DOI: 10.14744/cm.2024.54154
Comprehensive Medicine 2024;16(4):232-237

RESEARCH ARTICLE

Effect of Prophylactic Tranexamic Acid Use on the Amount of Bleeding in Previous Cesarean Deliveries

Hale Çetin Arslan[1], Kadir Arslan[2], Mustafa Göksu[1], Burak Demirdelen[1], Pakize Özge Karkın[1]

[1]Department of Gynecology and Obstetrics, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye
[2]Department of Anesthesiology and Reanimation, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye

ABSTRACT

Objective: This study aimed to evaluate the effect of prophylactically administered tranexamic acid (TXA) on the amount of perioperative bleeding in previous cesarean deliveries.

Materials and Methods: Patients who underwent previous cesarean section between January 2022 and January 2023 in our hospital, a tertiary care center, were retrospectively screened. Patients who received 1 g of TXA intravenously 10 minutes before the incision during previous cesarean delivery were defined as the study group, and patients who did not receive it were defined as the control group. The patients' demographic findings, clinical characteristics, preoperative and postoperative 24th-hour hemogram levels, uterotonic and blood transfusion needs, and side effect profiles were compared between the two groups.

Results: A total of 203 cases were included: 103 cases in the study group and 100 cases in the control group. There were no significant differences between the groups in terms of demographic characteristics, operation duration, and clinical outcomes such as fetal macrosomia. The groups' preoperative hemoglobin levels were similar, but postoperative hemoglobin levels were significantly higher in the study group (p=0.015). Estimated blood loss and transfusion needs were also significantly lower in the study group (p=0.003, p=0.03, respectively). No thromboembolic events were observed in any patient.

Conclusion: Our study determined that TXA applied prophylactically in previous cesarean section operations reduced perioperative bleeding and the need for blood transfusion. Its use will be advantageous to clinicians, especially in cases where resources are limited or in anemic patients, as it reduces the need for banked blood.

Keywords: Cesarean section, postpartum hemorrhage, tranexamic acid

How to cite this article: Çetin Arslan H, Arslan K, Göksu M, Demirdelen B, Karkın PÖ. Effect of Prophylactic Tranexamic Acid Use on the Amount of Bleeding in Previous Cesarean Deliveries. CM 2024;16(4):232-237

INTRODUCTION

Postpartum hemorrhage (PPH) is a life-threatening bleeding that causes hemodynamic disturbances and may require transfusion of blood and blood products. It is known that PPH is responsible for approximately 25% of maternal deaths and severe anemia in 12% of survivors.[1] More blood loss occurs in cesarean births than in vaginal births. Nowadays, there is an increase in the prevalence of PPH along with the cesarean section trend in developed and developing countries. Even in countries with limited resources, such as Africa, the prevalence of PPH reaches 5.1–25.7%.[2] Therefore, early intervention and active management in the third stage of labor, especially in patients at risk of obstetric bleeding, will contribute significantly to reducing bleeding-related morbidity and mortality.[3] While oxytocin is the first-line treatment uterotonic agent in the third stage of labor, prostaglandins (E1, E2, and F2α), ergot alkaloids, carbetocin, and tranexamic acid are other treatment options.[4]

Tranexamic acid (TXA) is a synthetic lysine derivative that binds to lysine-binding sites in plasminogen and prevents plasmin activation. It shows its reducing effect on bleeding by inhibiting fibrinolysis.[5] TXA is an antifibrinolytic agent used to decrease bleeding and the need for blood transfusions in trauma settings, coronary artery bypass grafting (CABG), or

Address for Correspondence: Hale Çetin Arslan, Department of Gynecology and Obstetrics, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye
E-mail: halecetin90@gmail.com **ORCID ID:** 0000-0002-5392-2434

Received date: 24.07.2024
Revised date: 19.09.2024
Accepted date: 22.09.2024
Online date: 17.10.2024

Comprehensive Medicine published by Kare Media.

orthotopic liver transplantation. Mainly, the usage of TXA in the early stages of treatment of trauma patients has been shown to reduce mortality.[6] However, in cases of PPH where blood transfusion is limited, the World Health Organization (WHO) has developed different strategies besides standard uterotonics. The WHO 2012 guideline also recommends the use of tranexamic acid in cases where oxytocin and other uterotonic drugs fail to stop bleeding or when bleeding is caused by trauma.[7] At the same time, in a study conducted on patients with PPH, it was revealed that TXA applied significantly reduced the overall mortality rates.[8] With this study, we aimed to examine the effectiveness and side effect profile of prophylactically administered TXA during previous cesarean delivery in our clinic, which is a tertiary center, by comparing it with the patient group in which we did not use it.

