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ORIGINAL ARTICLE

Comparison of the Effect of Intravenous Tranexamic Acid and Sublingual Misoprostol on Reducing Bleeding After Cesarean Section: A Double-Blind Randomized Clinical Trial

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Abstract

Purpose To evaluate the effects of intravenous tranexamic acid (TA) and sublingual misoprostol on reducing bleeding after cesarean section.

Materials One hundred and fifty-eight participants with term pregnancies scheduled for cesarean section were randomly divided into two groups. In M group, two sublingual misoprostol pills (400 mg) were administrated, immediately after the delivery. In TA group, ten minutes before skin incision, TA ampoule (1 g) was injected. In both groups, immediately after the delivery, 20 units of oxytocin in 1 L ringer lactate with speed of 1000 CC/h was injected. At the end of the operation, the amount of bleeding was measured based on the number of small and large gauzes, the blood in the suction container and the difference of patient's hemoglobin before and 24 h after surgery.

Results Hemoglobin level reduction in the TA group was higher than the M group (-2.45 ± 0.84 vs

− 2.14 ± 1.38 g/dL) ($P < 0.001$). Furthermore, number of used gauze and blood suction in the TA group was significantly higher compared to sublingual misoprostol (4.67 ± 1.34 vs 3.25 ± 1.31 and 260.25 ± 79.06 vs 193.94 ± 104.79 cc, respectively) ($P < 0.001$). Mean blood pressure during the entire duration of surgery in the TA group decreased significantly as compared to the M group ($P < 0.001$).

Conclusion Total bleeding was significantly lower in sublingual misoprostol as compared to the tranexamic acid group. Furthermore, in misoprostol group hemodynamic variables were stabilized greater than tranexamic acid group.

Registration Number IRCT201708308611N6

Keywords Tranexamic acid · Misoprostol · Postpartum hemorrhage · Cesarean section

Introduction

The rate of cesarean section (CS) is increasing. CS is the most common major surgical procedure performed on females, worldwide, and is the main cause of the rising numbers of deaths due to cesarean-related hemorrhage [1, 2]. Different causes have been proposed for CS-related hemorrhage, such as uterine atony, trauma to the genital tract, and retained placenta [3, 4]. Due to increasing CS and related complications, there is concern about the lack of appropriate management of females with severe bleeding during and after CS [5]. Different uterotonic agents administration, mainly oxytocin, has been routinely used to reduce the frequency of CS-related hemorrhage [6]; however, some studies reported that oxytocin use in the setting of CS may result in maternal adverse effects, including hypotension and tachycardia [7]. Therefore, investigating other therapeutic agents with lower adverse effects and higher efficacy is needed.

Recently, a number of studies reported a correlation between fibrinogen decrease and cesarean-related hemorrhage [8]. Furthermore, extensive tissue injury increases fibrinolysis by shifting the hemostatic equilibrium and contributing to bleeding [9]. Therefore, anti-fibrinolytic agents, such as tranexamic acid (TA), reduce the risk of death in bleeding trauma patients [10]. On the other hand, it has been suggested that TA administration reduces blood loss and the incidence of postpartum hemorrhage (PPH) in females after vaginal or elective CS [11–16].

Moreover, misoprostol is a prostaglandin E1 analogue which has been introduced as an uterotonic agent for preventing PPH following CS. A recent study reported that oral or sublingual misoprostol is more effective than the placebo in reducing severe PPH, following CS [17]. However, some other studies demonstrated that oral misoprostol is associated with a higher risk of severe PPH with greater administration of additional uterotonics after delivery when compared to routine uterotonic agents [18]. Despite searching available recent evidence, it was found that there is a dearth in the number of studies about the efficacy of intravenous TA and sublingual misoprostol tablets on reducing bleeding after CS; therefore, this study was designed to evaluate and compare these two new therapeutic options in controlling PPH following CS.

