http://www.ijwhr.net

doi 10.15296/ijwhr.2023.41

Open Access Original Article

IJWHR

International Journal of Women's Health and Reproduction Sciences
Vol. 10, No. 1, xx 2022, x–x

ISSN 2330-4456

Effect of Tranexamic Acid on Intra- and Postoperative Bleeding Ratio and Complications in Placenta Accreta Syndrome: A Double-Blind Clinical Trial

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Abstract

Objectives: Placenta accreta syndrome (PAS) is one of the main problems of women during childbirth, also the most important cause of maternal morbidity and mortality. Tranexamic acid (TXA) is widely used to reduce blood loss and deaths due to bleeding in trauma patients and patients with postpartum hemorrhage. This study aimed to investigate the effect of TXA in reducing bleeding and complications during and after surgery in women with PAS.

Materials and Methods: This double-blind clinical trial was performed on 46 women who underwent cesarean section with PAS diagnosis. The participants were randomly assigned in two groups (n=23/each): the TXA group received 1 g TXA intravenously and the control group received 50 mL of normal saline immediately after the surgery. Then, the postoperative estimated blood loss (EBL), amount of blood products transfusion, complications during and after delivery, including the need for hysterectomy, duration of hospitalization, and the number of days staying in the intensive care unit (ICU) were compared between the two groups

Results: The mean EBL during and after surgery in the TXA group was significantly lower than the control group ($P<0.0001$). The TXA group received fewer blood products, including packed red blood cells (PRBCs), fresh frozen plasma (FFP), and platelet. The duration of surgery, duration of hospitalization, and the number of days in the ICU were significantly lower in the TXA group ($P<0.001$). Hysterectomy was observed in 10 participants of the TXA group and 13 women in the control group, but the difference was not significant ($P=0.556$).

Conclusions: TXA administration effectively reduced postpartum hemorrhage, the need for postpartum blood transfusion, the duration of surgery, and the duration of hospitalization in women with PAS. TXA is a practical, inexpensive, safe, and readily available treatment and can be recommended as a prophylactic intervention to prevent blood loss in women with PAS.

Trial Registration: https://www.irct.ir/, identifier: IRCT20201003048909N1

Keywords: Placenta accreta, Tranexamic acid, Cesarean section, Hemorrhage

Introduction

Placenta accreta syndrome (PAS), commonly known as placenta attachment, is a clinical condition in which all or a part of the placenta penetrates too much into the myometrium of the uterine wall (1) and is considered as one of the severe complications of pregnancy (1-3). The PAS incidence has increased due to the increasing cesarean section rate in the last few decades (1,4). These patients are exposed to severe and life-threatening bleeding during and after delivery (5). Maternal morbidity and mortality due to severe bleeding have been reported in 60% and 7% of PAS women, respectively (5,6).

Anti-fibrinolytic therapy is one of the adjuvant therapies that can be effective in PAS patients, especially in the field of bleeding (1). Tranexamic acid (TXA) is a potent anti-fibrinolytic agent that blocks lysine binding sites in plasminogen molecules, inhibits clot breakdown (fibrinolysis), and ultimately reduces bleeding, complications, and mortality (7, 8).

TXA is widely used in patients with trauma in orthopedic surgeries and heart surgeries to reduce bleeding (5,9). Recently, a large multicenter randomized clinical trial on women with postpartum hemorrhage showed that TXA decreases bleeding-related death (8). There is a lot of evidence that shows that the use of TXA can effectively reduce postpartum hemorrhage (10-14). Also, it has been observed that the prescription of TXA as prophylaxis after umbilical cord ligation during labor can reduce the risk of bleeding in PAS cases (5,15). However, some studies had design problems, or their samples were rare and small, but serious side effects have been reported, such as postpartum renal cortex necrosis (15,16). Although TXA is an effective, safe, and inexpensive drug for postpartum hemorrhage treatment (17), its prophylaxis prescription for cesarean section is not routinely recommended. Further studies are needed in this regard (1). Since PAS is one of the emergency problems during pregnancy and bleeding and coagulopathy are the major causes of