MATERIALS and METHODS

The study was conducted on 203 pregnant women who underwent previous cesarean sections in a tertiary referral center's obstetrics and gynecology department between January 2022 and January 2023. It was conducted in accordance with the principles of the Declaration of Helsinki and following ethics committee approval from the local ethics committee (KAEK/2022.06.158). A written informed consent form was obtained from all participants.

In our clinic, previous cesarean section is generally performed after the 37th week of pregnancy, according to the last menstrual period. Singleton pregnant women who were over 18 years of age and had previous cesarean section in our clinic between 37–42 weeks of gestation were included in this study. Antenatal bleeding (placenta previa, placental abruption, etc.), intrauterine death, multiple pregnancies, polyhydramnios, maternal anemia (hemoglobin <7 mg/dl), myoma uteri, known bleeding diathesis, heart, liver and kidney diseases, hematuria, aneurysmal subarachnoid hemorrhage and trauma-related intra- or extracranial hemorrhage were determined as exclusion criteria.

When calculating the sample size of the study, Maged et al.[9] based on their work. Considering α:0.05 and the power of the study (1-β):0.8 in the calculation, at least 75 patients were needed for each group. Approximately 2400 cesarean births occur annually in our clinic. This study was planned as an experimental study to see the preliminary results of TXA, which is frequently used during previous cesarean section. Two hundred ten patients who underwent previous cesarean section in our clinic were retrospectively screened from the hospital database. Patients who received 1 g intravenous TXA in addition to the routine procedure during cesarean section constituted the study group (n=103), and patients who did not receive it constituted the control group (n=100). Seven patients were excluded from the study because they met the exclusion criteria (Fig. 1).

In previous cesarean section operations performed in our clinic, 1 g of cefazolin is administered intravenously at least 10 minutes before the skin incision. After consulting the patient, the surgeon and anesthesiologist decide together on the type of anesthesia. Some of our clinicians administer 1 g of TXA as an intravenous infusion 10 minutes before the incision in cesarean section. Then, within 1 minute following the birth of the baby, 10 IU intravenous oxytocin is given, and the placenta is delivered with controlled cord traction. To understand the presence of uterine atony, uterine massage is continued, and tone is evaluated by palpation. In the presence of loss of tone and perioperative bleeding 10 minutes after oxytocin injection, the clinician requests additional uterotonics. Some additional uterotonics that the anesthesiologist and surgeon will decide on include 40 IU oxytocin or intramuscular methylergometrine maleate, 0.5 mg or 600 µg rectal misoprostol. The researchers followed all procedures identically. The difference between hematocrit values taken before and 24 hours after cesarean section was used to calculate the estimated blood loss during the operation. EBV (estimated blood volume) is calculated by multiplying the woman's weight in kg by 85 (Fig. 2).

The participants' demographic and clinical results were recorded. The patient's age, parity, body mass index, previous cesarean delivery history, gestational age at birth, type of anesthesia applied, operation duration, and fetal macrosomia (>4000 g) rates were recorded. Preoperative and postoperative hemoglobin, hematocrit values, delta hemoglobin (difference between hemoglobin values), estimated blood loss, additional uterotonic agent and blood transfusion requirement, and side effect profile (headache, nausea, vomiting, diarrhea, anaphylaxis, visual disturbances, seizures, and thromboembolic events) were obtained.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) 22.0 for Windows 24 (SPSS Inc., Chicago, IL) program was used to analyze the data. Normal distribution in study data was evaluated by Shapiro–Wilks test. Parameters that were distributed normally were used by student t test while Mann–Whitney U test was used for data without normal distribution. Pearson and Fisher's exact test examined the qualitative data between the groups. Numerical data were expressed as standard deviation and categorical data as frequency and percentage. p values <0.05 were considered statistically significant.