Methods and Materials

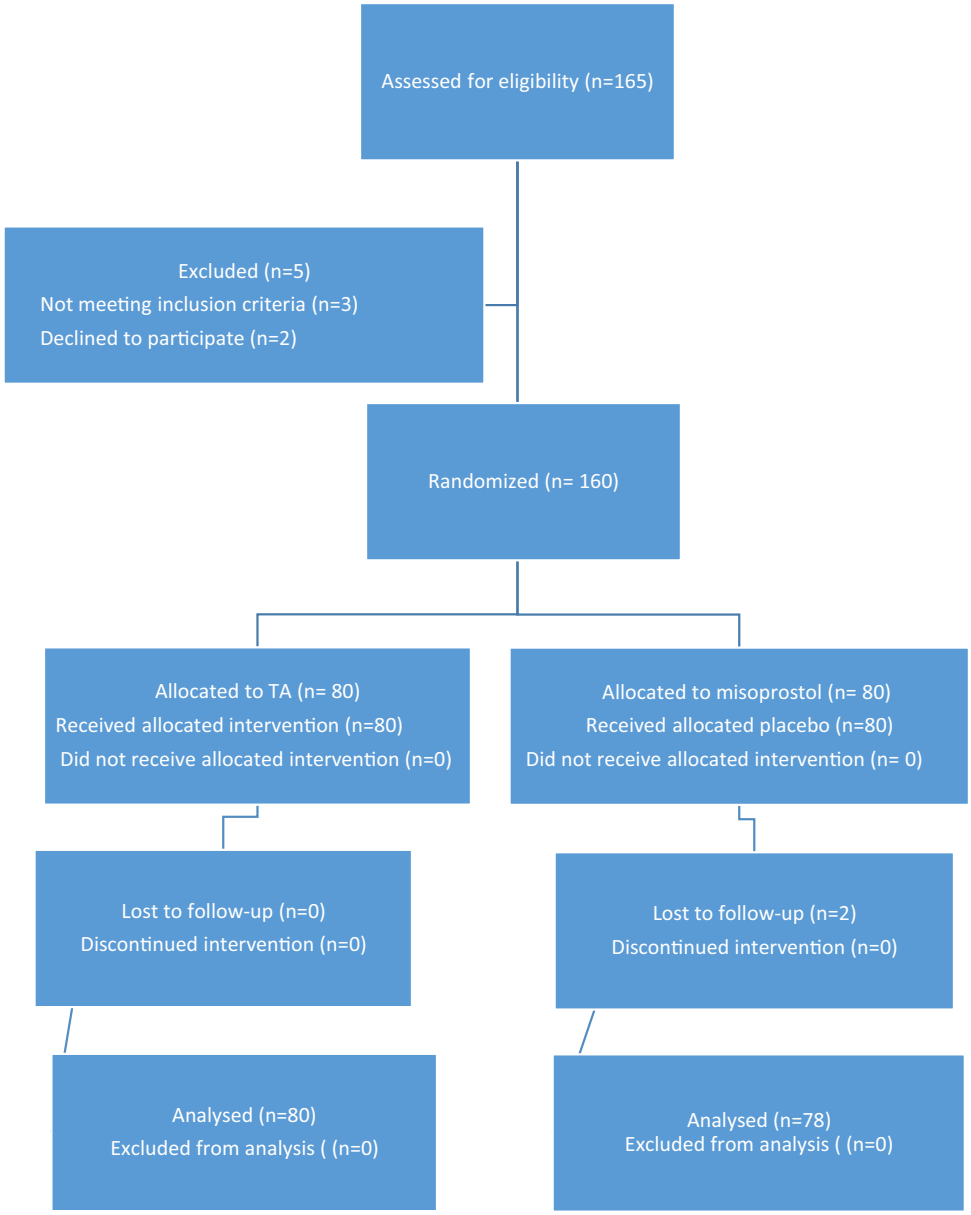
Study Design and Target Group

This prospective double-blind randomized clinical trial (Registration No. IRCT201708308611N6 URL: http://www.irct.ir/trial/9115) was conducted at the obstetrics and gynecology department of Qazvin Kowsar Hospital, Northwest of Iran, from November 2016 to May 2017. PPH following CS of participants receiving sublingual misoprostol (M group) was compared to participants receiving intravenous TA (TA group). Inclusion criteria consisted of participant's referral to the obstetrics and gynecology department with indication of CS, signed consent form to participate in the study, age between 18 and 40 years, gestational age of 37–40 weeks, singleton pregnancy, CS with inferior segment incision, and spinal anesthesia. Exclusion criteria consisted of having underlying disease (heart, liver, kidney, pulmonary, etc.), eclampsia and severe preeclampsia, allergy to TA (such as known allergy or thromboembolic event during pregnancy) and misoprostol, coagulation disorders, abnormal placenta (placental abruption, placenta previa, etc.), risk factors for PPH (such as multiple pregnancies, macrosomia, polyhydramnios), history of two or more CS, previous history of uterine rupture, and dissatisfaction to continue participation in the study. The researchers also excluded participants with incomplete data or inadequate information.

Participants

One hundred and sixty-five pregnant women with indication for CS (emergency or elective), who had been diagnosed by an obstetrician–gynecologist and based on clinical and para-clinical findings and inclusion and exclusion criteria, were included in the study. The participants were randomly allocated to two groups, using the computer-generated randomization list with matched subjects in age. One hundred and fifty-eight patients completed the study: 78 in M group and 80 in TA group (Fig. 1).

Fig. 1 Consort flow diagram



Signed informed consents were also obtained from all participants. The researchers were committed to the ethical guidelines of the Declaration of Helsinki (1964), and approval for the study was obtained from the Ethics Committee of Qazvin University of Medical Sciences.

Intervention

After obtaining an informed consent, eligible participants were enrolled. Spinal anesthesia was performed with needle 25 using marcaine in L4 to L5 level. For all the subjects, CS was performed with inferior segment incision. In M group, immediately after the delivery, two sublingual misoprostol pills (400 mg) were administrated and 20 units of oxytocin in 1 L of ringer lactate with speed of 1000 CC/h was injected [19].

In TA group, 10 min before skin incision, 5 mL (equivalent of 1000 mg) of TA ampoule was injected slowly with 20 mL of dextrose 5% in water. Immediately after the delivery, 20 units of oxytocin in 1 L of ringer lactate with speed of 1000 CC/h was injected.

