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Comparison of the Effect of Tranexamic Acid and Misoprostol on Blood Loss During and After Cesarean Section: A Randomized Clinical Trial

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Abstract

Background: One of the methods proposed for the reduction of blood loss during and after cesarean section is the use of such drugs as Tranexamic acid and Misoprostol. Therefore, the present study aimed to compare the effect of Tranexamic acid and Misoprostol on blood loss during and after cesarean section.

Methods: This randomized clinical trial was performed in Dr. Ali Shariati and Persian Gulf Hospitals of Bandar Abbas, Iran, between 2015 and 2016. The study population included all candidates for the cesarean section. A total of 300 pregnant women aged 18-40 years with a gestational age of 37-42 weeks were included and assigned to three groups (n=100 in each group): Group A received tranexamic acid, group B received misoprostol, and group C received 200 cc normal saline. During cesarean section, all patients received 20 and 30 units of oxytocin, respectively. The level of blood loss during the operation was determined after measuring the whole blood volume suctioned after the removal of the placenta, as well as differences in the weight of bloody sterile pads and surgical sheets before and after the operation.

Results: Based on the results, the mean scores of hemoglobin before the operation were obtained at 11.96±1, 11.62±1.21, and 12.28±1.26mg/dl in the Tranexamic acid group, the Misoprostol group, and the placebo group, respectively, demonstrating a statistically significant difference (P=0.001). Postoperative hemoglobin level was reduced about 1.02±0.35 (10.9±0.99 mg/dl) in the Tranexamic acid group, 1.19±0.52 (10.46±1.04 mg/dl) in the Misoprostol group, and 1.36±0.50 (10.93±1.34 mg/dl) in the placebo group. There was a significant difference among the three groups in the amount of blood loss during and the first two hours after the operation (P<0.001). According to the post-hoc test analysis, there were significant differences between the two groups (P<0.001).

Conclusion: As evidenced by the obtained results, both medicines are effective in reducing the amount of blood loss during and after cesarean section; nonetheless, Misoprostol is more effective than Tranexamic acid.

Keywords: Postpartum hemorrhage, Cesarean section, Tranexamic acid, Misoprostol

Introduction

Cesarean section (C-section) is an alternative means of terminating a pregnancy proposed as a medical indication if necessary (1). Among the complications of the C-section, bleeding during and after surgery is one of the leading causes of maternal mortality. It accounts for 25% of maternal deaths across the globe, and 12% of the survivors suffer from severe anemia (2,3). Severe postpartum hemorrhage is characterized by the need for blood transfusion or hematocrit loss of more than 10% (4-6). Severe postpartum hemorrhage occurs within the first 24 h after delivery with incidence rates of 3.9% and 6.6% in vaginal delivery and C-section, respectively (4). Uterine atony, as well as the rupture of the cervix and vagina, are the most common causes of severe postpartum hemorrhage after vaginal delivery. Among the other causes, we can refer to the retained placenta, uterine rupture, placenta accrete, and acquired coagulopathies (6)

Risk factors for severe hemorrhage during C-section include general anesthesia, chorioamnionitis, preeclampsia, classical uterine incision, placenta accreta and previa, anterior placenta, vertical presentation of fetus, and high maternal body mass index (BMI). Classical uterine incision and Asian race are also risk factors that have been investigated less frequently; nonetheless, there is a significant relationship between these factors

and severe hemorrhage after C-section (4). One of the major interventions to minimize these complications is the reduction of bleeding during and after C-section. The intravenous administration of Tranxacic acid has been routinely used to reduce bleeding during or after surgical procedures, such as coronary artery bypass graft (CABG), scoliosis, oral cavity surgeries, liver transplant, knee or pelvic arthroplasty, and urinary tract surgeries (7-9).

Misoprostol is also a medicine recently used as one of the most effective preventive drugs for gastric ulcers, postpartum hemorrhage, labor induction, termination of pregnancy, and cervical ripening. Despite scientific advances, postpartum hemorrhage lead to over 300,000 deaths worldwide, and its complications include anemia, blood transfusions, and ischemic complications in several organs (10,11). Considering the benefits of Misoprostol, compared to Tranexamic acid, the current study aimed to determine the superiority of each of these medicines in preventing bleeding during and after C-section.