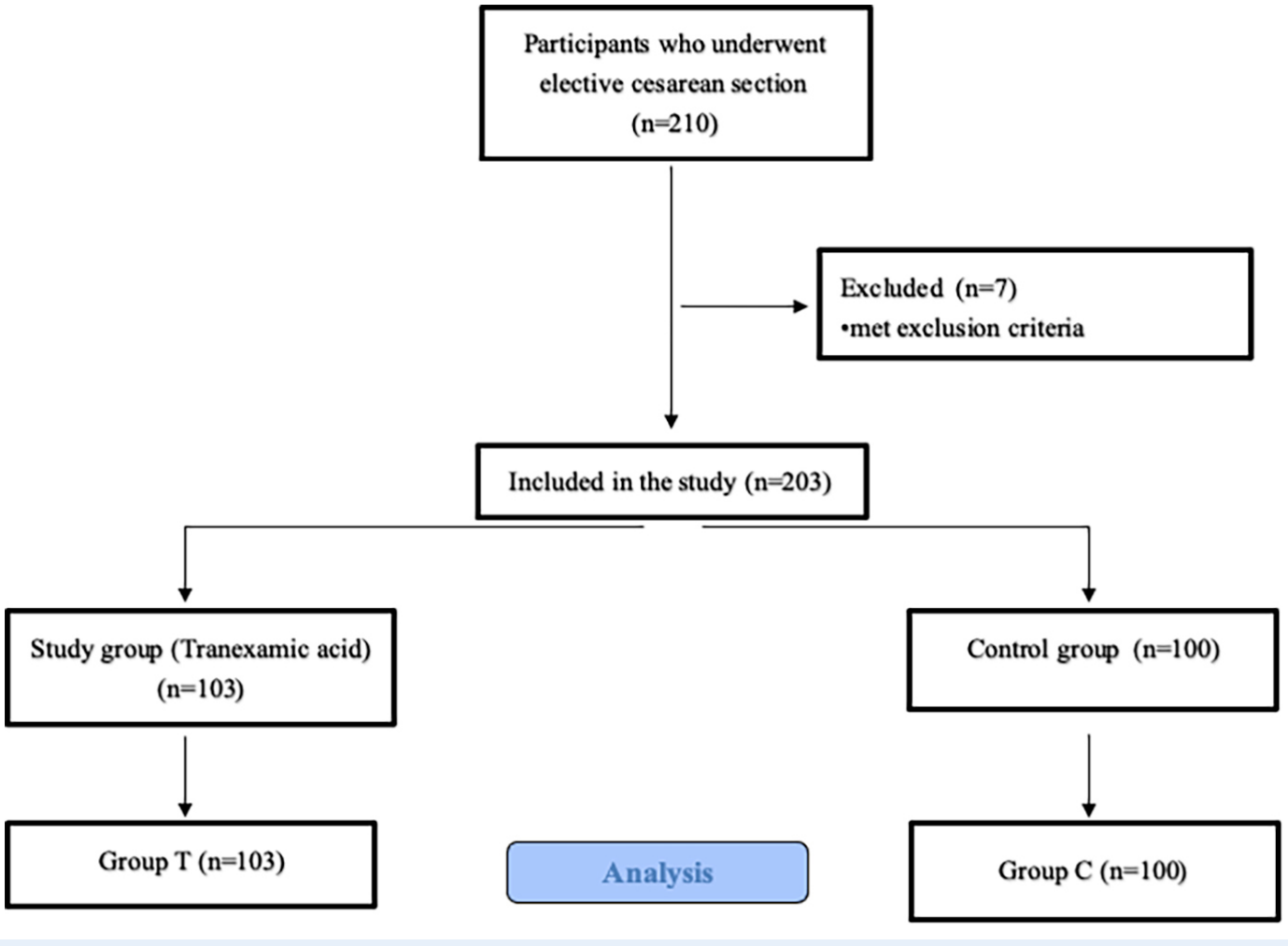

Figure 1. Flow chart of the study population

RESULTS

Two hundred ten patients were evaluated for eligibility, but seven met the exclusion criteria, resulting in 203 patients being included in the study. The population was divided into two groups: the study group was patients using TXA (n=103), and the control group (n=100) was patients not using it. There was no difference between the groups regarding age, body mass index, previous cesarean delivery history, fetal macrosomia, or duration of cesarean operation, except parity and gestational weeks at delivery (p=0.004, p=0.043, respectively). It was observed that the rate of cesarean deliveries performed with spinal anesthesia was significantly higher (Table 1). There was also no significant difference between the groups regarding preoperative hemoglobin and hematocrit levels. It is essential to have a similar patient group for the safety of the study. The study group's postoperative hemoglobin and hematocrit levels remained significantly higher (p=0.015). Likewise, when the estimated blood loss was calculated according to the formula, it was observed to be significantly less in the study group (p=0.003). The needs for blood transfusion were statistically different among the groups. Blood transfusion was performed in 2.9% of the study group and 10% of the control group (p=0.03). However, no significant difference was detected between the groups in delta hemoglobin value or the need for additional uterotonic agents. During follow-ups, no severe side effects, such as

$$\text{Estimated blood loss} = \text{EBV} \times \frac{\text{Preop hematocrit} - \text{Postop hematocrit}}{\text{Preop hematocrit}}$$

Figure 2. Estimated blood loss calculation

EBV: Estimated blood volume

Table 1. Demographic data and distribution of clinical characteristics of the groups

	Study group (n=103)		Control group (n=100)		p
	n	%	n	%	
