

Tranexamic Acid in the Control of Uterine Atony During Labor

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Background: Death from hemorrhage is still the leading cause of maternal mortality.

Objectives: The aim of this study was to determine the effect of tranexamic acid on the control of uterine atony during labor.

Patients and Methods: A randomized clinical trial was conducted on 90 pregnant women who had uterine atony in Qazvin, during the year 2012. The control group (n = 45) received the routine treatment of uterine atony. The second group (n = 45), in addition to the routine treatments, received 1 gram of tranexamic acid diluted in 100 mL saline of 5% dextrose in water by intravenous infusion within 10 minutes. The amount of blood loss, changes in hemoglobin level, need for surgical intervention and transfusion of blood products and duration of hospitalization were compared between the two groups. Data were analyzed using the chi-square test and t test.

Results: Hemoglobin level was 9.9 ± 5.1 in the control group six hours after hemorrhage while it was 8.10 ± 2.1 in the treatment group ($P = 0.004$). Hemoglobin level was 5.8 ± 4.1 in the control who did not receive transfusion of blood products during the first 24 hours after hemorrhage, while this level was 7.9 ± 4.1 in the treatment group ($P = 0.001$). The amount of bleeding significantly declined in the intervention group compared to the control group ($P < 0.001$). Moreover, the need for transfusion of blood products decreased by a third ($P < 0.001$) while the number of hospitalization days significantly decreased as well ($P < 0.04$).

Conclusions: Tranexamic acid can significantly reduce the rate of postpartum hemorrhage.

Keywords: Postpartum Hemorrhage; Tranexamic Acid; Caesarean Section

1. Background

Every year nearly 530 thousand women die of pregnancy and pregnancy-related complications around the world. One of the main causes of maternal mortality in the world is obstetric hemorrhage. The World Health Organization (WHO) estimated that 25% of maternal deaths in the world were due to severe bleeding after childbirth in 1990, and morbidity rate caused by severe bleeding after childbirth was estimated at 20 million each year (1, 2). Given that, mothers were admitted to the hospital for delivery, where there are abundant blood products for transfusion, maternal mortality rates markedly declined.

However, death from hemorrhage is still the leading cause of maternal mortality (3). More than 18% of maternal deaths were related to pregnancy and were directly caused by postpartum hemorrhage based on the results of the Centers for Disease Control and Prevention of the United States from 1977 to the end 1991. Half of all postpartum deaths are due to severe postpartum hemorrhage in developing countries (3, 4). The uterine atony can be considered as the most important cause of obstetric hemorrhage. Correct and active management of uterine contraction medications and other important measures are essential in treatment of this disease. In order to inhibit the activation of the fibrinolytic system, anti-fibrinolytic

drugs such as tranexamic acid should be used.

Several studies were conducted on tranexamic acid for reduction of hemorrhage during surgery and consequently reduction in the need for blood transfusions in patients under anesthesia during spinal surgery, urinary tract surgery, orthopedics, cardiac surgery and liver transplantation. The prophylactic administration of anti-fibrinolytic drugs such as tranexamic acid was also proposed despite differences of opinions between researches. It was noted that this medication improves blood homeostasis in certain recovery procedures (5). Anti-fibrinolytic amino acid drugs such as tranexamic acid or 4-amino-methyl cyclohexane carboxylic acid act by reversible binding to plasminogen and inhibit the binding of plasminogen to fibrin and activation of conversion to plasmin. This ultimately results in delay in fibrinolysis and degradation of the formation of blood clots. In other words, these drugs improve the clot structure and stability by inhibiting tissue fibrinolysis (6, 7).