Received 10 February 2021, **Accepted** 14 August 2021, **Available online** 28 October 2021

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Key Messages

- Prophylactic administration of TXA can effectively reduce intra- and postoperative blood loss in women with PAS.
- TXA effectively reduces the need for blood products transfusions in women with PAS undergoing cesarean section.
- TXA administration reduces the duration of surgery and hospitalization in women with PAS with no adverse effects.

maternal mortality, this study investigated the effect of TXA in reducing the bleeding ratio and complications during and after surgery in women with PAS.

Materials and Methods

Design and Setting

In this double-blind controlled clinical trial, 46 women undergoing cesarean section with a diagnosis of PAS referred to Imam Khomeini hospital, Ahvaz, Iran, from November 2019 to October 2020 were enrolled.

The sample size of 23 for each group was calculated according to $\alpha = 0.5$, $\beta = 0.2$ and standard deviation of 1000 mL of blood loss in PAS women.

Participants

The inclusion criteria were women >18 years, singleton pregnancy, diagnosed with PAS syndrome on ultrasound, and candidate for cesarean section or cesarean section hysterectomy to terminate the pregnancy. All women with a history of cardiovascular diseases, including coronary artery disease, myocardial infarction, severe arrhythmias, and congestive heart failure, history of the bleeding disorder including antiphospholipid syndrome, liver and kidney disease, known coagulation disorders, anemia preoperatively (hemoglobin level [Hb] <8 mg/dL), thrombocytopenia, history of preeclampsia or eclampsia in the current pregnancy, and contraindication to TXA use (history of TXA allergy, venous thromboembolism, active thrombolytic diseases, acquired color vision disorders, history of seizure, pre-known hematuria, and renal failure) were excluded from the study.

Grouping and Interventions

The baseline characteristics of all participants were collected at the beginning of the study, including demographic and clinical information (age, medical history, smoking, and body mass index [BMI]). Also, the number of pregnancies, gestational age, ultrasound results, PAS degree (PAS1: mild; PAS2: moderate, and PAS3: severe) were recorded.

PAS diagnosis has been done based on FIGO grading (18,19). This PAS grading system is based on the presence of PAS sonographic signs in women with placenta previa:

- PAS1: Presence of ≥2 placental lacunae, loss of the clear zone, and bladder wall interruption.
- PAS2 : PAS1 + uterovesical hypervascularity.
- PAS3: PAS1/PAS2 + evidence of elevated vascularity in the inferior part of the lower uterine segment extending into the parametrial region.

The latest preoperative ultrasound was used to assess the PAS symptoms and to grade this disorder (Figure 1).

The participants were randomized into two groups of TXA and normal saline (control) using the random permuted block method. The TXA group received 1 g of TXA intravenously immediately after infant birth and umbilical cord ligation within 10 min. Women in the control group received 50 mL of normal saline after umbilical cord ligation. An anesthesiologist who knew the groupings but had no role in intraoperative or postoperative management prepared syringes containing TXA or normal saline. In addition, participants and caregivers were blinded to the grouping and interventions.

Blood loss was carefully investigated during and after surgery, and Hb level was measured continuously. Blood transfusion was performed if the Hb level was <8 g/dL, and the advanced transfusion protocol was performed when the blood loss was > 1000 mL, that in this case fresh frozen plasma (FFP) and platelet were transferred along with packed red blood cells (PRBCs) units. If intubation was required, women were transferred to the intensive care unit (ICU).

Outcomes

Preliminary outcomes included postoperative estimated blood loss (EBL) ratio and complications during and after delivery, including the need for hysterectomy. The postpartum hemorrhage ratio was measured with a collector bag. The secondary outcomes also included the amount of PRBCs, platelets, and FFP transfusion during surgery and the first 24 hours after delivery. Also, the duration of surgery, the duration of hospitalization, and the number of days staying in the ICU were investigated.

