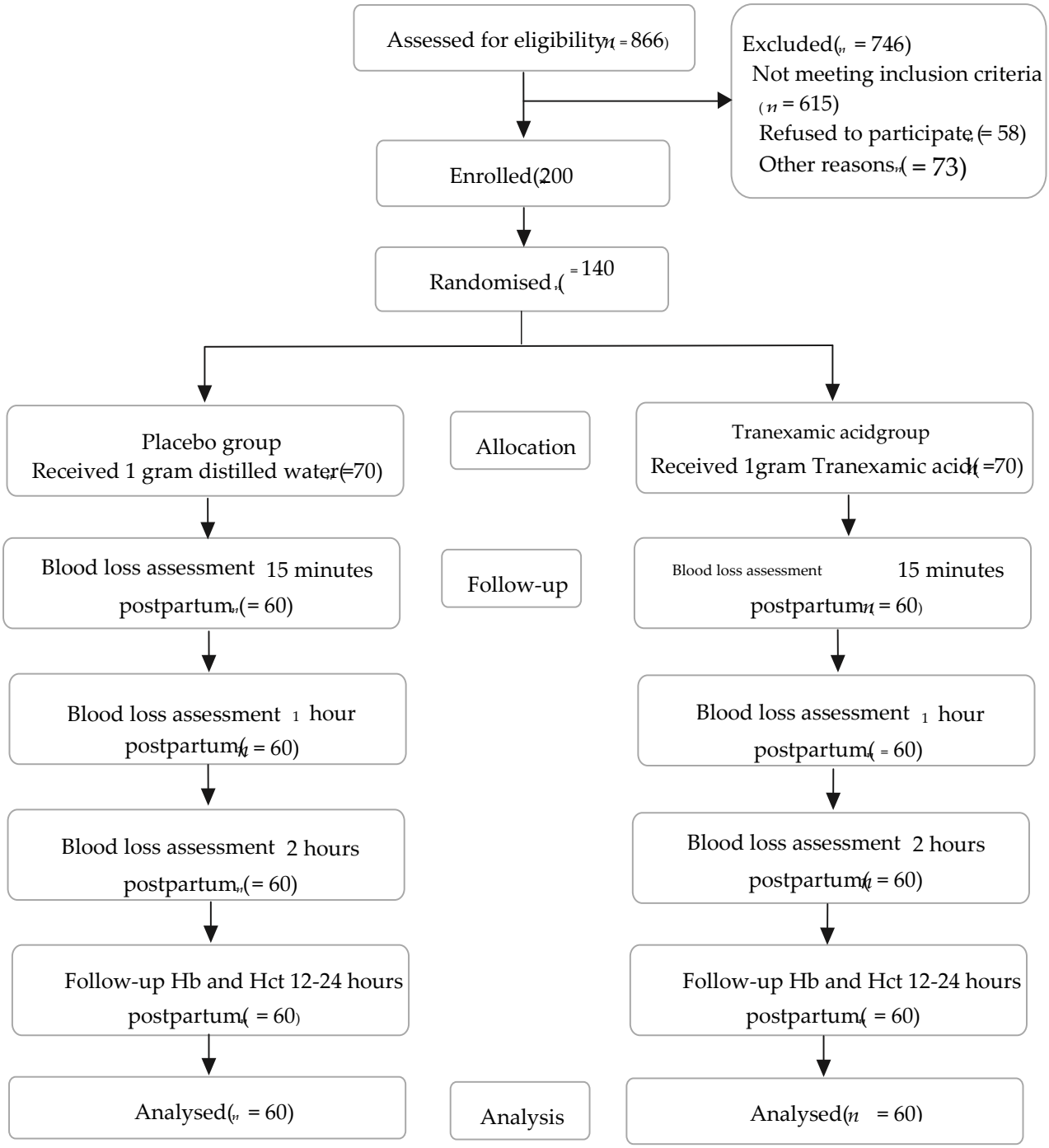
Assessed for eligibility (n = 866)
Excluded (n = 746)
Not meeting inclusion criteria (n = 615)
Refused to participate (n = 58)
Other reasons (n = 73)
Enrolled (200
Randomised (n = 140
Placebo group
Received 1 gram distilled water (n=70)
Allocation
Tranexamic acidgroup
Received 1gram Tranexamic acid (n=70)
Blood loss assessment 15 minutes postpartum (n = 60)
Follow-up
Blood loss assessment 15 minutes postpartum (n = 60)
Blood loss assessment 1 hour postpartum (n = 60)
Blood loss assessment 1 hour postpartum (n = 60)
Blood loss assessment 2 hours postpartum (n = 60)
Blood loss assessment 2 hours postpartum (n = 60)
Follow-up Hb and Hct 12-24 hours postpartum (n = 60)
Follow-up Hb and Hct 12-24 hours postpartum (n = 60)
Analysed (n = 60)
Analysis
Analysed (n = 60)