Materials and Methods

Patients

This randomized clinical trial was conducted in women's wards of Persian Gulf Hospital (affiliated to Hormozgan University of Medical Sciences) and Dr. Shariati Hospital of Bandar Abbas between 2015 and 2016. The study population included all candidates for C-section who met the inclusion criteria.

The inclusion criteria entailed pregnant women aged 18-40 years with a gestational age of 37-42 weeks (according to the First- and second-trimester ultrasound assessment), and the candidates for lower uterine segment C-section. On the other hand, the exclusion criteria were as follows: multiple pregnancies, placental abnormalities, preeclampsia, macrosomia, polyhydramnios, history of previous C-section or intra-abdominal surgery, cardiovascular disease, renal disease, liver disease, brain problems, blood disorders, coagulopathy, severe anemia (Hb less than 8 mg/dL), thrombophilia, thromboembolic disorders, allergy to Tranexamic acid, any uterine bleeding leading to hysterectomy, BMI>30, general anesthesia, and all contraindications to spinal anesthesia.

Samples

A total of 300 patients were included in the study using convenience sampling. According to the inclusion and exclusion criteria, as well as the table obtained from the random allocation, they were assigned to three groups (n=100). In the case of exclusion of any patient during the study, another patient replaced her to retain constancy in the number of patients in each group.

Study Protocol

At the commencement of the study, pregnant women were assessed for inclusion and provided with information about the interventions. Thereafter, upon their willingness, they signed the informed consent form and received an identification code. The subjects were assigned to three groups: A, B, and C. Group A received a slow (5 min) intravenous injection of 10 mg/kg Trancexamic acid diluted in 200 cc normal saline 20 min before the C-section . Group B received 600 µg Misoprostol rectally 20 min before the operation, and group C received only 200 cc normal saline in 5 min. During the operation, all patients received 20-unit oxytocin in 500 ml normal saline intravenously in 20 min; subsequently, they received 30 unit oxytocin in 1000 ml of normal saline intravenously during the first 8 h of operation.

The amount of blood loss during the operation was determined after measuring the total blood volume soaked after the removal of the placenta, as well as differences in the weight of bloody sterile pads and surgical sheets before and after the operation. It is noteworthy that the amniotic fluid and bleeding caused by the incision of uterine and abdominal layers was collected in another suction and was not included in the calculations.

The level of blood loss during and 2 h after the operation was measured. The hemoglobin level was measured before and 24 h after the operation. The blood transfusion was performed if hemoglobin was less than 8 g/dl. In all cases, the surgeon remained constant, a lower segment uterine incision was made, and all patients received spinal anesthesia. In total, a 5 ml ampoule containing 500 mg tranexamic acid (Caspian Tamin Pharmaceutical Co., Rasht, Iran) and 600 µg misoprostol tablets (Sami Mousavi Pharmaceutical Co.) were used in the present study. All the medicines used in this study were approved by the Ministry of Health.

Statistical Analysis

Data were collected and analyzed in SPSS software (version 22) using descriptive statistics (frequency, mean, and standard deviation) and inferential statistics(t-test, Chi-Square, Pearson's correlation, and ANOVA). A p-value less than 0.05 was considered statistically significant.

Results

Based on the analysis of the data of 300 patients, there was no statistically significant difference among the groups in terms of age, gravidity, and parity. Table 1 presents the data collected from the patients.

The causes of the C-section in the three groups are separately illustrated in Table 2.

Table 1. Characteristics of the pregnant women in terms of age, gravidity, and parity

Variable	Subgroup	Groups			Statistical Test	P-value
		Tranexamic Acid	Misoprostol	Placebo		
		Frequency (Percentage)	Frequency (Percentage)	Frequency (Percentage)		
Age (year)	<25	51(51%)	36 (36%)	49 (49%)	8.871	0.064
	25-35	43(43%)	47 (47%)	39 (39%)		
	35<	6 (6%)	17 (17%)	12 (12%)		
	Total	100 (100%)	100 (100%)	100 (100%)		
Number of pregnancy	1	69 (69%)	52 (52%)	67 (67%)	5.407	0.078
	2-5	27 (27%)	38 (38%)	28 (28%)		
	5<	4 (4%)	10 (10%)	5 (5%)		
	Total	100 (100%)	100 (100%)	100 (100%)		
Number of delivery	0	72 (72%)	64 (64%)	76 (76%)	8.406	0.496
	1	14 (14%)	14 (14%)	12 (12%)		
	2-5	13 (13%)	18 (18%)	10 (10%)		
	5<	1(1%)	4 (4%)	2 (2%)		
	Total	100 (100%)	100 (100%)	100 (100%)		

Table 2. Frequency of the causes of C-section in the three groups.