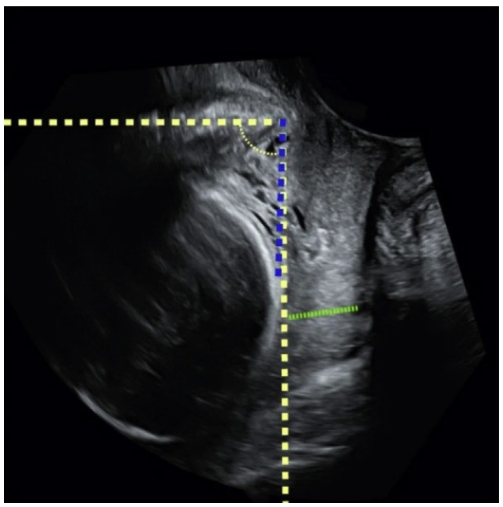

Figure 1. Doppler Ultrasound Assessment of Cervical Length, Head-to-Symphysis Distance, and Angle of Progression.

Data Analysis

Statistical Package for the Social Sciences (SPSS) software version 22 was used for statistical analyses. Data expressed as mean ± standard deviation and frequency (percentage). The chi-square test (or Fisher's exact test), student's *t* test, and Mann-Whitney U test were used to examine the differences between the two groups and compare the qualitative and quantitative variables, respectively. Partial spearman correlation coefficient was also used to determine the relationship between quantitative variables. The significance level was considered as $P<0.05$.

Results

Initially, 63 women were assessed for eligibility to the participant the study. Out of them, 17 women were excluded due to not meeting inclusion criteria (n = 10), dissatisfaction with participating in the study (n = 5), and other reasons (n = 2). Finally, 46 women were assigned to two groups (n = 23/each), and their data were analyzed (Figure 2).

The baseline characteristics of the participants are presented in Table 1. The results showed that there was no significant difference between the two groups in terms of gestational age, weight, age, BMI, number of previous pregnancies, and the PAS degree. In addition, there was not any considerable difference between the groups in terms of heart rate, respiration, and diastolic and systolic blood pressure.

It was evident from the results that the mean EBL and transferred platelet, PRBCs, and FFP in the TXA group were significantly lower than the control group ($P \leq 0.0001$) (Table 2). The results related to comparing the two groups demonstrated that the duration of surgery and hospitalization, and the number of days staying in the ICU in the TXA group were significantly lower than the controls (Table 3).

In addition, the need for hysterectomy was observed in 10 (43.47%) women of the TXA group compared to 13 (56.52%) women in the control group which did not show any significant difference ($P = 0.556$). None of the two groups observed no side effects, including intestine rupture hypogastric ligation and the need for laparotomy. In the control group alone, there was one case (4.34%) of bladder rupture. There were no thrombotic events and mortality in either group.

The partial correlation coefficient between the amount of bleeding and different variables considering the studied groups as the covariate showed that no significant relationship between the age, BMI, gestational age, and the number of pregnancies with the bleeding rate after cesarean section, but the amount of bleeding was significantly correlated with the PAS degree ($P = 0.017$) (Table 4).

Discussion

This study investigated the effect of TXA in reducing bleeding and complications during and after surgery in women with PAS. Our results showed that 1 g intravenous TXA injection for 10 minutes immediately after delivery and umbilical cord ligation significantly reduced the postpartum hemorrhage in these women. In addition, the mean of transfused platelet, PRBCs, and FFPs during and after cesarean section were significantly lower in the TXA group. In this study, we used a low dose of TXA (1 g) to prevent possible neonatal complications and injection at the time of umbilical cord ligation.