Immediately after removal of the placenta, fibrinogen and fibrin are degraded rapidly, whereas the plasminogen activator and fibrin degradation products are increased by the activation of the fibrinolytic system. This activation can cause severe postpartum hemorrhage

about six to ten hours after delivery (6). Tranexamic acid inhibits the binding of fibrin to plasminogen in the homeostasis procedure, which is essential for binding to fibrin. The mechanism of action of this drug may inactivate the plasminogen binding on fibrin surfaces. It also inhibits fibrin degradation (8). The half-life of this drug is approximately 80 minutes provided that renal function is normal. Its side effects are dose dependent. Often, gastrointestinal symptoms such as nausea and vomiting, abdominal pain, and diarrhea are reported as side effects of this drug (6). The main risk of this drug is thromboembolic complications, which are caused by the inhibition of fibrinolysis. This inhibition is the natural defense mechanism against thrombosis formation (6). However, the risk of thrombosis formation was not reported in intravenous injection of tranexamic acid drug during surgery (9). In order to prevent postpartum hemorrhage to reduce maternal mortality, it is logical to conduct a study on prescription of tranexamic acid to control postpartum hemorrhage (2). Several studies were conducted on this drug and its role in the control of postpartum hemorrhage, which consequently leads to less need for blood transfusions. However, an adequate number of studies was not conducted on the role of this drug to control postpartum hemorrhage (2).

2. Objectives

The purpose of this study was to investigate the effect of tranexamic acid drug in the treatment of uterine atony during labor (whether caesarean section or vaginal surgery). This study was conducted in order to reduce postpartum hemorrhage and control cardiovascular hemodynamics with the purpose of minimal side effects in the patients. It was also designed in order to prevent morbidity of pregnant woman.

3. Patients and Methods

This study was a randomized clinical trial. It was conducted on 90 pregnant women who visited the Kosar hospital of Qazvin. All patients met the inclusion criteria of the study. None of the patients were excluded from the study. Patients who were included in the study were diagnosed by a gynecologist with uterine atony during cesarean section or vaginal delivery.

The patients were randomly allocated to two equal groups, including the treatment and the control group. Each group consisted of 45 patients. Both groups received 30 units of oxytocin in 1000 mL of normal saline as infusion upon delivery. In addition the control group received 20 units of oxytocin and 0.2 mg of methergine as well as uterine massage. The intervention group, in addition to the above routine measures, received one gram of tranexamic acid diluted in 100 mL saline of 5% dextrose in water by intravenous infusion within 10 minutes. The anesthesia method in patients undergoing cesarean section was spinal or epidural. When the patients were ad-

mitted to the maternity ward, a blood sample was taken from each of them for Complete Blood Count (CBC), Rh (Rhesus factor), BG (Blood Group) or blood cross-matching. After delivery and conducting the above measures, the patients were monitored for vital signs (blood pressure, heart rate, RR (Respiratory rate), and temperature), urinary output, and the amount of uterine hemorrhage and contraction every 15 minutes for up to two hours. The CBC test was retaken from the patients under study (both intervention and control groups) at 6 and 24 hours after the hemorrhage. The indication was the prescription of cell pack; the hemoglobin level was less than or equal to seven or the vital signs were unstable.

3.1. Method of Data Collection and the Tools for Collecting the Data

The information about the patients under study was collected by a check-list. This information included age, parity, mode of delivery, history of disease, Body Mass Index (BMI), weight of the infant, hemoglobin level on admission, hemoglobin level at 6 and 24 hours after drug administration, the need for transfusion of blood products, the need for surgical interventions and duration of hospitalization after delivery.

3.2. Methods

This study was conducted on 90 pregnant women who were diagnosis by a gynecologist with atony during labor. This study was conducted at the Kosar hospital of Qazvin during 2012. The delivery procedures included both cesarean section and vaginal delivery. All 90 patients met the inclusion criteria of the study. None of the patients was excluded from the study. All the pregnant women were diagnosed by a gynecologist with atony after delivery by either cesarean section or vaginal delivery and they were all included in the study. Atony is presented by significant uterine prolapse with hemorrhage of more than 500 mL after vaginal delivery or more than 1000 mL after cesarean section or hemorrhage that causes unstable vital signs in the patient. The exclusion criteria of the research included patients with a history of cardiovascular disease, liver disease, kidney disease, hemolytic disease blood-clotting disorders and those with a history of thromboembolism or thrombophlebitis and those who received general anesthesia for cesarean section. The amount of bleeding in the patients with vaginal delivery was calculated by visual estimation and weight of the blood in the dish under the patient. This level in patients with cesarean section was calculated by estimated measurement of the gas and gas Leung, and the amount of blood in the suction. The amount of bleeding was classified to three levels 500 mL to 1000 mL, 1000 mL to 2000 mL and more than 2000 mL. In order to evaluate changes in hemoglobin level, the patients who had not received transfusion of blood products were evaluated during the first 24 hours of delivery. The indication was prescrip-

tion of cell pack for the patients; the hemoglobin level was less than or equal to seven or the vital signs of the patients were unstable.