Cesarean Section Causes	Groups		
	Tranexamic Acid	Misoprostol	Placebo
Abnormal presentation	30	26	30
Thick meconium	38	40	39
Drop in fetal heart rate	27	21	29
Lack of progress in labor	5	14	3
Total	100	100	100

Table 3. Results of covariance analysis for comparing between the group mean hemoglobin with that of pre-operative control

Source	Sum of Squares	FD	Mean Squares	F	P-value	Effect Size
Pre-intervention hemoglobin	303.964	1	303.964	1459.588	<0.001	0.840
Group	4.633	2	2.316	11.123	<0.001	0.074
Error	58.103	295	0.208			
Total	33367.340	299	---			

Table 4. Comparison of the mean and standard deviation during and 2 h after the operation among the groups

Level of Blood Loss (mL)	Groups			Kruskal–Wallis Test	FD	P-value
	Tranexamic Acid	Misoprostol	Placebo			
During the operation	444.70±100.58	299.98±162.79	568.84±147.07	129.838	2	<0.001
2 hours after the operation	56.20±18.37	90.10±20.64	73.23±20.00	92.211	2	<0.001

The mean scores of hemoglobin before the operation were obtained at 11.96±1, 11.62±1.21, and 12.28±1.26mg/dl in the Tranexamic acid group, the Misoprostol group, and the placebo group, respectively, demonstrating a statistically significant difference (F=6.966; P=0.001). The results of covariance analysis for comparing between-group mean hemoglobin with that of pre-operative control are presented in Table 3.

The mean score of post-operative hemoglobin in the Tranexamic group was reported as 10.94±0.99 mg/dl (1.02±0.35 mg/dl reduction), 10.46±1.04 mg/dl in the Misoprostol group (1.19±0.52 mg/dl reduction), and 10.93±1.34 mg/dl in the placebo group (1.36±0.50 mg/dl reduction). The volume of bleeding during and 2 h after the operation in the three groups is displayed in Table 4. As illustrated in this table, there was a significant difference

Table 5. Comparison of the mean hemorrhage volume among the subgroups in terms of age, gravidity, and parity

Variable	Subgroup	Intervention Group	Level of Blood Loss (mL)	
			During the Operation	2 hours after the Operation
Age (year)	<25	Tranexamic Acid	475.28±123.02	55.76 ± 19.83
		Misoprostol	322.57±158.53	92.13 ± 28.89
		Placebo	578.33±129.15	73.45 ± 19.08
	25-35	Tranexamic Acid	431.04±78.55	56.35 ± 17.13
		Misoprostol	288.10±172.39	88.73 ± 18.43
		Placebo	553.15±156.69	71.63 ± 18.47
	>35	Tranexamic Acid	457.50±51.74	58.33 ± 19.41
		Misoprostol	303.85±138.74	91.54 ± 8.28
		Placebo	598.18±175.05	79.09±29.05
Gravidity	1	Tranexamic Acid	445.29±109.09	55.22±19.30
		Misoprostol	295.96±173.85	88.56±22.03
		Placebo	569.24±141.97	74.17±20.35
	2≤	Tranexamic Acid	443.39±80.07	58.39±16.20
		Misoprostol	306.50±145.44	92.44±18.25
		Placebo	568.03±159.04	71.36±19.46
Parity	0	Tranexamic Acid	446.46±106.51	55.83±18.90
		Misoprostol	292.80±159.74	89.83±22.35
		Placebo	569.27±141.53	73.47±19.95
	1≤	Tranexamic Acid	440.18±85.04	57.14±17.24
		Misoprostol	322.95±174.42	72.50±20.59
		Placebo	567.50±166.45	90.95±14.26

among the three groups in terms of the bleeding volume during and 2 hs after the operation (P<0.001). According to the post-hoc test analysis, there was a significant difference between the two groups (P<0.001).