In line with our results, in a similar study, Ibrahim et al examined the effects of TXA in decreasing blood loss during and after cesarean section in women with PAS. They showed that the rate of intraoperative bleeding in the TXA group was significantly lower than in the control group (2232 mL vs. 3405 mL). Also, the need for blood products transfusions such as PRBC, FFP, and platelets during surgery and in the first 24 hours after surgery in

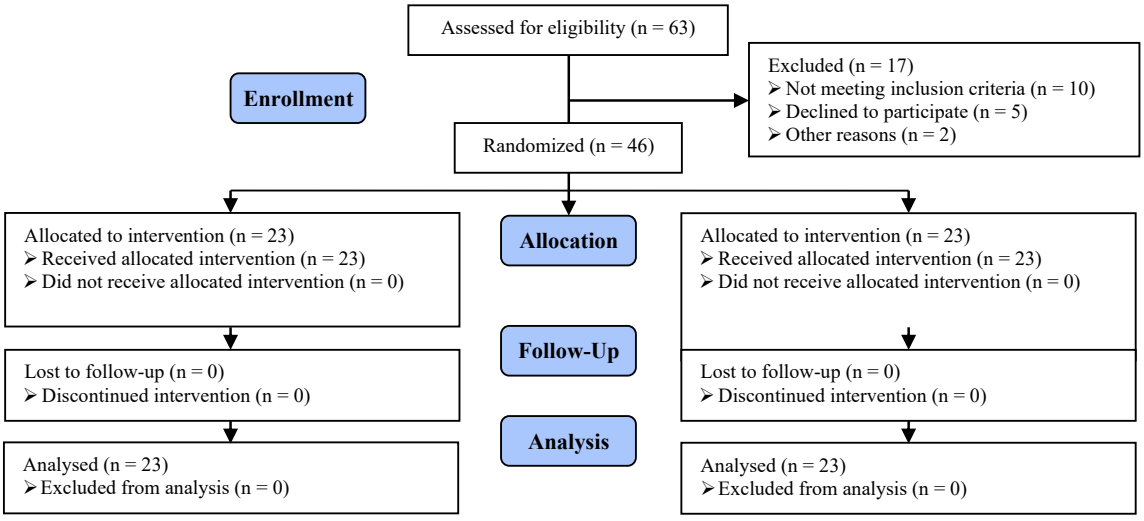

Figure 2. The Study CONSORT Flowchart.

Table 1. Demographic Characteristics of Participants in Two Groups

Variables	Control Group (n=23)	TXA Group (n=23)	*P* Value
Age (y), mean± SD	30.35 ± 5.329	32.34 ± 4.55	0186 [a]
Weight (kg), mean± SD	76.17 ± 6.71	74.78 ± 5.81	0.389 [a]
BMI (kg/m^2), mean± SD	30.17 ± 4.34	29.32 ± 3.20	0.326 [a]
Gravida, mean± SD	3.22 ± 0.85	3.52 ± 0.79	0.168 [a]
Gestational age (wk), mean± SD	36.35 ± 0.93	36.17 ± 1.79	0.659 [a]
Heart beat (bpm), mean± SD	82.22 ± 2.15	83.26 ± 3.52	0.119 [a]
Respiration rate (bpm), mean± SD	18.43 ± 1.89	18.87 ± 0.96	0.141 [a]
Systolic blood pressure (mm Hg), mean± SD	113.48 ± 5.72	114.52 ± 4.98	0.336 [a]
Diastolic blood pressure (mm Hg), mean± SD	73.61 ± 4.85	74.26 ± 4.75	0.817 [a]
PAS Grade 1, No. (%)	8 (34.78)	12 (52.17)	
PAS Grade 2, No. (%)	9 (39.13)	4 (17.40)	0.247 [b]
PAS Grade 3, No. (%)	6 (26.09)	7 (30.43)	

BMI: body mass index; PAS: placenta accrete syndrome; TXA: tranexamic acid.
[a] Student's t test; [b] Fisher's exact test.

