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Does preoperative tranexamic acid use in placenta previa have a positive effect on the results?

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Abstract

Objective: To investigate the effect of preoperative tranexamic acid administration in patients undergoing surgery with the diagnosis of placenta previa.

Methods: 162 patients performed surgery with the diagnosis of total placenta previa were included in the study. The study group included 79 patients who got tranexamic acid before surgery and 83 control individuals who did not. Patient demographics, obstetric and laboratory characteristics, blood product requirements, surgery length, further surgical procedures, hospital stay, and fetal outcomes were compared between groups.

Results: There was no significant difference between groups in terms of intraoperative erythrocyte suspension transfusion (p=0.128). Postoperative erythrocyte suspension transfusion requirement was significantly higher in the study group compared to the control group (p<0.001). Total erythrocyte suspension and total fresh frozen plasma transfusion requirement in the study group were significantly higher than the control group (p<0.001). The use of compression suture, uterine lower segment resection and bilateral hypogastric artery ligation were significantly higher in the study group compared to the control group (p<0.001). Preoperative and postoperative Hb and Htc values in the control group were statistically significantly higher than in tranexamic acid group (p<0.05). The difference between preoperative and postoperative Hb, Htc values was higher in the control group, while this difference was significantly less in favor of TA group (p = <0.001). No statistically significant difference was observed between the groups in terms of fetal outcomes (p>0.05).

Conclusion: Prophylactic tranexamic acid, used obstetrically to minimize bleeding risk, has no impact on placenta previa, a high-risk bleeding condition.

Keywords: Placenta previa, postpartum hemorrhage, tranexamic acid

Introduction

Placenta previa is one of the most important obstetric complications that causes serious maternal and fatal complications due to the placenta's implantation in the lower uterine segment. The disease is seen in approximately 5 out of every 1000 births. The prevalence is higher in women of Asian origin.[1] A prior cesarean section is the primary risk factor for placenta previa. Moreover, curettage, smoking, multiple gestation, high parity, and advanced maternal age are factors that elevate the risk.[2] The risk of placenta previa increases with the number of cesarean sections. The relative risk is 4.5 after one previous cesarean section and increases to 44.9 for 4 or more cesareans.[3] The most important tool in the diagnosis of placenta previa is ultrasonography. Especially in the 3rd trimester, it is important to determine the exact location of the placenta. In the sonography performed at the 28th-32nd week of pregnancy, it is possible to obtain important findings in the follow-up and treatment such as placental attachment anomalies (accreta syndrome), cervical length and placental edge thickness, as well as whether the placenta completely covers the cervical os or is close to the os.[4] Although any placenta closer than 20 mm to the internal cervical os increases the need for cesarean delivery, it has been determined that a normal delivery attempt does not increase the risk for placenta placements between 10 and 20 mm.[5] A cervical length of 30 mm or greater enhances the probability of a pregnancy reaching full term.[6]

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Difficulties and uncertainties in the management of pregnant women with placenta previa continue. There is always a risk of emergency cesarean section and preterm birth in these women. It is important to individualize the patient by considering the clinical condition. Planned cesarean delivery can be recommended at 36-37 weeks for women with risks such as short cervix and antepartum hemorrhage, and at 38-39 weeks for those with low risk.[7] However, the risk of severe intraoperative bleeding remains the biggest problem. Therefore, these patients should be operated on in a center where multidisciplinary management is possible, and every precaution should be taken against the possibility of bleeding.[8] During surgery, ongoing applications include blood product transfusion, compression sutures, balloon tamponade, bilateral hypogastric artery ligation, and antifibrinolytic use, depending on the bleeding status. Tranexamic acid (TA), a lysine analog, acts as an antifibrinolytic by competitively inhibiting the binding of plasmin to fibrin. It is widely used in cases such as postpartum hemorrhage, menorrhagia, or surgeries and traumas with a risk of acute bleeding.[9] There are studies in the literature that support the positive effect on intra- and postoperative outcomes in pregnant women with placenta previa.[10]

Therefore, based on our experiences in our hospital, we planned this study, thinking that it would be useful to investigate the effects of preoperative TA application in patients with placenta previa. The main purpose of the study was to observe whether the prophylactic use of tranexamic acid in the preoperative period affected patient outcomes such as primarily the amount of bleeding and secondarily the duration of operation and length of hospital stay.

