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Prophylactic Use of Tranexamic Acid on Blood Loss in Cesarean Delivery: A Randomized Controlled- Clinical Trial

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Abstract

Background: Post-partum haemorrhage (PPH) is a major cause of maternal mortality worldwide. Tranexamic acid, an anti-fibrinolytic agent, is a novel approach in an attempt to prevent this dreadful complication.
Objectives: This study aimed to evaluate the efficacy and safety of tranexamic acid in reducing blood loss during and after caesarean section (CS).
Methods: In this prospective randomised placebo-controlled clinical trial, 50 pregnant women were randomized into two groups. In the study group, 25 women received tranexamic acid 10 minutes before CS, whereas in the control group 25 women received distilled water. Blood was collected during two periods. The first time was from placental delivery to the end of CS and the second was from the end of CS to 2 h postpartum. The volume of blood was measured and compared between the two groups.
Results: Tranexamic acid significantly reduced the quantity of blood from the end of CS to 2 h postpartum, which was 65.15±31.97 mL and 101.14±44.94 mL in the study and control groups, respectively (P =0.002). It also significantly reduced the volume of total blood from placental delivery to 2 h postpartum, which was 616.32±176.87 mL and 731.45±178.79 mL in the study and control groups (P =0.028). Total blood loss in the study group was 18.7% less than the control group. No complications or side effects were reported in the groups.
Conclusion: Tranexamic acid statistically reduces the volume of blood loss from placental delivery to 2 h postpartum and its use was not associated with any side effects or complications. Therefore, tranexamic acid can be used as a safe and effective approach to reduce bleeding resulting from CS.

Keywords: Postpartum hemorrhage, Tranexamic acid, Cesarean section, Randomized controlled trials.

Introduction

Prevention of Postpartum haemorrhage

Postpartum haemorrhage (PPH) is the third-most common cause of maternal death in the United States and it is still the first prevalent cause of maternal death in developing countries.[1] PPH is classically defined as the loss of more than 500 mL of blood following vaginal delivery or more than 1000 mL loss following caesarean section (CS).[2] Cesarean section rate has increased to as high as 25-30% in many countries of the world. Hemorrhage can be a serious complication of cesarean delivery. In order to decrease maternal morbidity and mortality caused by bleeding, reduction of this severe bleeding is vital.[3,4]

Tranexamic Acid

Antifibrinolytic agents, mainly tranexamic acid (TA), have been demonstrated to reduce blood loss and transfusion requirements in various surgical procedures, such as coronary artery bypass, scoliosis surgery and knee arthroplasty.[4-6]

In the field of obstetrics, many randomized controlled trials and meta-analysis have suggested that TA administration in women after vaginal or elective caesarean delivery reduces blood loss and the incidence of PPH.[3,7-15]

Nevertheless, researchers concluded that there are insufficient available evidence regarding RCTs to reach any definitive conclusion.[6,9-11,15-18] Furthermore, the World Maternal Antifibrinolytic (WOMAN) trial is gathering data on the effect of TA on postpartum bleeding from a large number of centers worldwide [19] to provide reliable evidence in pregnant women.

Objectives

Hence, in this study, the effect of tranexamic acid in reducing blood loss after CS was investigated.

Materials and Methods

A randomized case-controlled clinical trial was conducted on 50 women undergoing cesarean, at Izadi Hospital, Qom, Iran, between August 15, 2016, and April 30, 2017. The study was approved by the Ethics Committee of Qom University of Medical Sciences (code: MUQ.REC.1394.154). It was prospectively registered with the Iranian registry of clinical trials (code: IRCT20091010002558N7). Written informed consent was obtained from all participants.

Inclusion criteria

Pregnant women who had planned to undergo elective cesarean delivery by Pfannenstiel incision under spinal anesthesia were eligible for inclusion in the study. Inclusion criteria were women aged 18–35 years with a singleton pregnancy at 38 weeks and 42 weeks' gestation and blood pressure less than 140/90 mmHg.

Exclusion criteria

Pregnancy complications such as pre-eclampsia, polyhydramnios, macrosomia, preterm labour, multiple pregnancies, placenta praevia, abruptio placenta, abnormal placenta, thrombophilia, anemia, coagulopathy, cardiovascular, renal, liver disorders and allergy to tranexamic acid were excluded from the study.