Age (years)	30.0±5.0		28.9±5.6		0.239
Parity	1.8±1.1 (0–7)		1.5±1.3 (0–7)		0.004*
BMI (kg/m²)	28.5±4.0		27.7±4.4		0.267
Gestational age (weeks)	38.3±1.1		38.6±0.8		0.043*
Previous cesarean delivery	90	87.4	79	79.0	0.110
Fetal macrosomia	10	9.7	11	11.0	0.763
Duration of cesarean section (min)	39.1±14.9		36.2±13.1		0.098
Type of anesthesia					
Spinal	68	66.0	49	49.0	0.014*
General	35	34.0	51	51.0	

Data are expressed as mean±standard deviation, median (minimum-maximum), or number (%). *: p<0.05 statistically significant. BMI body mass index

Table 2. Clinical and laboratory outcomes and comparison of groups

	Study group (n=103)		Control group (n=100)		p
	n	%	n	%	
Preoperative hemoglobin (g/dL)	11.8±1.1		11.4±1.3		0.093
Postoperative hemoglobin (g/dL)	10.4±1.1		10±1.3		0.015*
Delta hemoglobin	1.4±0.6		1.3±0.7		0.208
Estimated blood loss (mL)	812.8±424.1		856.8±524		0.003*
Additional uterotonic agent	32	31.1	33	33.0	0.76
Blood transfusion	3	2.9	10	10.0	0.03*
Side effect profile					
Thromboembolic events	0	0	0	0	
Headache	3	2.9	0	0	
Nausea, vomiting	2	1.9	3	3	
Diarrhea	3	2.9	2	2	
Anaphylaxis	0	0	0	0	
Visual disturbances	0	0	0	0	
Seizures	0	0	0	0	

Data are expressed as mean±standard deviation, or number (%). *: p<0.05 statistically significant. Delta hemoglobin: Differences between before and after operation. Estimated blood loss (mL): It was calculated based on the difference between the hematocrit values taken before and 24th hours after the cesarean section

thromboembolic events (stroke, pulmonary embolism, deep venous thrombosis), were observed in any patient (Table 2).

DISCUSSION

In this study, we evaluated the effect of prophylactic TXA application on bleeding in previous cesarean deliveries in a tertiary care center. We found that TXA significantly reduced the amount of bleeding and the need for uterotonic agents. Additionally, no serious side effects, such as thromboembolic events, were detected in patients receiving TXA.