Table 2. Comparison of primary and secondary outcomes between the study groups

Outcomes	Intervention group (n =80)		Control group (n =80)		P
	Mean (SD)*	Median (p25 to p75)†	Mean (SD)*	Median (p25 to p75)†	
Primary outcome Calculated blood loss volume (mL)	518.9 (319.6)	–	659.3 (402.5)	–	0.03‡
Secondary outcomes Measured blood loss volume (mL) Fetus delivery to placental delivery	241.3 (171.5)	195.2 (108.8–332.3)	264.1 (215.8)	191.4 (105.2–345.2)	0.52‡
Placental delivery to 2 h postpartum	68.9 (39.0)	57.1 (42.8–85.4)	107.6 (52.6)	92.3 (71.4–139.7)	0.001‡
Pre- and postdelivery Hb difference	1.4 (0.8)	–	1.7 (1.0)	–	0.11‡
Pre- and postdelivery Hct difference (%)	3.7 (2.3)	–	4.8 (3.0)	–	0.03‡
Duration of third stage of labour (min)	6.30 (2.14)	–	9.03 (2.71)	–	0.001‡
Use of additional uterotonic agent§	3.0 (5.0)	–	7.0 (12.0)	–	0.32
Dizziness††	2 (3)	–	0 (0)	–	0.49‡‡
Nausea††	2 (3)	–	0 (0)	–	0.49‡‡
Blood loss >500 mL (calculated blood loss volume)††	27 (45)	–	34 (59)	–	0.14
Blood loss >500 mL (measured blood loss volume)††	9 (15)	–	15 (25)		0.25
Blood loss >1000 mL (measured blood loss volume)††	1 (2)		2 (3)		0.50
Blood loss >1000 mL (calculated blood loss volume)††	4 (7)		11 (18)		0.04

*Mean (standard deviation).

†Percentiles 25–75.

‡independent t-test.