The main outcome measures were the determination of blood loss at CS and change in hemoglobin levels. At the end of the operation, the amount of bleeding was measured based on the number of small and large gauzes and the blood in the suction container. In order to separate the amniotic fluid from bleeding during the operation, after cessation of incision of the uterus, the amniotic fluid was collected by suction in a suction container, and as soon as the placenta was removed, the suction tube was transferred to another container to collect the blood. Hemodynamic

variables were recorded 5 min before spinal anesthesia, and 5, 10, and 20 min after spinal anesthesia and after arrival to recovery room. In addition, the patient's hemoglobin was determined before and 24 h after surgery [19].

The obstetrician–gynecologist and resident delivered the medication to an anesthetist nurse and an anesthesiologist. The obstetrician–gynecologist evaluated the patients during the study to initiate necessary medical treatment if any problems and complications occurred. Drug side effects, including nausea and vomiting, abdominal pain and diarrhea, fever, and chills, were evaluated up to 24 h after surgery.

Statistical Analysis

Sample size estimation was based on the previous studies which reported that the mean amount of blood loss with the use of oxytocin during a CS is 600 cc, and misoprostol can reduce it up to 200 cc [19, 20]. Thus, considering 90% power and 5% error, the sample size was determined to be 70 cases in each group. We included 80 patients in each group to allow for dropouts and protocol violations.

Data were analyzed and reported only for patients with completed information. Statistical analysis of data was performed using SPSS version 24 software (SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov test was used in order to evaluate the normal distribution of all quantitative studied parameters. Student's *t* test and paired t test were used for variables with normal distribution. The effect of time on the hemodynamic parameters was analyzed using repeated-measures analysis of variance test. Chi-square test was used to compare qualitative variables between groups. The *P* values of less than 0.05 were considered significant.

Results

Seven participants dropped out of the study, and finally, 158 participants completed the study. Demographic features in terms of age ($P = 0.883$) in both groups (M and TA) were similar. Before the intervention, the studied variables, including gestational age and hemodynamic parameters, did not show a significant difference between the groups ($P > 0.05$). The hemoglobin before surgery was significantly higher in the TA group as compared to the M group (13.15 ± 0.79 vs 12.84 ± 1 g/dL) ($P = 0.037$). Moreover, duration of surgery in both groups was similar (Table 1).