Methods

The study was conducted retrospectively by examining the hospital's digital database and patient files. Patients who were followed up and treated with placenta previa diagnosis at the Mersin University Medical Faculty Hospital, a tertiary health center, between January 2018 and November 2024 were identified. Since the data were scanned retrospectively, there is no need to obtain consent forms from the participants. This study was conducted with the approval of the ethics committee of Mersin University Clinical Research Ethics Committee, dated 11.12.2024 and numbered 1230. We found that 402 patients were diagnosed with abnormal placenta (placenta previa, vasa previa, placenta accreta). Only patients with total placenta previa were selected for the study. Those with placental attachment anomalies (accreta, increta, percreta), marginal or low-line placenta, and vasa previa were not included. In addition, those with multiple pregnancies, hypertension, diabetes, hematological, and immunological diseases were also excluded. As a result, we identified 189 pregnant women who were followed up and treated with a diagnosis of total placenta previa. Apart from this, since November 2020, 1 gram of intravenous TA has been administered to pregnant women at risk of postpartum hemorrhage, just before the start of surgery, considering the situations in which the use of TA is not contraindicated. This practice is based on reasonable justifications in the literature.[11] In this case, 79 patients with complete records who underwent TA and 83 patients who did not undergo TA were identified between the mentioned dates. Demographic and obstetric findings of all patients such as age, body mass index, gravida, parity, number of previous cesarean sections and abortions, number of previous uterine surgeries and curettages, and smoking habits were recorded. Preoperative and postoperative hemoglobin (Hb), hematocrit (Htc), platelet (Plt), red blood cell distribution volume (RDW), activated partial thromboplastin time (APTT) and prothrombin time (PT) values and the difference between these values were calculated and recorded from the laboratory data of the patients. Whether the patients underwent emergency or elective surgery, the duration of surgery, the number of preoperative, intraoperative, postoperative and total erythrocyte suspension (ES), and fresh frozen plasma (FFP) transfusions, additional surgical procedures performed during surgery (compression sutures, Bakri balloon tamponade, bilateral hypogastric artery ligation, lower uterine segment resection, adjacent organ injury and hysterectomy) and the duration of postoperative hospital stay (hours) were recorded. In addition, the gestational age of the fetus, birth weight, first and fifth minute Apgar scores, umbilical cord blood pH value and neonatal intensive care unit (NICU) admission data were also recorded.

Data analysis was performed using SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used to test whether continuous variables were normally distributed. Mean differences between two groups were compared using the Independent Sample t test or Mann-Whitney U test, depending on their suitability for normal distribution. Continuous variables are presented as mean ± standard deviation (mean ± S.D.) or median [IQR]. Differences between categorical data were evaluated using the Chi-square test. Categorical variables are expressed as number (%). $p<0.05$ was considered significant.

Results

When the demographic data of the intraoperative tranexamic acid group and the control group were evaluated; there was no difference between the mean age of the study (32.22±5.76) and control (32.60±5.52) groups (p>0.05). There was a significant difference between the groups in terms of gravida (p=0.021). There was no significant difference between the groups in terms of births, abortions and living children (p>0.05). The number of previous cesarean section and previous curettage in TA group was significantly higher than in the control group (p= 0.030, p = 0.019, respectively). The number of previous uterine surgeries in the TA group was significantly higher (p = <0.001). There was no significant difference between the groups in terms of previous placenta previa history (p > 0.05). There was no significant difference between the groups according to BMI (p> 0.05). Smoking was significantly higher in the control group than in TA group (p = 0.001) (Table 1).