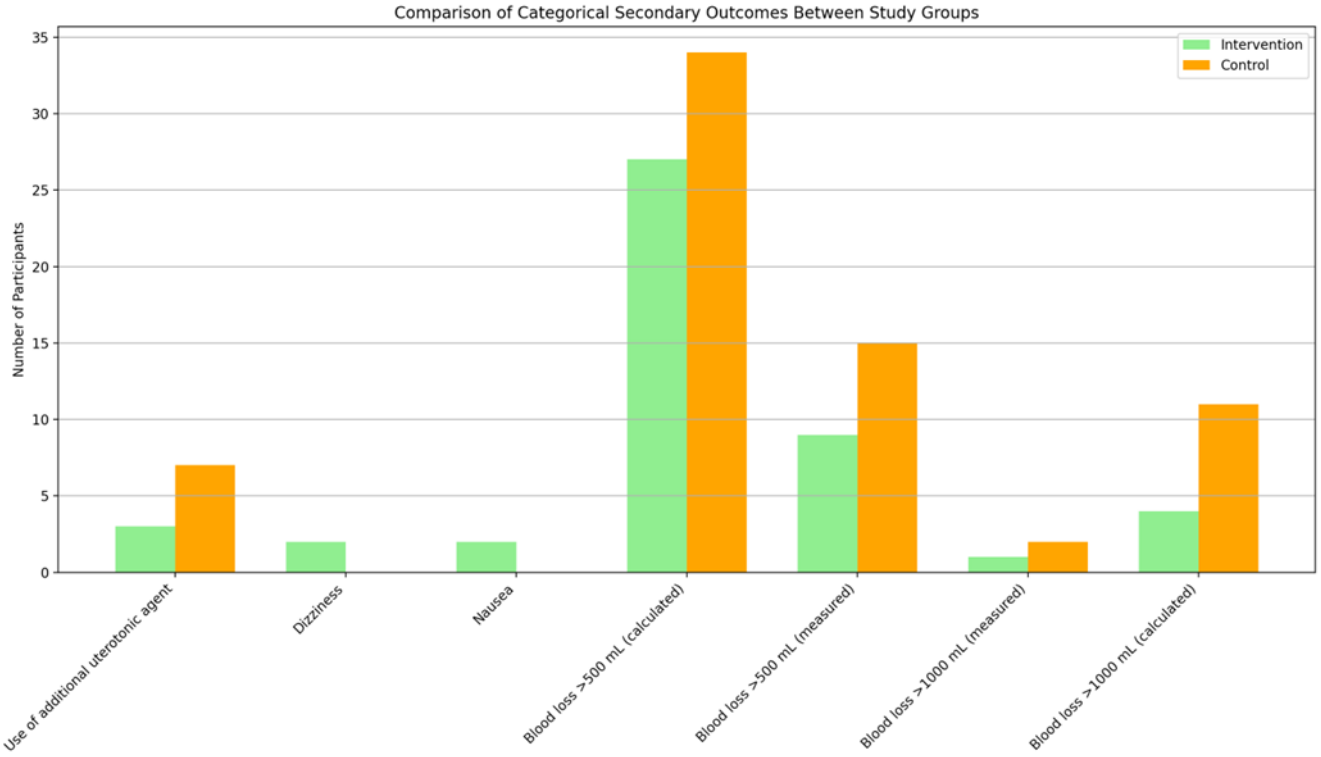

Figure 1. Comparison of categorical secondary outcomes between study groups.