TXA has been used for a long time in the treatment of bleeding as an antifibrinolytic agent, and studies on its use in the field of obstetrics have been conducted in recent years. As the placenta separates from the uterine wall, the fibrinolytic sys-

tem is activated, and coagulation decreases. Thus, fibrinogen and fibrin break down rapidly, increasing fibrin degradation products. This process may last until the 6th to 10th postpartum hour and lead to increased postnatal bleeding.[10] Based on this mechanism, it is thought that TXA may affect the amount of postpartum bleeding. Our study also observed that prophylactically administered TXA during previous cesarean operation reduces the estimated blood loss and the need for blood transfusion, thereby improving postoperative hemoglobin and hematocrit levels. However, no difference was observed between the groups regarding additional uterotonic requirements. A severe side effect profile, such as a thromboembolic event, has not been found in any patient. When we look at the literature, it has been seen that it is similar to the findings of the study conducted by Abdel-Aleem et al.[11]

There are twelve randomized controlled trials in the Cochrane systematic review involving 3285 participants to evaluate the effect of TXA on the amount of bleeding after previous cesarean section and vaginal delivery.[12] Compared to the groups that did not receive a placebo or additional intervention of TXA (routine uterotonic use), it was found that the average blood loss was significantly lower in the TXA group, similar to cesarean and vaginal delivery. In addition, it has been found that TXA is more effective in reducing the incidence of blood loss over 1000 ml after cesarean section compared to vaginal delivery. Similarly, in our study, a significant decrease in estimated blood loss was observed after administration of TXA.

In the literature, TXA has been shown to reduce maternal mortality in a double-blind, randomized controlled trial (WOMAN) conducted in women complicated with PPH.[13] Otherwise, in the TRAAP study, no significant decrease in postpartum bleeding of at least 500 ml was detected with 1 g of TXA in addition to prophylactic oxytocin compared to placebo. Its prophylactic use has been described as controversial.[14] It has also been stated that the mixture of amniotic fluid may lead to erroneous results when calculating blood loss after a cesarean section.[15] Our study calculated estimated blood loss based on the difference between the hematocrit levels before and 24 hours after surgery and the participant's height and weight.

It is known that the incidence of thrombosis during pregnancy and puerperium is 5-6 times higher than in the general population.[16] Therefore, the relationship between TXA, which acts as an antifibrinolytic, and the risk of thromboembolism during the puerperal period is essential. In a systematic review, mild side effects such as nausea, vomiting, and dizziness were partially observed after the use of tranexamic acid. Still, insufficient evidence was found for severe morbidity, such as thromboembolism.[17] It has been observed that administered TXA crosses the placenta, is present in cord blood, and even partially passes into breast milk. However, it is not thought to have an antifibrinolytic effect at low concentrations in infants.[16] In the study by Gungorduk et al.[18] no significant difference was found in neonatal morbidity and 5th minute APGAR score after TXA usage compared to placebo.

Our study's limitations include being retrospective and single-center. We were also unable to evaluate the long-term side effects of TXA. We believe that larger-sample-size, multi-center, prospective, randomized controlled studies are needed to be routinely applied in cesarean section operations.

CONCLUSION

TXA administered prophylactically during previous cesarean deliveries significantly reduced perioperative blood loss, thus resulting in less postoperative decrease in hemoglobin and hematocrit. It may benefit clinical use by reducing the need for blood banks, especially in anemic patients and areas with limited resources. We want to point out that no severe side effects such as thromboembolism are observed with the current findings, but more comprehensive studies are needed on the side effect profile.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (No: 2022.06.158, Date: 23/06/2022).

Authorship Contributions: Concept: H.Ç.A., K.A.; Design: H.Ç.A., P.Ö.K., M.G.; Supervision: H.Ç.A., M.G.; Materials: H.Ç.A., M.G., B.D.; Data Collection or Processing: M.G., B.D., P.Ö.K.; Analysis or Interpretation: K.A.; Literature Search: H.Ç.A., K.A.; Writing: H.Ç.A., K.A., P.Ö.K.; Critical review: H.Ç.A., M.G., B.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Informed Consent: Written informed consent was obtained from all patients.