Table 1. Comparison of demographic data in the study and control groups

	Tranexamic acid group (n:79)	Control group (n:83)	p
Age Mean ± S.D.	32.22 ± 5.76	32.60 ± 5.52	0.674*
Gravida Median [IQR]	4 [8]	3 [7]	0.021
Parity Median [IQR]	2 [8]	2 [4]	0.227
Abortus Median [IQR]	0 [8]	0 [3]	0.902
Number of living children Median [IQR]	2 [6]	2 [4]	0.069
Previous cesarean section Median [IQR])	2 [4]	2 [4]	0.030
Previous curettage Median [IQR]	0 [4]	0 [3]	0.019
Previous uterine surgery n (%)	69 (87.3%)	23 (27.7%)	<0.001''
Previous placenta previa n (%)	4 (5.1%)	3 (3.6%)	0.650''
Smoking n (%)	4 (5.1%)	19 (22.9%)	0.001''
BMI Mean ± S.D.	28.09 ± 2.94	28.22 ± 3.56	0.880

IQR: Inter Quantile Range, Mean ± S.D.: mean ± standard deviation. BMI: body mass index.p: Mann Whitney U test *Independent Sample t test '': Chi-Squared test

There was no significant difference between the preoperative Plt, RDW, aPTT, PT and postoperative Plt levels between the groups (p>0.05). Preoperative and postoperative Hb and Htc values in the control group were statistically significantly higher than in TA group (p<0.05). The difference between preoperative and postoperative Hb, Htc values was higher in the control group, while this difference was significantly less in favor of TA group (p = <0.001). The difference between preoperative and postoperative Plt values between the groups was statistically significant (p=<0.001) (Table 2).

Table 2. Comparison of Laboratory and bleeding parameters in the study and control groups

	Tranexamic acid group (n:79)	Control group (n:83)	p
Preoperative Hb (g/dL) Mean ± S.D.	11.19 ± 1.23	11.81 ± 1.08	0.002
Preoperative Htc (%) Mean ± S.D.	33.1 ± 3.74	34.8 ± 2.98	0.006
Preoperative Plt ($\times10^3$/µl) Mean ± S.D.	235.17 ± 78.19	221.77 ± 55.58	0.592
Postoperative Hb (g/dL) Mean ± S.D.	9.54 ± 1.62	10.29 ± 1.4	<0.001
Postoperative Htc (%) Mean ± S.D.	27.92 ± 4.57	30.45 ± 4.04	<0.001
Postoperative Plt ($\times10^3$/µl) Mean ± S.D.	191.73 ± 65.84	195.49 ± 65.35	0.529
Pre-Postoperative Hb (g/dL) difference Median [IQR]	-6,66 [1.9]	-7.32 [1.6]	<0.001^^
Pre-Postoperative Htc (%) difference Median [IQR]	-6.86 [6]	-6.95 [4.8]	<0.001^^
Pre-Postoperative Plt ($\times10^3$/µl) difference Median [IQR]	-6.09 [41]	-4.21 [31]	<0.001^^
Preoperative RDW Mean ± S.D.	14.78 ± 2.58	14.5 ± 1.44	0.405
Preoperative aPTT Mean ± S.D.	29.16 ± 6.55	28.11 ± 4.28	0.358
Preoperative PT Mean ± S.D.	12.72 ± 1.18	12.88 ± 1.5	0.727

IQR: Inter Quantile Range, Mean ± S.D.: mean ± standard deviation, Hb: Hemoglobin, Htc: hematocrit, Plt: Platelet, RDW: Red cell distribution width, aPTT: Activated partial thromboplastin time, PT: Prothrombin time, g/dL: grams per deciliter, µl:Microliter

p:Mann Whitney U test ^^:Wilcoxon Signed Ranks Test

Table 3. Comparison of Neonatal and surgery parameters in the study and control groups