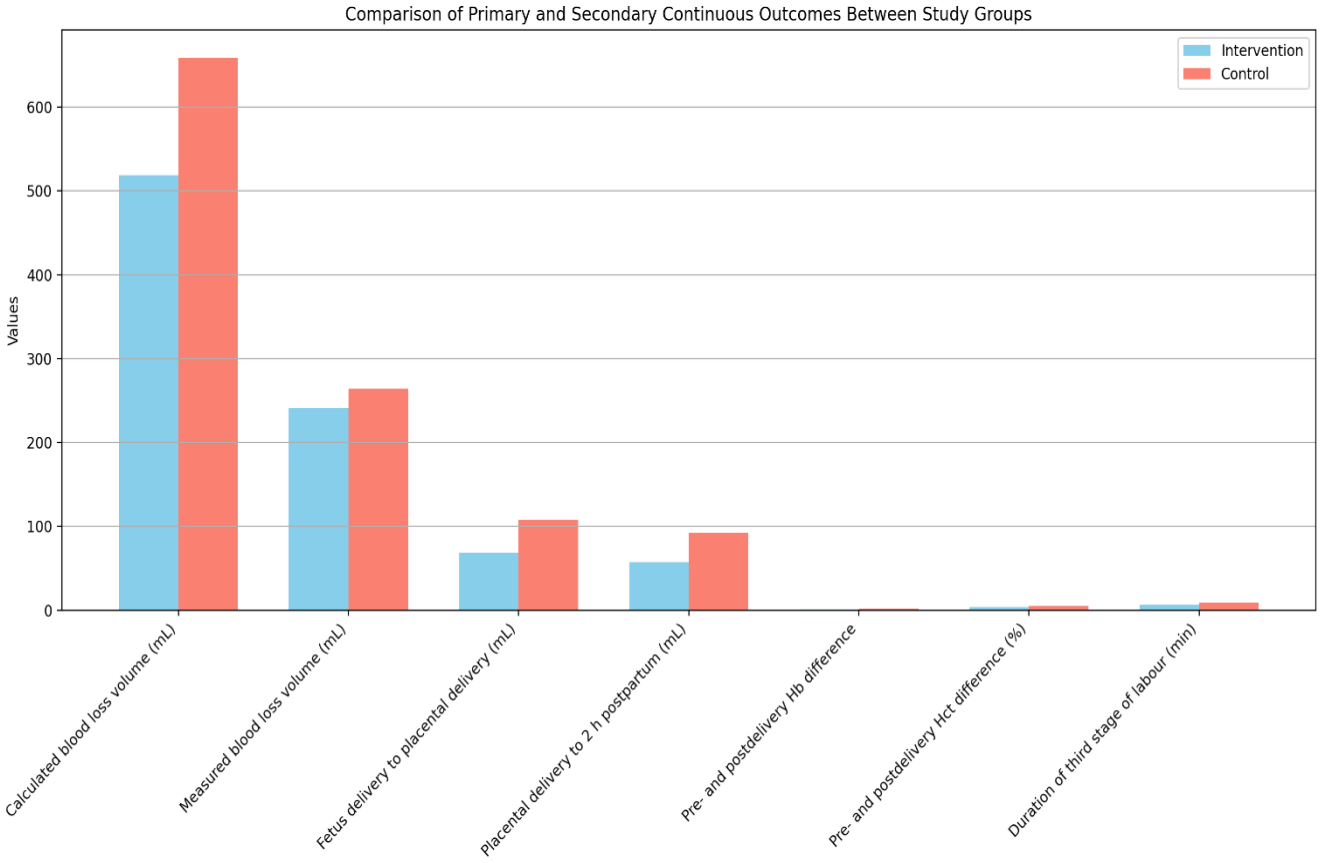

Table 2. Comparison of categorical secondary outcomes between study groups.

4. Discussion

Compared to the control group, the mean estimated blood loss was significantly lower in the tranexamic acid (TA) group. Additionally, from the moment of placental separation until two hours after delivery, the TA intervention group had a lower mean measured blood loss than the control group. These findings are consistent with the findings of two additional studies. Specifically, TA was utilized to prevent postpartum blood loss following a normal vaginal delivery in a trial conducted by Yang et al. (19) with 400 primiparous women in China. Four groups were randomly assigned to trial participants: 0.5 g of TA, 1 g of TA, or a normal saline placebo.

The current study's methodology for administering tranexamic acid (TA) is similar to the previous study by Yang et al. (19), where TA was administered intravenously 2-3 minutes after delivery, along with an immediate injection of 10 units of oxytocin post-delivery. However, the study by Yang et al. had several limitations. It was not blinded, and the allocation concealment was unclear, as the details of the randomization process were not provided.

Furthermore, five macrosomia instances were eliminated following randomization, which would have added bias. Notwithstanding these drawbacks, Yang et al.'s (19) findings supported the current study's findings. The results of the current study are consistent with previous studies, which found no significant difference in mean blood loss from fetal to placental delivery between the TA intervention and control groups ($P > 0.05$). Additionally, Yang et al. found that the TA intervention group had significantly lower mean total blood loss from placental delivery to two hours postpartum (129.7 vs. 178.2 mL) and fetal delivery to two hours postpartum (243.3 vs. 314.8 mL) than the placebo group ($P < 0.05$).