The results showed that hemoglobin levels, 24 h after surgery, did not show a significant difference between the groups ($P = 0.985$), while hemoglobin levels reduction in the TA group was higher than the M group (-2.45 ± 0.84 vs -2.14 ± 1.38 g/dL) ($P < 0.001$). Furthermore, number of used gauze and blood suction in the TA group was significantly higher in contrast to sublingual misoprostol (4.67 ± 1.34 vs 3.25 ± 1.31 and 260.25 ± 79.06 vs 193.94 ± 104.79 cc, respectively) ($P < 0.001$) (Table 2).

Mean blood pressure during the entire duration of the surgery in the TA group decreased significantly as compared to the M group ($F = 6.7$ (4, 620), $P < 0.001$), while pulse rate did not show a significant difference by analyzing repeated-measure analysis of variance (ANOVA) ($F = 1.41$ (4, 576), $P = 0.23$) (Table 3).

Moreover, the researchers did not observe significant differences between the two groups in terms of diarrhea, vomiting, nausea, fever, hysterectomy, and blood transfusion ($P > 0.05$) (Table 4).

Discussion

According to the results, total bleeding was significantly lower in sublingual misoprostol as compared to the TA group. Furthermore, in M group hemodynamic variables were stabilized greater than TA group.

In contrast to results of the current study, Sahhaf et al. [21] showed that hemoglobin levels after 6–12 h and bleeding amount did not differ between intravenous TA and misoprostol. The discrepancy of these results may be due to differences in type and dosage of administered misoprostol. The results of the study conducted by Abdel-Aleem et al. [15] showed that administration of intravenous

Table 1 Main outcome measures

Variables	Groups		
	Sublingual misoprostol ($n = 78$)	TA ($n = 80$)	*P* value
Age (year)	27.25 ± 5.85	27.12 ± 5.28	0.883
Gestational age (week)	39.25 ± 1.3	39.05 ± 2.31	0.522
Hemoglobin before surgery (g/dL)	12.84 ± 1	13.15 ± 0.79	0.037
Systolic blood pressure before surgery (mmHg)	121.85 ± 13.51	124.35 ± 12.48	0.23
Diastolic blood pressure before surgery (mmHg)	77.11 ± 9.51	77.01 ± 10.32	0.948
Pulse rate before surgery	92.53 ± 6.66	95.47 ± 10.99	0.051
Surgery duration (min)	39.54 ± 1.82	38.64 ± 2.1	0.08

Table 2 Demographic data of study

Variables	Groups		
	Sublingual misoprostol (n = 78)	TA (n = 80)	P value
Number of used gauze	3.25 ± 1.31	4.67 ± 1.34	<0.001
Blood suction (cc)	193.94 ± 104.79	260.25 ± 79.06	< 0.001
Hemoglobin 24 h after surgery (g/dl)	10.68 ± 1.61	10.69 ± 0.99	0.985
Hemoglobin reduction (g/dl)	− 2.14 ± 1.38	− 2.45 ± 0.84	< 0.001
Need for additional uterotonics	3 (3.8%)	4 (5%)	1

Table 3 Hemodynamic variables

Variables		Groups					
		Sublingual misoprostol (n = 78)	TA (n = 80)	P value	df, error	F	Sig.
Mean blood pressure (mmHg)	5 min before spinal anesthesia	92.02 ± 10.25	92.79 ± 10.03	0.638	(4, 620)	6.7	< 0.001
	5 min after spinal anesthesia	87.67 ± 9.74	82.79 ± 13.45	0.01			
	10 min after spinal anesthesia	84.55 ± 10.3	77.9 ± 11.91	< 0.001			
	20 min after spinal anesthesia	81.46 ± 9.17	75.31 ± 11.42	< 0.001			
	Recovery room	81.73 ± 9.29	75.5 ± 12.22	< 0.001			
Pulse rate	5 min before spinal anesthesia	92.53 ± 6.66	95.47 ± 10.99	0.051	(4, 576)	1.41	0.23
	5 min after spinal anesthesia	90.47 ± 6.5	94.37 ± 14.09	0.029			
	10 min after spinal anesthesia	88.92 ± 5.45	94.36 ± 15.19	0.003			
	20 min after spinal anesthesia	88.84 ± 6.89	94.35 ± 14.65	0.003			
	Recovery room	88.34± 7.74	93.36 ± 11.5	0.002			