3.3. The Method to Describe the Data and Data Analysis

The Data were collected through a check list. Then, the collected data was entered in the SPSS 16 software. The data was evaluated using t test and chi-square tests. The P value was determined as $P < 0.05$.

First, the terms of the research was described to the patients under study. Although side effects of tranexamic drug are minimal and spontaneously limiting, the pregnant women under study were given an informed consent form. The informative form with information relevant to the investigation and the complete address and telephone number of the person responsible for the study were given to the patients and their husbands, so that they could obtain complete information about the trial. Written informed consent was obtained from the subjects, so that they could participate in the study.

4. Results

Among the 90 pregnant women participating in this study, 45 patients were placed in the control group while 45 patients were in the intervention group. The patients in the intervention group received the tranexamic drug. The BMI of the patients was the same in both groups. The mean age of the subjects in the control group was 24.7 ± 56.5 years old while this figure was 19.24 ± 23.5 years old in the intervention group. There was no significant difference regarding the age of the subjects between the two groups ($P = 0.9$). Regarding parity, 6.84% (38 cases) of the participants in the control group had a parity less than or approximately equal to three while 6.15% (7 patients) had a parity greater than three. In the intervention group, 6.95% ($n = 43$) had a parity less than or equal to three and 4.4% (2 patients) had a parity more than three. This difference was not significant ($P = 0.15$). Regarding the type of delivery, 40% ($n = 18$) had vaginal delivery while 60% (27 patients) had cesarean delivery in the control group. In the intervention group, 9.48% (22 patients) had vaginal delivery while 1.51% (23 patients) had cesarean delivery. This difference was also not significant ($P = 0.52$). Approximately, seven patients in the control group and five patients in the intervention group needed transfusion of blood products during the first 24 hours after delivery. These patients were not considered in the procedure of measuring change in hemoglobin level in the two groups (note that this difference was not statistically significant). Next, changes in hemoglobin level were measured among patients who received transfusion of blood products during the first 24 hours after delivery (38 patients in the control group and 41 patients in the intervention group). Overall, 8.57% (26 patients) of patients needed to receive a cell pack in the control group while this figure was 20% (nine pa-

tients) in the intervention group. This difference was statistically significant ($P = 0.001$). In the control group, four patients (8.8%) and in the intervention group two patients (4.4%) were found to need FFP (Fresh-Frozen Plasma). This difference was not significant ($P = 0.67$). About three cases (6.6%) from control subjects needed to receive platelet while no patients were needed to receive platelet in the intervention group. This difference was also not statistically significant (0.4). Approximately 14 cases (1.31%) of the control group and eight patients (8.17%) in the intervention group underwent uterine artery ligation. The difference was not significant ($P = 0.22$). About three patients in the control group (7.6%) and one patient (2.2%) in the intervention group underwent hypogastric artery ligation. This difference was not significant ($P = 0.61$). The need for hysterectomy in the control group was observed in two patients (2.2%) and no need for hysterectomy was seen in the intervention group. The difference was not significant ($P = 0.49$) (Table 1).

Regarding the hemoglobin level on admission of the patients, there was no significant difference between the two groups ($P = 0.26$). The hemoglobin level on the time of admission of the patients in the control group was 7.11 ± 5.1 while this level was 1.12 ± 1.1 in the intervention group. The hemoglobin level at six hours after the hemorrhage was 7.9 ± 5.1 in the control group while this level was 6.10 ± 3.1 in the intervention group. This difference was statistically significant ($P = 0.004$). The hemoglobin level was 5.8 ± 4.1 at 24 hours after bleeding in the control group while this level was 7.9 ± 4.1 in the intervention group. This difference was statistically significant ($P = 0.001$) (Table 2).

