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Original Article

Effect of Tranexamic Acid Use on Estimated Blood Loss in Postpartum Hemorrhage

Traneksamik Asit Kullanımı Postpartum Kanamada Tahmini Kan Kaybına Olan Etkisi

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Abstract

Objective: Postpartum hemorrhage is one of the most critical obstetric emergencies. This study aims to evaluate the effect of tranexamic acid on vital signs in cases of postpartum hemorrhage.

Material and Method: In this retrospective case-control study, the vital and laboratory values of the patients were recorded at the time of initial hospitalization, and at 2 and 6 hours after delivery. Mean arterial pressure (MAP) was calculated as Diastolic Blood Pressure + 1/3 (Systolic Blood Pressure- Diastolic Blood Pressure). The 2nd and 6th hour ΔHb was determined as the difference between the admission Hb and the Hb at 2 and 6 hours, respectively. Patients who received tranexamic acid treatment were compared to those who did not, based on these data.

Results: A total of 156 patients with postpartum hemorrhage who underwent cesarean section were included in our study. Of these patients, 83 received tranexamic acid treatment in addition to postpartum hemorrhage protocols and were included in the study group. The group that received the standard protocol without tranexamic acid treatment was included in the control group, consisting of 73 patients. The mean age of the patients in the study was 30.86±6.09 years, and the mean body mass index was 30.06±5.18 kg/m². Mean arterial pressure was higher in the study group compared to the control group (68.51±34.92 mm Hg vs. 56.20±40.33 mm Hg; p=0.001). The difference in hemogram values at 2 hours and 6 hours was significantly lower in the group that did not receive tranexamic acid compared to the study group (p=0.018, p=0.001).

Conclusion: It was observed that the addition of tranexamic acid to the treatment of postpartum hemorrhage significantly increased the mean arterial pressure of the patients and resulted in notable differences in hemogram changes.

Keywords: Postpartum hemorrhage; tranexamic acid; vital signs; blood loss

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Öz

Amaç: Postpartum kanama en önemli obstetrik acillerden birisidir. Traneksamik asidin postpartum kanamada vital bulgular üzerindeki etkisinin değerlendirilmesi planlanmıştır.

Gereç ve Yöntem: Bu retrospektif vaka kontrol çalışmada, hastaların vital ve laboratuvar değerleri için hastaneye ilk yatışında alınan değerler ile doğum sonrası 2. ve 6. saatlerindeki değerler alınmıştır. Ortalama arteryel basınç (MAP) = Diyastolik kan basıncı + 1/3 (sistolik kan basıncı – diyastolik kan basıncı) formülü ile hesaplanmıştır. 2. ve 6. saat ΔHb'leri hastanın giriş Hb ile 2. ve 6. saatlerindeki Hb'leri arasındaki fark olarak hesaplanmıştır. Traneksamik asit tedavisi alanlar ve almayanlar bu veriler üzerinden kıyaslanmıştır.

Bulgular: Çalışmamıza, postpartum kanaması olan ve sezaryan geçirmiş toplam 156 hasta dahil edilmiştir. Bu hastaların 83'üne postpartum kanama protokollerine ek olarak traneksamik asit tedavisi de verilmiştir ve çalışma grubuna dahil edilmiştir. Standard protokolün uygulanıp, traneksamik asit tedavisi almayan grup ise kontrol grubuna dahil edilmiştir ve bu grupta 73 hasta bulunmaktadır. Çalışmaya dahil edilen hastaların yaş ortalaması, 30.86±6.09 yıl iken, vücut kitle indexi ortalaması 30.06±5.18 kg/m2'dir. Çalışma grubunda ortalama arteriyel basıncın kontrol grubuna göre daha yüksek olduğu tesbit edilmiştir(56.20±40.33mm Hg, 68.51±34.92 mm Hg; p=0.001) . Yapılan çalışmada ek tedavi olarak traneksamik asit almayan grupta 2 saat ve 6 saat hemogram değerlerindeki farklılık çalışma grubuna göre anlamlı olarak daha düşüktür (p=0.018, p=0.001).

Sonuç: Postpartum kanama tedavisine eklenen traneksamik asit ile hastaların özellikle ortalama arteriyel basınçlarda yükselme olduğu ve hemogram değişimlerinde farklılık olduğu gözlemlenmiştir.