Table 2. Comparison of the Effectiveness of TXA in Two Study Groups

Variables	Control Group (n=23)	TXA Group (n=23)	*P* Value
RBCs (unit)	3.26 ± 0.78	1.13 ± 0.34	≤0.001
Platelets (units)	0.83 ± 0.61	0.13 ± 0.03	≤0.001
FFP (unit)	1.83 ± 0.71	0.72±0.35	≤0.001
EBL (mL)	1956.52 ± 674.75	634.78±269.02	≤0.001

TXA: Tranexamic acid; RBC: packed red blood cells; FFP: Fresh frozen plasma; EBL: Estimated blood loss. Data presented as mean± standard deviation; Mann-Whitney test.

Table 3. Comparison of the Effectiveness of TXA on Duration of Surgery and Hospitalization in Two Study Groups

Variables	Control Group (n=23)	TXA Group (n=23)	*P* Value
Duration of surgery (h)	1.83 ± 0.62	1.15 ± 0.27	≤0.001
Duration of hospitalization (day)	3.91 ± 0.84	3.13 ± 0.48	<0.001
ICU hospitalization (day)	1.52 ± 0.73	0.78 ± 0.42	≤0.001

TXA: Tranexamic acid; ICU: Intensive care unit.
Data presented as mean ± standard deviation; Mann-Whitney test.

the TXA group was significantly lower than the controls (5). In a study by Kremer and Cortez, it was shown that the mean EBL in the TXA group (3.11 ± 3.94 mL) was lower than the placebo group (9.42 ±12.47 mL), but the difference was not significant (*P*=0.3). Of course, only 11 women were investigated, and therefore the sample size was not sufficient for EBL evaluation. Also, the mean of PRBCs transfusion during surgery in the TXA group was lower than the control group (15). In another study, the mean of EBL for women who received TXA at the time of umbilical cord ligation was significantly lower than those who did not receive TXA (672 vs. 1072 mL) (13). These results are in line with our study. Therefore, TXA can be utilized as a preventive intervention to prevent bleeding and its complications in women at risk of postpartum hemorrhage.

Table 4. Relationship Between Various Variables and the Amount of Bleeding after Cesarean Section, Considering the Study Groups as the Covariate

Variables	Correlation *	Sig (2-tailed)
Age (y)	0.063	0.682
BMI (kg/m^2)	-0.110	0.472
Gestational age (wk)	0.149	0.330
Number of pregnancy	0.167	0.273
PAS degree	0.345	0.017*

BMI: Body mass index; PAS: Placenta accrete syndrome.
*Partial correlation coefficient (*P* value less than 0.05 is statistically significant).

The results of a clinical trial investigating the efficacy of TXA in decreasing blood loss in women undergoing elective cesarean section showed that the mean of intraoperative and postoperative blood loss in the TXA group was lower than the control group (241.6 vs. 510 mL). In addition, the mean of hematocrit and hemoglobin levels in the TXA group was significantly lower than in the control group. Finally, it was stated that this drug could be useful for women with anemia or women who cannot receive blood products (20).

In a meta-analysis consisting of 9 trials with 2,365

participants, it was reported that TXA administration before cesarean section significantly reduced postpartum hemorrhage, need for blood transfusion during and after surgery, Hb reduction, and the emergence and severe postpartum hemorrhage, and is associated with no special side effects (14). The results of another meta-analysis, with 12 trials, also showed a significant decrease in bleeding after cesarean section and vaginal delivery in women receiving TXA (21). In addition, the results of three other controlled trials showed that TXA prescription exactly before cesarean section reduces intraoperative and postoperative bleeding and is not associated with any maternal side effects or adverse neonatal effects (22-24). In another study, Sentilhes et al reported that TXA prophylaxis prescription reduced vaginal postpartum hemorrhage (25). All of the mentioned studies support the high effect of TXA in reducing postpartum hemorrhage.