	Tranexamic acid group (n:79)	Control group (n:83)	p
Delivery week Median [IQR]	38 [15]	37 [10]	0.315
Delivery weight (g) Median [IQR]	3100 [3440]	2990 [2670]	0.279
Apgar 1. Minute Median [IQR]	7 [9]	8 [8]	0.256
Apgar 5. Minute Median [IQR]	9 [5]	9 [7]	0.695
Umbilical cord pH Mean ± S.D.	7.31 ± 0.06	7.34 ± 0.05	0.015
NICU n (%)	31 (39.2%)	24 (28.9%)	0.165''
Surgery n (%) **Emergency** **Elective**	 45 (57%) 34 (43%)	 36 (43.4%) 47 (56.6%)	 0.084''
Duration of surgery (minute) Mean ± S.D.	63.29 ± 16.63	60.66 ± 19.82	0.204
Preoperative ES transfusion n (%)	0 (0%)	4 (4.8%)	0.049''
Intraoperative ES transfusion n (%)	48 (60.8%)	31 (36.6%)	0.128''
Postoperative ES transfusion n (%)	69 (87.3%)	34 (40.9%)	<0.001''
Total ES transfusion Mean ± S.D.	2.25 ± 1.58	1,31±1,48	<0.001
Total FFP transfusion Mean ± S.D.	1.22 ± 1.35	0.57 ± 1.06	<0.001
Postoperative hospital stays (hours) Mean ± S.D.	75.13 ± 23.56	68.98 ± 29.81	0.021
Compression suture n (%)	72 (91.1%)	31 (37.3%)	<0.001''
Lower uterine segment resection n (%)	41 (51.9%)	17 (20.5%)	<0.001''
Bakri balloon tamponade n (%)	22 (27.8%)	15 (18.1%)	0.138''
Bilateral hypogastric artery ligation n (%)	43 (54.4%)	21 (25.3%)	<0.001''
Total abdominal hysterectomy n (%)	15 (19%)	10 (12%)	0.222''
Adjacent organ damage n (%)	6 (7.6%)	6 (7.2%)	0.929''

IQR: Inter Quantile Range, Mean ± S.D.: mean ± standard deviation, NICU: Neonatal intensive care unit, ES: Erythrocyte suspension, FFP: Fresh frozen plasma.

p: Mann Whitney U test '': Chi-Squared test

Neonatal and surgery parameters of the patients

When the neonatal outcomes of the groups were examined, there was no significant difference between TA and control groups in terms of gestational age, birth weight, 1st and 5th minute Apgar scores, and neonatal intensive care admission rates ($p > 0.05$). Umbilical cord pH value was significantly higher in TA group compared to the control group ($p < 0.05$). There was no significant difference between the groups in terms of emergency or elective surgery and duration of surgery ($p > 0.05$). Postoperative hospital stay was significantly higher in TA group ($p = 0.021$). There was no significant difference between the groups in terms of intraoperative ES transfusion ($p = 0.128$). Preoperative ES transfusion requirement was significantly less in TA group ($p < 0.05$). Postoperative ES transfusion requirement was significantly higher in TA group ($p = <0.001$). Total ES transfusion a requirement and total FFP transfusion requirement in TA group were significantly higher ($p = <0.001$). The use of compression suture, lower uterine segment resection and bilateral hypogastric artery ligation were significantly higher in TA group ($p = <0.001$), however there was no statistically significant difference between the groups in terms of Bakri balloon tamponade use, total abdominal hysterectomy number and adjacent organ damage ($p>0.05$) (Table 3).

Discussion

In our study, we found that TA administered immediately before surgery did not cause significant changes in critical parameters such as intraoperative or postoperative blood product requirements, operative time, need for additional surgical procedures for bleeding control, and hospital stay.