Anahtar Kelimeler: Postpartum kanama; traneksamik asit; vital bulgular; kan kaybı

1. Introduction

Postpartum hemorrhage is one of the most critical obstetric emergencies and a major cause of maternal mortality in both developed and developing countries worldwide. Postpartum hemorrhage affects 5-6% of all pregnancies worldwide and is responsible for 25% of maternal deaths (1). Postpartum hemorrhage can be caused by various factors. The etiology generally includes uterine atony, trauma-related lacerations, placental retention and bleeding diatheses. In addition, conditions such as pre-eclampsia, placenta accreta spectrum, placenta previa and multiple pregnancies increase the risk of hemorrhage.

Most deaths from obstetric hemorrhage occur within the first few hours, and 90% of these deaths are preventable. Early diagnosis and treatment saves lives. Visual assessment of bleeding can be deceptive and may not reflect the actual amount of blood loss. Therefore, symptoms of hypovolemia should be monitored after each birth. According to the World Health Organization (WHO), bleeding of more than 500 ml within 24 hours of delivery is defined as postpartum hemorrhage. Severe postpartum hemorrhage is characterized by bleeding of more than 1000 ml within 24 hours (2). Many health organizations recommend active management of the third stage of labor to prevent postpartum hemorrhage. Several studies have shown that active management reduces the amount of postpartum hemorrhage. Active management consists of three components.

1. Administration of uterotonics (oxytocin)
2. Massage of the uterus
3. Controlled pulling of the umbilical cord

Several studies have shown that the prophylactic use of uterotonics reduces the need for therapeutic doses of these drugs (3). Although it makes no difference whether 10 units of oxytocin are administered intramuscularly (IM) or intravenously (IV), this remains the most effective prophylactic method with the fewest side effects and is still used as the first choice today. According to the FIGO (International Federation of Obstetrics and Gynecology) guideline for the prevention of postpartum hemorrhage (4):

1. The use of uterotonics to prevent postpartum hemorrhage in the third stage of labor is recommended for all deliveries. Oxytocin 10 units can be administered either intramuscularly (IM) or intravenously (IV), regardless of the mode of delivery.

2. If oxytocin is not available, 200 µg ergometrine/methylergometrine intramuscularly (IM) or intravenously (IV), 400-600 µg oral misoprostol or 100 µg carbetocin IM or IV can be administered as an alternative.

3. For bleeding greater than 500 mL, the combination of oxytocin with methylergometrine or misoprostol may be more effective; however, the possible side effects must be carefully considered.

4. Oral misoprostol may be administered in the absence of a physician experienced in labor; however, controlled cord traction is not recommended.

5. Continuous uterine massage is not recommended for patients receiving prophylactic oxytocin.

6. Uterine examination is recommended for all women to detect atony.

Oxytocin: Oxytocin, released from the posterior pituitary gland, triggers uterine contractions by initiating intracellular calcium release and increasing local prostaglandin production. There are no oxytocin receptors in the uterus until the 13th week of pregnancy, but the number of receptors gradually increases thereafter. Consequently, pregnancies respond to lower doses of oxytocin. Repeated doses lead to a desensitization of the receptors and thus to a lower response (5).

Misoprostol: Misoprostol is a prostaglandin E1 analog that triggers uterine contractions. It can be administered orally, sublingually, buccally and rectally. Its ease of use and storage conditions are significant advantages over oxytocin. FIGO and WHO recommend a dosage of 400-600 µg orally if oxytocin is not available (6). The most common side effect is fever, which typically begins with chills. Fever can be treated with paracetamol.

Ergot alkaloids: ergometrine and methylergometrine are agonists of serotonergic receptors in smooth muscle, weak agonists of dopaminergic receptors and partial agonists of alpha-adrenergic receptors. They trigger rapid and rhythmic uterine contractions. Due to their vasoconstrictive effect, they are contraindicated in patients with hypertension, Raynaud's phenomenon and coronary heart disease. A dose of 0.2 mg is administered intramuscularly (IM) and can be repeated every 2-4 hours.

Carbetocin: Carbetocin is a long-acting synthetic analog of oxytocin that has the same pharmacological properties but a 4 to 10 times longer duration of action. It is administered as a single dose of 100 mcg intravenously (IV) after a normal vaginal delivery or cesarean section (7). It is used prophylactically.

Tranexamic acid (TXA): Tranexamic acid has been shown to be beneficial when used in combination with uterotonics, with effects extending beyond its antifibrinolytic properties (8). A dose of 1 gram is administered intravenously (IV) over 10 minutes. Although there is a theoretical concern of an increased risk of thrombosis, studies have shown that it does not statistically increase the risk of thrombosis compared to the control group (9).