Our results also showed that the duration of surgery, the duration of hospitalization, and the number of days staying in the ICU in PAS women in the TXA group were significantly shorter than the control group. Considering the more postpartum hemorrhage and the need to receive more blood products in the control group than the TXA group, this result seems sensible. However, Abdel-Aleem and colleagues earlier showed no significant difference in the duration of hospitalization in women undergoing elective cesarean section receiving TXA and placebo (20). These results are not consistent with our findings, which could be related to the differences in the study population. The target population in the present study were women with PAS diagnoses, but Abdel-Aleem and colleagues have investigated women under elective cesarean section (20). However, both studies reported reduced bleeding during and after delivery in the TXA group.

In general, women with PAS require more hysterectomy during or after delivery and have a longer hospitalization time (1,3). In Asian countries where many women have anemia, hysterectomy is often performed as an initial intervention to prevent death from severe bleeding (exsanguination) (8,26). In the present study, hysterectomy was also performed for half of the participants, and no significant differences were observed between the two groups. Shakur et al were also reported that TXA administration in women with postpartum hemorrhage had no significant effect on the need for hysterectomy; in other words, the need for hysterectomy in women with postpartum hemorrhage did not show a significant difference between the groups receiving TXA and placebo (8).

In the present study, no side effects were observed during and after surgery in the TXA group, while 1 case of bladder rupture was reported in the control group. A large double-blind controlled clinical trial on more than 20 000 women with postpartum vaginal bleeding after vaginal delivery or cesarean section who received 1 gr intravenous TXA or control showed that TXA significantly reduces death from bleeding and has any side effects, including embolism events (8). Kremer and colleagues examined the efficacy of TXA prescription in women with PAS and found no TXA prescription complication in umbilical cord ligation (15). In two investigations by Sadek et al and Shakur et al, any side effect, including thromboembolism, has not been reported in the prescription of TXA prophylaxis at the time of umbilical cord ligation in women undergoing cesarean section or vaginal delivery (8,13). In general, the results indicated that no side effects had been observed in the prescription of TXA prophylaxis in women undergoing cesarean section (including women with PAS) or vaginal delivery. It should be mentioned that in all the mentioned studies and the current study, a low dose of TXA was used. Advantages and Limitations

Finally, the present study showed that intravenous TXA is effective in PAS women with no side effects and can be used as a cost-effective and safe drug to prevent bleeding and the need for blood products. Also, it reduces the hospitalization and ICU duration. It should also be noted that the present study is among the limited studies on the effectiveness of TXA in PAS women to obtain valuable information by examining its effect on various parameters.

However, the most important limitation of the study was the small number in each group. In addition, a fixed-dose of 1 g of TXA was used for all women without considering the patient weight; however, no specific side effect was observed. Therefore, by conducting more studies with larger sample sizes, better results can be achieved.

Conclusions

Our study showed that TXA administration effectively reduced postpartum hemorrhage, the need for postoperative blood transfusion, the duration of surgery, and the duration of hospitalization in women with PAS. TXA is an effective, inexpensive, safe, and readily available treatment and can be recommended as a prophylactic intervention to prevent blood loss in women with PAS.

Authors' Contribution

All authors had equal roles in the design, work, statistical analysis, and manuscript writing. All authors read and approved the final version of manuscript and take responsibility for the integrity of the data.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

This study proposal was approved by the Ethics Committee of the Vice Chancellor for Research, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Code: IR.AJUMS.REC.1399.485), also registered in the Iranian Registry of Clinical Trials center (identifier: IRCT20201003048909N1). All participants signed informed written consent before the study starts. Also, the ethical principles of the Helsinki Declaration and participant's confidentiality were considered in all stages of this research.

Financial Support

None declared.

Acknowledgments

This article was extracted from the student dissertation with the

research project number FIRC-9912 in the Faculty of Medicine, Jundishapur University of Medical Sciences, Ahvaz, Iran.

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