The amount of bleeding in the control group was less than 1000 mL in two patients (20%), while in the intervention group the amount of bleeding less than 1000 mL was in 16 patients (6.35%). This difference was significant ($P = 0.001$) (Table 3).

The number of hospitalization days in the control group was 8.3 ± 7.1 days while this figure was 9.2 ± 82.0 in the intervention group. This was statistically significant ($P = 0.004$). In this study, no adverse effects of thromboembolism caused by prescription of tranexamic acid drug were seen in the patients after delivery.

Table 1. Comparison of the Frequency of Patients Who Needed Transfusion of Blood Products and Surgical Intervention in Both Groups ^{a,b}

Variables	Control ^c		Case ^c		P Value
	Yes	No	Yes	No	
Packed cell	28.9	21.1	10	40	0.001
FFP	4.4	45.6	2.2	47.8	0.67
Platelets	3.3	46.7	0	50	0.24
Uterine artery ligation	15.6	34.4	8.9	41.1	0.22
Hysterectomy	2.2	47.8	0	50	0.49
Hypogastric artery ligation	3.3	46.7	1.1	48.9	0.61

^a Abbreviation: FFP, Fresh-Frozen Plasma.

^b Data are presented for 90 patients.

^c Data are presented for 45 patients.

Table 2. The Frequency Distribution, Mean and Standard Deviation of the Hemoglobin Level in the Intervention and Control Groups on Admission, 6 and 24 Hours After Bleeding^a

Hgb	Control ^b	Case ^c	P Value
First	11.17 ± 1.5	12.1 ± 1.1	0.2
6 hours	9.7 ± 1.4	10.8 ± 1.2	0.004
24 hours	8.4 ± 1.4	9.9 ± 1.5	0.004

^a Abbreviation: Hgb, Hemoglobin.

^b Data are presented for 48 patients.

^c Data are presented for 41 patients.

Table 3. The Frequency Distribution of the Amount of Bleeding in the Intervention and Control Groups^a

	Total	Case	Control	P Value
Amount of Bleeding				0.001
500 - 1000, mL	6.7	17.8	2.3	
1000 - 2000, mL	73.3	31.1	42.2	
> 2000, mL	20	1.1	5.6	

^a Data are presented for n = 90.

5. Discussion

This study investigated the effect of tranexamic acid drug on uterine atony during labor. Based on the results of this study, there was no significant difference regarding age, mode of delivery, hemoglobin level on admission of the patient and parity between the two groups. The results indicated that the amount of bleeding and the need to receive a cell pack and changes in hemoglobin levels in patients who received tranexamic acid significantly declined compared to the control group who did not receive this medication. Moreover, the mean number of hospitalization days also decreased in the intervention group compared to the control group. There were no significant differences between the two groups regarding the need for invasive procedures (uterine artery ligation and hypogastric artery ligation). Moreover, there was no significant difference between the two groups regarding the need for emergency hysterectomy. In our study, no complications relevant to thromboembolism and other side effects related to tranexamic acid were observed. No case of mortality was observed during the follow-up. In addition, all infants were born healthy without any problems. There was no significant difference regarding the need for receiving FFP and platelets between the two groups under study. In the study of Horrow et al. (3) tranexamic medication clearly reduced obstetric hemorrhage from the time of delivery up to two hours (7.42 ± 4.0 in the treatment group and 77 ± 9.73 in the control group) ($P = 0.001$). No drug-related side effects were observed in this study. It was concluded that tranexamic acid could safely reduce hemorrhage after cesarean section. The results of the above-mentioned study were in line with