In light of this information, this study investigated the effect of adding tranexamic acid to the standard postpartum hemorrhage management protocol on vital signs and laboratory values in the postpartum period.

2. Material and Methods

Patients who delivered between January 1, 2023 and February 1, 2024 at Etlik Zübeyde Hanım Gynecology and Obstetrics Training and Research Hospital, a reference hospital, were evaluated by retrospective chart review. Approval for non-interventional studies was obtained from the Ethics Committee of Etlik Zübeyde Hanım Research and Training Hospital prior to the start of the study (approval date: April 24, 2024; issue no.: 04/08).

The study enrolled 156 patients who had no known medical conditions, had an uneventful pregnancy, were of reproductive age, had a BMI <29.9, had a singleton pregnancy, had delivered by cesarean section, and had postpartum hemorrhage according to the study criteria. Exclusion criteria were multiple pregnancy, fetal anomaly, maternal age under 18 years or over 45 years, duration of pregnancy under 25 weeks, severe anemia (Hb <7 g/dL), stillbirth, maternal bleeding disorders, maternal heart diseases and maternal infections (chorioamnionitis, sepsis).

The total sample size was determined retrospectively from the hospital records. The files of all patients who had received intrapartum tranexamic acid were analyzed individually. The patients' medical records were accessed via their files and the hospital's patient files. Demographic data (age, parity, body mass index [BMI = weight/height² = kg/m²] before and during pregnancy, concomitant diseases, smoking status), information on delivery (type of delivery, birth weight, type of delivery, Single or multiple pregnancy and whether assisted reproductive techniques were used), vital signs (pulse rate 2 and 6 hours after delivery) and laboratory values (hemoglobin [Hb], white blood cell count, hematocrit and platelet count). For the vital and laboratory values of the patients, the values recorded on admission to hospital and 2 and 6 hours after delivery were used. Mean arterial pressure (MAP) was calculated using the following formula: MAP = Diastolic blood pressure + 1/3 (Systolic blood pressure - Diastolic blood pressure). The ΔHb of the 2nd and 6th hour was calculated as the difference between the Hb at admission and the Hb after 2 and 6 hours, respectively.

Adverse effects considered in the study included blood transfusion, repeat parotomy, repair of vaginal lacerations in the operating room, curettage, hysterectomy, balloon tamponade, arterial ligation, need for intensive care, and multiple organ failure (including impaired renal function tests, impaired liver function tests, consumption-related coagulopathy, and pulmonary edema). The study enrolled 156 patients with no known medical problems who had had an uneventful pregnancy, were of childbearing age, had a BMI <29.9 and had singleton pregnancies.

Exclusion criteria for subjects: multiple pregnancies, fetal anomalies, pregnancies in those under 18 or over 45 years of age, pregnancies of less than 25 weeks, severe anemia (Hb <7 g/dL), stillbirth, maternal bleeding disorders, maternal heart diseases, maternal infections (chorioamnionitis, sepsis).

Statistical analysis

All statistical analyses were performed using the SPSS 25.0 package program (SPSS Inc., Chicago, IL). The conformity of continuous numerical variables to normal distribution was checked by the Shapiro-Wilk test. Quantitative variables were expressed as mean ± standard deviation or median (minimum-maximum), and qualitative variables were expressed as relative frequency (%). The Kruskal-Wallis test was used to compare non-normally distributed parametric variables across three groups. For normally distributed variables, a one-way ANOVA was performed for group comparisons. The Mann-Whitney U test and Student's t-test were used to compare parametric variables between two groups with and without normal distribution, respectively. The Pearson chi-square test was used to compare categorical variables between groups. A p-value <0.05 was considered statistically significant.

3. Results

A total of 156 patients were included in our study. Tranexamic acid was administered to 83 of these patients, while 73 patients were included in the control group. The mean age of the patients was 30.86±6.09 years, and the mean body mass index was 30.06±5.18 kg/m². The demographic data of the two groups are presented in Table 1. According to Table 1, there was no significant difference between the two groups in terms of age, body mass index, smoking status, reasons for cesarean delivery, and baby birth weight.