Sample size

Sample size was calculated to be 22 subjects in each group to detect the difference with 80% power and 5% probability of type 1 error. In order to adjust for drop out, recruitment target was set at 25 subjects per group. Figure 1 shows overall study design.

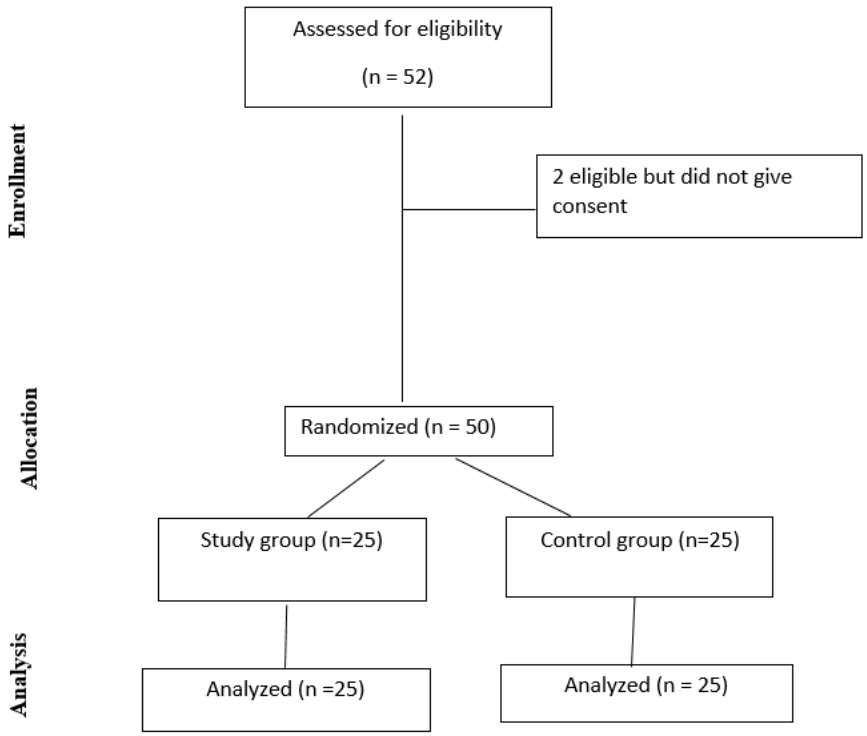

Figure-1. CONSORT flow diagram

Random allocation & Intervention

The women were randomly classified into two groups based on the block randomization: Women in the intervention group (n=25), received one gram intravenous TA, 10 min before skin incision, and the control group (n=25), received one gram placebo (distilled water) in 200 mL normal saline over 10 min. In this study, TA was supplied in 2×500 mg/5 mL ampoules obtained from kharazmi Pharmaceutical Company in Iran. The placebo comprised 2×5 mL of distilled water ampoules from Shahid Ghazi Pharmaceutical Company in Tabriz - Iran.

In order to hide the medication allocation, two vials of the tranexamic acid and distilled water were placed in similar opaque, sequentially numbered and sealed in packages by an operating room technician that was not involved in the sampling and analysis. The technician maintained the medication administration code. In this regard, the data analyzers and the participants were not aware of the used medication.

Outcome measures

Haemoglobin and haematocrit levels were measured before and 12–24 h after cesarean delivery. Blood loss was measured at two time intervals. The first time was from expulsion of the placenta to end of cesarean, (the blood and amniotic fluid before expulsion of the placenta was not collected or measured. During CS, after draining the amniotic fluid completely and delivery of placenta, blood was drained in a separate suction container). The second measurement was performed from end of cesarean to two hours after cesarean section. Blood-soaked gauzes, gowns, sheets and tampons were all weighed before and after consumption, and blood loss was estimated in accordance with Gai et al.[4]

Method: The volume of blood (mL)=(weight of used materials _ weight of materials prior to use)/1.05 and then plus the volume included in the suction container after placental delivery.

Immediately after cesarean delivery, a sterile disposable plastic cover with a determined weight was placed under the woman to collect blood loss and then was weighted. In this study, an electronic scale (with a 1-g deviation range) was used for measuring the weight of gauzes, gowns, sheets and pads. All operation was conducted by the researcher. The data was collected by a person.