The current study's findings are also consistent with the results of a double-blind randomized controlled trial conducted by Gungorduk et al. (20) involving 228 women in Turkey. In that study, participants in the intervention group received 1 g of TA, dissolved in 10 mL, along with 20 mL of 5% glucose intravenously at the time of anterior shoulder delivery. The control group was administered 30 mL of 5% glucose, in addition to standard active management during the third stage of labor. The Gungorduk et al. study found that the mean total blood loss from fetal delivery to two hours postpartum, as well as the mean blood loss from placental delivery to two hours postpartum, was significantly lower in the TA intervention group compared to the placebo group. Furthermore, the intervention group demonstrated higher mean hemoglobin and hematocrit levels than the placebo group. These results align with the findings of the current study.

In Gungorduk et al. [20] research, the group that received tranexamic acid (TA) showed significantly lower mean blood loss from birth to placental delivery compared to the control group. Their methodology included delivering the placenta through controlled umbilical cord traction and administering 10 units of oxytocin within two minutes post-delivery. A key difference was in the timing of TA administration - Gungorduk et al. administered it within five minutes, whereas the current study implemented it within ten minutes after anterior shoulder delivery.

Most of the existing research has focused on the effectiveness of tranexamic acid (TA) in reducing blood loss during cesarean sections. Multiple studies encompassing 2,267 women have shown positive results with the use of TA [12,13,15-18,25,26]. The evidence demonstrates that the mean blood loss during the period from the completion of cesarean section to two hours postpartum was significantly reduced in the groups receiving TA compared to the control groups. Furthermore, analysis from low-middle income countries has shown even more pronounced benefits from TA use, with greater reductions in total blood loss compared to results from upper-middle or high-income countries [12,13,15-18,25,26].

Studies by Movafegh et al. [18] and Senturk et al. [17] show that the intervention group experienced a considerably reduced mean blood loss during the intrapartum

period than the control group. The intervention and control groups in this trial did not, however, have different mean blood losses from placental delivery to the completion of the caesarean section.

Studies on the effect of tranexamic acid (TA) have consistently shown its ability to reduce hemorrhage [20]. However, the variability in some results could be attributed to factors such as the timing and dosage of TA administration, differences in the management of the third stage of delivery and prevention of bleeding, variations in coagulation mechanisms, and study inclusion criteria [17] [18]. This study found that the frequency of blood loss greater than 1000 mL was significantly higher in the control group compared to the TA group, which aligns with the findings of Gungorduk et al. [20] [20]. TA is a readily available and inexpensive drug [27]. Although there have been concerns about the increased risk of thromboembolic events due to TA's ability to inhibit fibrinolysis, previous studies have confirmed the safety of this drug for use in non-pregnant women without thromboembolic complications [11, 21, 28].

This study was not primarily designed to assess the safety of tranexamic acid (TA), and any side effects were documented as a secondary outcome. No serious events were reported in this study or in similar studies by Yang et al. and Gungorduk et al. [19,20]. However, the ongoing Woman Trial will provide more reliable evidence on the safety of TA in pregnant women [11].

Both the frequency of postpartum hemorrhage and the amount of blood loss following delivery were comparatively higher than anticipated in this study. It's unclear why postpartum blood loss has increased, but it might be because blood loss measurements are being done more carefully. The very small sample size, which was not powered to evaluate postpartum bleeding, was one of the study's weaknesses. In order to more accurately assess the effects of TA in lowering blood loss following vaginal birth, particularly in situations of postpartum hemorrhage, it is advised that further research be carried out with larger sample numbers.

5. Conclusion

According to the analysis, patients who received tranexamic acid (TA) demonstrated significantly reduced blood loss during the period from placental delivery through two hours postpartum compared to those who did not receive TA. These findings support TA's preventive role in reducing postpartum hemorrhage (PPH) risk. The evidence suggests that TA could serve as a valuable supplementary medication alongside conventional uterotonic agents for preventing excessive blood loss in low-risk women during the postpartum period. This is further supported by research showing that prophylactic TA administration reduced PPH incidence by 32% and decreased the need for additional uterotonics when compared to placebo.

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