The bleeding volume during and 2 h after the operation was measured in the three groups. In each age group, according to the Kruskal-Wallis test analysis, there was a significant difference among the three groups in terms of hemorrhage volume (P<0.001). According to the results of the post-hoc test, the groups differed in the age groups of under 25 and 25-35 years (P<0.05). Nonetheless, in the age group of above 35 years, there was only a difference between the control and Misoprostol groups (P<0.001).

In each age group, according to the Kruskal-Wallis test, there was a significant difference among the three groups in terms of hemorrhage volume 2 h after the operation (P<0.05). According to the results of the post-hoc test, in the age group of under 25 years, there was a significant difference between the Tranexamic acid and control groups (P=0.001), as well as Tranexamic acid and Misoprostol groups in the age group of under 25 years (P<0.001). In the age group of 25-35 years, there was a significant difference among the groups (P<0.05). However, in the age group of over 35 years, there was only a difference between the Tranexamic acid and Misoprostol groups (P=0.034).

In terms of gravidity, the patients were assigned to two groups (1 and 2≤). In both groups, according to the Kruskal-Wallis test analysis, there was a significant difference among the three groups in terms of hemorrhage volume (P<0.001). According to the post-hoc test analysis, in both groups (1 and 2≤ pregnancy), there was a significant difference among the groups (P<0.05). Based on the Kruskal-Wallis test, there was a significant difference among the three groups in terms of hemorrhage volume 2 h after the operation (P<0.001). As illustrated by the post-hoc test, in the primiparous group, there was a significant difference among the groups (P<0.05). Nevertheless, in the multiparous group, there was no difference between the Tranexamic acid and control groups (P=0.054).

In terms of parity, the patients were assigned to two groups of nulliparity and parity of one delivery or more. In both groups, according to the Kruskal-Wallis test, there was a significant difference among the three groups in terms of intraoperative hemorrhage volume (P<0.001). According to the post-hoc test, in the nulliparity group, there was no significant difference among the groups (P<0.001). However, in the group with parity of one delivery or more, there was no difference between the Tranexamic acid and control groups (P=0.064).

In both groups, according to the Kruskal-Wallis test, there was a significant difference among the three groups in terms of hemorrhage volume 2 h after the operation (P<0.001). According to the post-hoc test, in both groups (nulliparity and parity of ≥1 delivery), there was a significant difference among the groups (P<0.05). The mean hemorrhage volume in each subgroup is separately reported in Table 5.

Discussion

Tranexamic acid exerts its anti-fibrinolytic effect on plasmin and plasminogen molecules by blocking the lysine-binding sites, and therefore, prevents plasmin and plasminogen from binding to fibrin substrate. It also prevents the transformation of plasminogen into plasmin by plasminogen activators. Tranexamic acid as a strong inhibitor of fibrinolysis which was first introduced by OKaMoro in 1962 (12) been widely used for the treatment of abnormal menstrual bleeding and the reduction of hemorrhage in elective surgeries and the amount of blood transfusion to about one-third (13,14).

Williams et al. (2010) indicated that timely administration of tranexamic acid reduces motility rate in patients with traumatic bleeding (15). This medicine has long been used for the treatment of various forms of bleeding, such as menorrhagia, as well as intra- and post-operative bleeding. After removal of the placenta, due to the activity of the fibrinolytic system, fibrin degradation products (FDPs) increase. The activity of this system lasts 6-10 h after delivery and leads to further bleeding that can be treated with anti-fibrinolytic agents. Therefore, the use of Tranexamic acid can decrease the amount of blood loss.

Severe anemia following postpartum hemorrhage is an important cause of maternal morbidity and may predispose women to post-delivery fetal hemorrhages in subsequent pregnancies (16). Numerous studies reported Misoprostol as an effective medication in the treatment of postpartum hemorrhage and C-section (12-14,17,18). It was also reported that Misoprostol leads to uterine smooth muscle contraction and cervical dilatation in labor induction and termination of pregnancy (19). In addition, multiple studies on the effect of Misoprostol on gastrointestinal ulcers pointed out that this medicine is effective in preventing these ulcers (20-22).