Both groups received 20 IU oxytocin in 1000 mL of normal saline over 20 min after placental delivery. The dose of oxytocin received and other additional uterotonic administered were recorded for both groups.

Vital signs (heart rate, blood pressure and respiratory rate) were recorded before operation, 1 and 2 h after cesarean delivery. Complete blood count (CBC), BUN, cratinin and urine analysis were performed before delivery, and 48-72 hours after delivery.

Statistical analysis

The data were analysed using SPSS/version 17 (IBM SPSS, New York, NY, USA) and t-test was used to compare differences between the two groups were described with 95% confidence intervals (95% CI), and p-value 0.05 was considered significant statistically.

Ethical statement

The study was approved by the ethics committee of Qom University of Medical Sciences (code: MUQ.REC.1394.154). It was prospectively registered with the Iranian registry of clinical trials (code: IRCT20091010002558N7). Written informed consent was obtained from all participants. Helsinki metrics were respected.

Results

The women characteristics in the two groups were similar, with no statistical difference was observed between the two groups (Table-1).

The volume of blood from the end of CS to 2 h postpartum was significantly decreased in the intervention group compared to the control group (P=0.002). Calculated total blood loss from placental delivery to 2 h postpartum was also reduced in the intervention group with a statistical difference between the two groups (P=0.028). While there was no statistical difference in the volume of blood from the time of placental delivery to the end of CS between the two groups (P=0.103) (Table-2).

According to our findings, in the intervention group, there was total reduction in blood loss by about 18.7%. No significant difference was found in the pre-operative hemoglobin and hematocrit value between both groups. The hemoglobin and hematocrit values decreased slightly after CS in the two groups, but there was no statistical difference. There was no significant difference in the BUN, Cr and urine analysis before and 48-72 h after CS between the two groups.

There was no significant difference in the vital signs (including heart rates, respiratory rates and blood pressures) before and 1-2 h after CS between the two groups. Moreover, there was no significant difference in the APGAR scores at 1 min and also at 5 min between the two groups. No side effects of tranexamic acid such as nausea, vomiting and diarrhea were reported in the intervention group.

There were no episodes of thrombosis in any of the studied women in the intervention group. Also, no PPH was reported and also, no blood transfusion was needed in each group in our study.

Additionally, there was no statistical difference in the additional uterotonic drugs between the two groups.

Discussion

The present study demonstrated that 1 gr intravenous tranexamic acid 10 min before skin incision, significantly reduced bleeding from the end of CS to 2 h postpartum. In the intervention group, the calculated total blood loss from placental delivery to 2 h postpartum was significantly

reduced compared to the control group. Thus, in the intervention group, about 18.7% reduction was observed in blood loss. According to Gungorduk et al.[7] and Gia et al. studies,[4] the reduction in total blood loss was about 17% and 18%, respectively. However, in the short time period, there was no significantly difference in the volume of bleeding between placental delivery to the end of CS.

A similar study was carried out by Jianjun xu et al.[10], which administered 10 mg/kg tranexamic acid immediately before caesarean delivery. Blood loss in the period between the end of CS and 2 h postpartum and the quantity of total blood from placental delivery to 2 h postpartum in the TA group were significantly lower than that in the control group. However, the amount of blood loss in the period from placental delivery to the end of CS did not differ between the TA and control groups.

According to Ming-ying Gai et al.[4] by administering 1 gr tranexamic acid, 10 min before caesarean delivery, the blood loss in the period between the end of CS and 2 h postpartum and the quantity of total blood from placental delivery to 2 h postpartum were significantly lower in the TA group than that in the control group. However, the amount of blood loss in the period from placental delivery to the end of CS did not differ between the TA and control groups. These results are comparable with our findings. This may be due to the time of tranexamic acid administration and suggest that it should be administered earlier.

Movafegh et al.[3] performed their study with intravenous injection of 10 mg/kg of tranexamic acid 20 min before skin incision. Mean blood loss was significantly less in the intervention group compared with the control group for both intra-operative bleeding and post-operative bleeding. These results were consistent with the present study.