Table 1. Demographic data of the participants			
	Control group (n=73)	Study group (n=83)	P
Age (years)	31.01±5.980	30.72±6.218	.643
Parity	2.00±1.17	1.59±1.51	.051
Body mass index (kg/m2)	30.45± 4.37	29.72±5.77	.085
Smoking			
No	56 (89.1%)	71 (95.0%)	.108
Yes	17 (10.9%)	12 (5.0%)	
Indication for caesarean section			.147*
Cephalopelvic discordance	6	17	
Oligohydramnios	-	3	
Previous caesarean section	49	38	
Placental abnormality	1	2	
Malpresentation	5	8	
Multiple pregnancy	2	2	
Fetal distress	8	10	
Macrosomy	2	3	
Birth weight (gram)	3066.18±569.07	3050.82±625.50	.334

Table 2. Comparison of vital parameters in study groups			
	Control group (n=73)	Study group (n=83)	P
Pulse			
0.hour[c]	86.8±13.2	90.8±14.1	.239
2. hour[c]	83.4±12.8	83.7±14.3	.966
6. hour[c]	87.7±12.8	87.5±11.3	.740
Systolic blood pressure (mm Hg)			
0. hour[c]	119.31±14.31	118.08±11.30	.208
2. hour[c]	115.55±13.07	113.83±12.97	.701
6. hour[c]	113.63±10.05	111.47±12,36	.489
Diastolic blood pressure (mm Hg)			
0. hour[c]	65.94±9.70	68.65±9.47	.943
2. hour[c]	69.98±9.31	68.89±7.99	.428
6. hour[c]	69.33±7.37	68.56±8.48	.287
Mean arterial blood pressure			
0. hour[c]	**56.20±40.33**	**68.51±34.92**	**.001**
2. hour[c]	**57.16±41.03**	**67.50±34.34**	**<.001**
6. hour[c]	**56.44±40.19**	**66.69±33.98**	**<.001**

Table 3. Prevalence of maternal adverse effects due to postpartum bleeding	
Maternal Adverse effects	Prevelance n (%)
Transfusion	18 (11.5%)
Relaparotomy	1 (%0.6)
Artery Ligation	3 (%1.9)
Hysterectomy	1 (%0.6)
Need for referral / intensive care	1 (%0.6)

In Table 2, the vital signs of the patients who received tranexamic acid were compared with those of the control group. The results indicate that the mean arterial pressure was higher in the study group compared to the control group (56.20±40.33 mm Hg vs. 68.51±34.92 mm Hg; p=0.001). Additionally, the mean arterial pressure values at the postoperative 2nd and 6th hours were significantly lower in the control group (p=0.001,p=<0.001, p=<0.001, respectively).

Eighteen (11.5%) of the patients with postpartum hemorrhage received blood transfusions. Three patients (1.9%) underwent arterial ligation after cesarean section. One patient (0.6%) required relaparotomy and peripartum hysterectomy. One patient was referred to the intensive care unit (Table 3).

In the study, the treatment administered significantly affected the difference between the 2-hour and 6-hour hemogram values (p=0.018, p=0.001). Accordingly, delta hemogram values were found to be lower in the control group compared to the study group (0.46±0.96 g/dL vs. 1.02±0.90 g/dL) (Table 4).

Table 4. Comparison of laboratory parameters in study groups			
	Control group (n=73)	Study group (n=83)	P
WBC (10^9/L)			
0. hour[c]	10268.49±2645.06	10444.57±3662.40	.530
2. hour[c]	14371.23±5619.07	16380.84±4994.09	.061
6. hour[c]	14950.68±4981.55	14950.68±4981.55	.817
Hb (g/L)			
0. hour[c]	11.81±1.36	11.60±1.34	.762
2. hour[c]	11.35±1.52	10.88±1.42	.510
6. hour[c]	10.79±1.34	10.48±1.41	.715
Δ 2. hour hb[c]	**0.46±0.96**	**0.71±1.32**	**.018**
Δ 6. Hour hb[c]	**1.02±0.90**	**1.12±1.34**	**.001**
Plt (10^9/L)			
0. hour[c]	232.64±64.42	235.29±68.19	.361
2. hour[c]	216.96±63.04	206.63±59.95	.971
6. hour[c]	210.88±64.74	211.46±64.16	.729
Fibrinogen	380.11±74.89	390.20±74.44	.890

[a]Ki kare analizi, [b]Fisher's Exact Test, [c]Mann Whitney test, WBC (10^9/L): beyaz kan hücresi, Hb (g/L): hemoglobin, Hct: hematokrit, Plt (10^9/L): platelet