Placenta previa, defined as a condition in which the placenta partially or completely covers the cervical internal os, is an obstetric complication that carries serious maternal and fetal risks. For this condition, which is seen at a rate of one in every 200 births; previous operations such as cesarean section, curettage, multiple pregnancy, smoking, maternal age and increased parity are the main risk factors.[12] It is also known that assisted reproductive techniques pose a risk for placenta previa.[13] Placenta previa paves the way for fetal complications such as preterm birth, malpresentation, intrauterine growth retardation, and maternal complications such as thrombophlebitis, massive transfusion, long hospital stay, adjacent organ injury, and hysterectomy risk, in addition to excessive bleeding before and after delivery. It is considered appropriate for placenta previa to be monitored and treated in a center with sufficient resources. The center must have a blood bank that can provide blood products, and a gynecologist, anesthesiologist, and interventional radiology specialist with sufficient experience for such surgeries. In addition, if there is anemia, it must be corrected for the optimization of the patient before surgery.[14] Although ultrasonog-

raphy is critical in the diagnosis of placenta previa, it has been shown to be ineffective in predicting intraoperative bleeding status and timing of surgery.[15]

Various studies have been conducted and continue to be conducted to minimize the risk of bleeding in cases with a high risk of postpartum hemorrhage, such as placenta previa. Among these is the application of TA to reduce bleeding. In a meta-analysis conducted by Feanchini et al., they concluded that TA reduces bleeding in women who have had a cesarean delivery.[16] In our center, 1 gram of TA has been administered intravenously to patients at high risk for postpartum hemorrhage before surgery (just before skin incision) for the last 3 years. This study was designed to compare the results of placenta previa patients who were administered TA and those who were not administered before. In our study, the need for blood product transfusion was higher in the TA group compared to the non-TA group, and as expected, it did not decrease. Sentilhes et al. found in their study that prophylactic TA administration in women who delivered by cesarean section decreased the need for ES transfusion.[17] In the study conducted by Ortuanya et al., the use of TA before cesarean section was found to be effective in reducing blood loss.[18] In our study, this effect of TA was not observed. Our findings are consistent with the results of the randomized controlled study conducted by Pacheco et al., which found that prophylactic TA use did not reduce the need for blood transfusion and maternal death.[19] Another factor that could explain this situation could be that the number of cesarean sections and curettages we saw in our study was higher in the TA group. It is already known that the risk of placenta previa increases with the number of cesarean sections.[20] In addition, Oben et al. found in their study that the increase in the number of cesarean sections caused an increase in the need for blood transfusion in women with placenta previa.[21] In conclusion, we believe that the high transfusion requirement and the need for additional surgical procedures (such as Bakri balloon tamponade, bilateral hypogastric artery ligation) in our study group may be related to the high cesarean section rates in this group.

In our study, we observed that the difference between preoperative and postoperative Hb and Htc values in the TA group was less than in the control group. This finding is generally consistent with studies investigating the effect of TA.[22] However, it should not be forgotten that the studies are generally related to routine cesarean deliveries and it can be seen that this effect becomes controversial when we go into subgroups. For example, in a randomized clinical study conducted by Sentilhes et al., prophylactic TA use was not found to be effective in reducing blood loss in women with multiple pregnancies who gave birth by cesarean section.[23] Although the use of TA in high-risk pregnancies reduces the need for uterotonic agents, it does not affect postoperative hemoglobin levels, as observed in the meta-analysis conducted by Stortroen et al. The authors concluded that there is insufficient data on the use of TA in high-risk pregnancies.[24]

The main limitation of our study is that it is a single-center and retrospective study. In addition, we believe that the clinical features of placenta previa are variable, the amount and characteristics of bleeding are difficult to predict in advance, the surgical teams performing the operations have different experiences and approaches, and some parameters (such as the number of cesarean sections) are different between the groups, which may affect the results.

Conclusion

Although there is evidence in the literature that TA use is effective among postpartum hemorrhage prevention strategies, this effect remains uncertain in some special groups. In our study, we observed that preoperative tranexamic acid application for prophylaxis did not show the expected effect. Randomized controlled trials are seriously needed to investigate the real effect of TA use in patients with high risk of bleeding, such as placenta previa.

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