Use of AI for Writing Assistance: Artificial intelligence (AI) supported technologies (such as Large Language Models [LLM], chatbots or image generators, ChatGPT) were not used in this study.

Financial Disclosure: The authors declared that this study received no financial support.

Peer-review: Externally peer reviewed.

REFERENCES

1. AbouZahr C. Global burden of maternal death and disability. Br Med Bull 2003;67:1–11. [CrossRef]
2. Calvert C, Thomas SL, Ronsmans C, Wagner KS, Adler AJ, Filippi V. Identifying regional variation in the prevalence of postpartum haemorrhage: a systematic review and meta-analysis. PLoS One 2012;7:e41114. [CrossRef]
3. Petersen EE, Davis NL, Goodman D, Cox S, Mayes N, Johnston E, et al. Vital Signs: pregnancy-related deaths, United States, 2011e2015, and strategies for preven tion, 13 states, 2013e2017. MMWR Morb Mortal Wkly Rep 2019;68:423–9. [CrossRef]
4. Kadirogullari P, Aslan Cetin B, Goksu M, Cetin Arslan H, Seckin KD. The effect of uterine massage after vaginal delivery on the duration of placental delivery and amount of postpartum hemorrhage. Arch Gynecol Obstet 2024;309:2689–95. [CrossRef]
5. Pacheco LD, Hankins GDV, Saad AF, Costantine MM, Chiossi G, Saade GR. Tranexamic acid for the management of obstetric hemorrhage. Obstet Gynecol 2017;130:765–9. [CrossRef]
6. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, et al; CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376:23–32. [CrossRef]
7. World Health Organization. WHO Recommendations for the Prevention and Treatment of Postpartum Haemorrhage. Geneva: World Health Organization; 2012.
8. Pacheco LD, Clifton RG, Saade GR, Weiner SJ, Parry S, Thorp JM Jr, et al. Tranexamic acid to prevent obstetrical hemorrhage after cesarean delivery. N Engl J Med 2023;388:1365–75. [CrossRef]
9. Maged AM, Hassan AMA, Shehata NAA. Carbetocin versus oxytocin in the management of atonic post partum haemorrhage (PPH) after vaginal delivery: a randomised controlled trial. Arch Gynecol Obstet 2016;293:993–99. [CrossRef]
10. Gai MY, Wu LF, Su QF, Tatsumoto K. Clinical observation of blood loss reduced by tranexamic acid during and after caesarian section: a multi-center, randomized trial. Eur J Obstet Gynecol Reprod Biol 2004;112:154–57. [CrossRef]
11. Abdel-Aleem H, Alhusaini TK, Abdel-Aleem MA, Menoufy M, Gülmezoglu AM. Effectiveness of tranexamic acid on blood loss in patients undergoing elective cesarean section: randomized clinical trial. J Matern Fetal Neonatal Med 2013;26:1705–09. [CrossRef]
12. Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2015;6:CD007872. [CrossRef]
13. Roberts I, Fawole B, Chaudhri R, El-Sheikh M, Akintanet A; WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with postpartum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet 2017;389:2105–16.
14. Sentilhes L, Winer N, Azria E, Sénat MV, Le Ray C, Vardon D, et al. Tranexamic acid for the prevention of blood loss after vaginal delivery. N Engl J Med 2018;379:731–42. [CrossRef]
15. Stafford I, Dildy GA, Clark SL, Belfort MA. Visually estimated and calculated blood loss in vaginal and cesarean delivery. Am J Obstet Gynecol 2008;199:519. [CrossRef]
16. Mousa HA, Alfirevic, Z. Major postpartum hemorrhage: survey of maternity units in the United Kingdom. Acta Obstet Gynecol Scand 2002;8:727–30. [CrossRef]
17. Henry DA, Moxey AJ, Carless PA, O'Connell D, McClelland B, Henderson KM, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2001;1:CD001886.
18. Gungorduk K, Yıldırım G, Asıcıoğlu O, Gungorduk OC, Sudolmus S, Ark C. Efficacy of intravenous tranexamic acid in reducing blood loss after elective cesarean section: a prospective, randomized, double-blind, placebo-controlled study. Am J Perinatol 2011;28:233–40. [CrossRef]