4. Discussion

Postpartum hemorrhage, a major cause of maternal mortality and morbidity, affects the lives of millions of women (10). Timely treatment of postpartum hemorrhage, which has numerous negative effects on the mother, is crucial. In this study, we aimed to investigate the impact of tranexamic acid treatment given in addition to the standard protocol on the prognosis of patients. We observed an increase in mean arterial pressure in the patients. In contrast, we found that the change in hemogram values was lower in the control group. This is probably due to the fact that more bleeding occurred in the tranexamic acid- treated group, which necessitated the use of additional agents during treatment. It was also found that the number of blood transfusions was higher in the group of patients receiving this treatment.

Postpartum hemorrhage is usually diagnosed based on the estimated amount of blood observed visually. However, this estimate is often inaccurate. The amount of bleeding can be misleading as it can be mixed with other fluids and can occur in areas that are not visible. Therefore, when making a diagnosis, we should consider not only the 1000 ml of bleeding within 24 hours of delivery, but also the symptoms of hypovolemia associated with postpartum hemorrhage (6). Laboratory values are also unreliable in acute hemorrhage, as it may take some time for hemoglobin and hematocrit levels to drop. It is crucial to treat women with clinically diagnosed postpartum hemorrhage promptly. An estimated blood loss of more than 500 ml after a vaginal delivery or more than 1000 ml after a cesarean section, or a blood loss sufficient to jeopardize hemodynamic stability, is defined as postpartum hemorrhage (11). Women with postpartum hemorrhage receive a fixed dose of 1 g tranexamic acid. This dose, 10 ml (100 mg/ml), is administered intravenously as soon as possible after delivery (1 ml per minute). If bleeding continues after 30 minutes, a second dose of 1 g can be administered intravenously. Tranexamic acid is intended as an adjunct to the usual therapies for the treatment of postpartum hemorrhage.

Tranexamic acid is a safe, effective and cost-effective treatment for postpartum hemorrhage. Current research is focused on interventions to prevent postpartum hemorrhage, particularly in high-risk groups. The TRAAP trial (Tranexamic Acid for the Prevention of Postpartum Hemorrhage Following Vaginal Delivery) was a multicenter, double-blind, placebo-controlled trial in which 4,079 women were randomized to receive either tranexamic acid or placebo. While the trial did not show a reduction in postpartum hemorrhage, it did result in a 25%

reduction in clinically significant postpartum blood loss (12). These results suggest that tranexamic acid has prophylactic potential. In healthy volunteers, intramuscular tranexamic acid reaches therapeutic levels (>10 mg/L) in about 30 minutes. Healthcare professionals are trained in the administration of intramuscular oxytocin, and if proven effective, intramuscular tranexamic acid could be life-saving. Advances in emergency obstetric care, including the use of tranexamic acid as an initial treatment, have resulted in more women surviving postpartum hemorrhage than ever before.

The literature review shows that administration of tranexamic acid (TXA) for prophylaxis of obstetric hemorrhage decreases blood loss after cesarean section and reduce the need for blood transfusions (13). Studies on blood pressure have shown that the additional administration of tranexamic acid leads to favorable results (14,15). Randomized controlled trials have confirmed that maternal mortality and the number of emergency transfusions during surgery are reduced.

This study was not powered to examine the adverse effects of TXA in the treatment of postpartum hemorrhage on the mother. Our review of the results is consistent with previous reports and indicates that more information is needed. Well-designed studies with larger numbers of participants are needed. In addition, the association between this treatment and thromboembolic events is based on assumptions and has not yet been proven.

As shown in various studies, tranexamic acid has been used for almost 50 years but has only recently found its place in the postpartum population. Despite the timeliness of these studies, further research with larger patient series is needed to contribute to the literature. Due to the small number of patients undergoing hysterectomy, curettage, multiple organ dysfunction syndrome (MODS), balloon tamponade and arterial ligation, meaningful results have not been obtained in these groups. Therefore, multicenter prospective studies with larger patient series are required.

Author contribution

Study conception and design: MC and MBB; data collection: MC; analysis and interpretation of results: MC, MBB, and ÖYC; draft manuscript preparation: MC, MBB, and ÖYC. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Non-Interventional Studies Ethics Committee of Etlik Zübeyde Hanım Women's Health Training and Research Hospital (Decision no: 11/23.11.2023).

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Conflict of interest

The authors declare that there is no conflict of interest.

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