those obtained by our study. However, the subjects under study in the above study were all primipara women and only women who underwent cesarean section were evaluated. On the other hand, in our study, all subjects including both primipara and multipara women were studied. Our study also included both types of delivery (vaginal delivery and cesarean section). In another study conducted by Ferrer et al. (10) it was concluded that tranexamic medication could reduce postpartum hemorrhage by 92 mL in the intervention group. In this study, the most common side effect of this drug was vomiting, as reported by the patients. In our study, no drug-related side effect was reported. However, in terms of reducing the amount of bleeding, the volumes of blood loss reported in our study were in line with those reported in the above study. Although the sample size was large in the above study, only cases with vaginal delivery were examined. Novikova et al. conducted a study on 273 patients in 2010 (2). In their study, it was concluded that prescription of 1 g tranexamic medication for controlling postpartum hemorrhage in the first group had no significant difference with prescription of 500 mg tranexamic medication in the second group. However, prescription of 1 g tranexamic medication in the second group significantly reduced postpartum hemorrhage compared to the third group who did not receive this medication. In our study, all patients in the intervention group received 1 g of intravenous tranexamic infusion spontaneously after delivery. The second dose of the drug might have been repeated at the same dose 30 minutes later if needed.

Shakur et al. conducted a study on 15000 patients with atony after cesarean section in 2010 and examined the impact of venous tranexamic infusion in controlling hemorrhage (11). In their study, it was revealed that tranexamic medication decreases the hemorrhage caused by uterine atony. They also found that this medication could reduce postpartum hysterectomy by three to four percent. This study was more precisely conducted considering its large sample size and the placebo effect of the drug compared to our study. However, the results of our study were in line with those obtained by the above study in terms of reducing blood loss after delivery. In the study of Eftekharian et al. on 40 pregnant women in 2008 (5), it was revealed that the control group needed transfusion of blood products almost double the number of blood transfusions in the treatment group. Moreover, the amount of blood loss was clearly reduced in the treatment group compared to the control group. As a result, it was revealed that tranexamic medication reduces hemorrhage during surgery. In this study, the sample size was less than our study. On the other hand, in our study, the dose of tranexamic medication was 1 g for all patients. The results of this study were in line with those obtained by our study regarding the reduced need for transfusion of blood products. None of the reviewed studies, examined and compared the hospitalization days of the

patients. However, we examined this in our study and found a significant difference between the control and intervention groups. Nevertheless, it is essential to conduct several other studies examining this issue in order to confirm the results obtained in this study regarding hospitalization days. In none of the studies, the need for platelet and FFP was examined between the two groups, whereas we evaluated this issue in this study. However, no difference was observed between the two groups. Cumulative incidences of emergency hysterectomy are different in different parts of the world. However, it is estimated to be between 1.25% and 0.04% for all births. In a prospective study conducted by Nayama (12) in 2006, the incidence of hysterectomy due to uterine atony was reported as 8.26%. In the study conducted by Eftekharian Jahromi et al. (5) it was reported that the incidence of hysterectomy decreased by a third in the intervention group. In the study conducted by Shakur et al. (11) it was reported that the incidence of hysterectomy was decreased by 3 - 4% in the intervention group. In our study, two patients (4.4%) of the control group needed hysterectomy while no patient needed hysterectomy in the intervention group. Although no significant differences were observed between the two groups, tranexamic acid medication can be effective in reducing postpartum emergency hysterectomy.

In conclusion, based on previous studies and our study, the prescription of tranexamic acid can be effective for controlling uterine atony and reducing the hemorrhage caused by this atony. This medication can also be used to reduce the need for transfusion of blood products. It may also be used to control bleeding caused by atony.

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Authors' Contributions

Study concept and design: Ameneh Barikani and Ezzatossadat Haj Seyed Javadi. Analysis and interpretation of data: Ameneh Barikani. Drafting of the manuscript: Ameneh Barikani and Ezzatossadat Haj Seyed Javadi.

Critical revision of the manuscript for important intellectual content: Zoya Sadeghipour and Maryam Javadi. Acquisition of data: Zoya Sadeghipour and Maryam Javadi. Statistical analysis: Ameneh Barikani. Administrative, technical and material support: Ameneh Barikani and Maryam Javadi. Study supervision: Ezzatossadat Haj Seyed Javadi.

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