Sekhavat et al.[5] performed a clinical randomized study on primipara women, and showed that 1 g/10 mL intravenous tranexamic acid 10 min before incision, significantly reduced blood loss from the end of caesarean section to 2 h post-partum. These results are consistent with findings of the present study. Although in the mentioned study, they have only studied primipara women, whereas our study had no inclusion criteria based on parity.

Also, there was no significant difference in pre-operative and post-operative haemoglobin and haematocrit levels between the two groups. There were no abnormalities in CBC, urinalysis, renal function tests before or after tranexamic acid administration. These results are comparable with the findings Movafegh et al.[3], Irene ray et al.[14] and Gai et al.[4]

Also, in this study, no significant abnormal vital signs occurred after TA administration as HR, BP, RR. This is in agreement with other studies Movafegh et al.[3], Gai et al.[4], Jianjun Xu et al.[10]and Irene ray.[14]

Table-1. Women characteristics of the intervention and control groups

	Intervention	control	p-value
age	30.48±4.71	31.46±4.85	0.973
Hight	159.76±5042	160.18±7.33	0.894
Weight	64.92±14.45	67.71±14.18	0.906
BMI	25.31±4.94	26.43±4.75	0.930
Weight gain	10.52±4.03	12.72±4.07	0.852
Gravida	2.32±0.74	2.29±0.80	0.739
Pariety	1.16±0.55	1.13±0.61	0.818
Gestational age	38.24±0.436	37.83±1.76	0.274
Number of CS	1.21±0.50	1.04±0.62	0.563

Table-2. Comparison of the extent of blood loss in the intervention and control group

Group	Placental delivery to the end of CS (ml)	The end of CS to 2 h postpartum (ml)	total blood loss from placental delivery to 2 h postpartum(ml)
Intervention	551.17±172.79	65.15±31.97	616.32±176.87
control	630.30±159.21	101.14±44.94	731.45±178.79
P-value	0.103	0.002	0.028

The side effects of intravenous tranexamic acid such as nausea, vomiting and diarrhea were similar in the TA and control groups. These results are consistent with the findings of the previous studies.[14]

In our study, no PPH was reported and the patients with a blood loss more than 1000 mL were defined as PPH in our study. While, PPH has been defined as more than 400 mL blood loss in Gai et al.[4] and Yang et al.[20] studies, and more than 500 mL in Jianjun Xu et al.[10]

Additionally, the administration of oxytocin and other uterotonic drugs was not significantly different in both groups. While, in Movafegh et al., study, oxytocin administration in the intervention group was significantly less than the control group.[3]

The incidence of thrombosis during pregnancy and puerperium is 5–6 times higher than that in the general population. When the antifibrinolytic drug tranexamic acid is administered, the increased risk of thrombosis should be considered, especially in the CS post-partum population.[4, 14] In our study, none of the mothers showed signs of thrombosis. Similar results were also reported in other studies.[3-5,10,14]

All data demonstrated that TA can be used safely without increasing the occurrence of thrombosis, but still further studies are required to confirm these findings.

The safety of giving TA (1 g) while the fetus was still in utero was an important concern. As a consequence, the neonatal outcome was accurately evaluated by a neonatologist. In our study, there was no significant difference in the APGAR scores at 1 min and also at 5 min between the two groups. None of the neonates required NICU admission. These results are comparable with the findings of previous studies.[4,14]

The main limitation of our study was the fact that the TA was found to be safe and did not increase the risk for thrombogenic episodes in the mother. However, the study was not powered to test these aspects of the drug. A large international study should be implemented to investigate the safety of TA in future research.

Conclusions

In conclusion, antenatal administration of intravenous TA 10 min before spinal anaesthesia significantly reduces the volume of blood loss during and after lower segment caesarean section without any untoward adverse effects on the mother or neonate health.

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Authors' Contribution

Study concept and design: Esmat Jafarbegloo. Sampling: Faridnyia. Analysis and interpretation of data: mohammad beigi. Drafting of the manuscript: ahangari and jafarbegloo. Critical revision of the manuscript for important intellectual content: Esmat Jafarbegloo, ahangari. Statistical analysis: mohammad beigi.

Conflict of Interests

We declare that we have no conflict of interest.

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