The results of the present study demonstrated that Tranexamic acid and Misoprostol significantly reduce the amount of delivery hemorrhage to 2 h postpartum in lower uterine segment C-section. According to the results of one-way ANOVA, there was a significant difference among the three groups in the pre-operative hemoglobin levels (P=0.001). Therefore, to evaluate and compare postoperative hemoglobin levels, covariance analysis was performed to make a comparison between the effects of controlled pre-operative difference and intervention on post-operative hemoglobin level among the groups. After the statistical analysis of the difference in the mean pre-operative hemoglobin level among the groups, it was revealed that the intervention influenced the mean scores of the dependent variable (hemoglobin) in the post-operative period (P<0.001).

Considering the effect size, 7.4% of changes in the dependent variable after the operation can be attributed to the intervention. Given that there were three groups in this study, Bonferroni's post-hoc test was used to determine the difference in the amount of post-operative hemoglobin level among the groups. The results of the stated test showed that the mean level of post-operative hemoglobin in the Tranexamic acid group was significantly higher, compared to that in the control and Misoprostol groups (P<0.05). There was no statistically significant difference in the mean postoperative hemoglobin between the control and Misoprostol groups (P=0.411). According to the results of one-way ANOVA, there was a significant difference among the three groups in hemoglobin decline (F=13.876; P<0.001). As suggested by the results of Bonferroni's post-hoc test, hemoglobin level was significantly reduced in the control group, compared to other groups (P<0.05). There was also a significant difference between the Tranexamic acid and Misoprostol groups in terms of hemoglobin decline (P=0.033).

In their study, G Acharya et al. (2001) observed no statistically significant difference in the intraoperative bleeding, as well as pre-and post-operative hemoglobin levels, between oral Misoprostol and intravenous oxytocin (23). Along the same lines, Gai et al. (2004) showed that Tranexamic acid reduced the amount of bleeding from initiation to the end of C-section, 351 ml in the Tranexamic acid group, compared to 444 ml in the control group (24). In the present study, Tranexamic acid reduced the intra- and post-operative bleeding from 568 ml in the control group to 500 ml in the Tranexamic acid group, and according to the mean volume of post-operative bleeding in the Misoprostol group (299 cc), it was revealed that Misoprostol is more effective than Tranexamic acid.

The administration of Tranexamic acid in pregnant women may give rise to concerns about the incidence of thromboembolism. Nevertheless, previous studies have confirmed the safety of this medicine for pregnant and non-pregnant women (25). In the present study, the incidence of thromboembolism was not assessed due to insufficient sample size. However, none of the women displayed symptoms of thromboembolism events, as well as other side effects, such as nausea and diarrhea. There were also no complications of Misoprostol, such as headache, nausea, uterine cramps, stomach ache, diarrhea, flatulence and fever, or serious complications, such as uterine rupture, coagulation disorders, as well as severe and abnormal vaginal bleeding.

Considering the limitations of the study, one can refer to the small sample size and absence of investigations into the long-term effects of Tranexamic acid on pregnant women and neonates. Moreover, the method used for measuring the amount of bleeding and lack of measurability

of blood clots formed in the uterus after its restraint led to insufficient accuracy of this study. Furthermore, the relationship between the causes of C-section and the level of bleeding was not assessed in the current study. Only in the misoprostol group, 14 C-sections due to labor failure were reported which was approximately three times more than those in the other two groups. Moreover, only two extensions in the lower uterine segment during delivery, followed by severe bleeding and receiving Packed cells, were observed in this group. Considering the similarity of the effect of these two medicines, as well as the type of use and ease of maintenance, it is recommended to completely investigate the effect of these two medicines in preventing postpartum hemorrhage in pregnant women.

Conclusion

Both Tranexamic acid and Misoprostol reduce n\ bleeding volume during lower uterine segment C-section. Nonetheless, the amount of blood loss during C-section in the Misoprostol group was less than that in the Transaxamic acid group. Nonetheless, bleeding volume 2 h after the operation and the rate of postoperative hemoglobin were reduced in both groups with no significant difference. However, Misoprostol is more efficient than Tranexamic acid due to its non-invasive application, ease of handling, and storage conditions. Therefore, it can be used safely and effectively in a prophylactic dose (600 µg) in patients undergoing C-section and atony-related postpartum hemorrhage.

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Ethical Rights

In all stages of the project, patients who met the inclusion criteria for this study and signed the consent form were ensured about the confidentiality of their information.

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