TA 10 min prior to CS significantly decreased blood loss, which is similar to the results of our study. Although the beneficial effects of TA have been shown on reducing blood loss, some obstetricians are still worried about risk of thrombosis. Similar to the results of this study, Sentürk et al. [16] confirmed the effect of TA on reducing blood loss without side effects and thrombosis. In another study performed by Al-Sawaf et al. [22], it was reported that sublingual misoprostol appears to be less effective than intramuscular oxytocin in the prevention of PPH; however, it has the potential advantage of being easily used, cost-effective, and stable at room temperature. Therefore, based on this study, the current used a combination of sublingual misoprostol and oxytocin and found that combination of these drugs is more effective than combination of TA and oxytocin. Pakniat and Khezri showed that the amount of blood loss during and after CS in the 200 mg of misoprostol–oxytocin group was significantly smaller than

Table 4 Side effects observed in study groups

Variables	Groups		
	Sublingual misoprostol (n = 78)	TA (n = 80)	P value
Diarrhea	0	0	–
Vomiting	12 (15.4%)	12 (15.0%)	1
Nausea	23 (29.5%)	31 (38.8%)	0.22
Fever	1 (1.3%)	11.2%	1
Hysterectomy	0	0	–
Need for blood transfusion	5 (6.4%)	1 (1.2%)	0.114

oxytocin and 400 mg misoprostol alone, and administration of combined misoprostol–oxytocin was not associated with any serious side effects and in the current study combination of misoprostol and oxytocin was more effective than combination of TA and oxytocin in reducing bleeding after CS [19]. Ugwu et al. [23] showed that blood loss and PPH occurrence did not differ by 200 μg and 400 μg of sublingual misoprostol and both dosages decreased bleeding after delivery, yet the 200 μg dose was associated with a reduction in adverse effects. It is important to mention that different dosages of sublingual misoprostol were not used, yet it was found that sublingual misoprostol is more effective in reduction of bleeding during and after caesarian section as compared to TA. However, in order to find the best dosage, future studies should evaluate different dosage in larger sample sizes.

Moreover, in an article performed by Othman et al., it was shown that sublingual misoprostol is more effective than intravenous oxytocin in reducing blood loss during and after CS. However, occurrence of temporary side effects, including shivering and metallic taste, was more frequent with the use of sublingual misoprostol [24]. The current study indicated that sublingual misoprostol did not increase the adverse effects in the participants. These differences may be due to different dosages of sublingual misoprostol, different population, and different inclusion and exclusion criteria. Atukunda et al. [25] demonstrated that sublingual misoprostol at 600 μg is inferior to oxytocin at 10 IU for prevention of primary PPH in active management of labor. Although the current study protocol was different to Atukunda et al.'s study, it was found that combination of sublingual misoprostol and oxytocin is more effective. In this regard, Chaudhuri et al. [26] showed that sublingual misoprostol as an adjunct to oxytocin seemed to more effectively reduce PPH than oxytocin alone. Furthermore, Ugwu et al. reported that addition of sublingual misoprostol to intravenous oxytocin reduces blood loss after delivery and decreases the need for additional uterotonics. They reported an increased risk of shivering and fever with this combination [27]. In another recent study performed by Okonofua et al., it was reported that although sublingual misoprostol is effective in reduction of blood loss due to PPH, it does not effectively treat all forms of PPH. They concluded that additional uterotonics and other ancillary treatments are required [28]. The current researchers did not observe a significant acceleration in adverse effects or additional uterotonics and other ancillary treatments. This study had some limitations; the dose response or the effects of multiple dose therapy were not evaluated. Furthermore, absolute accuracy in estimation of blood loss cannot be ensured despite the use of collection of amniotic fluid. Nevertheless, this limitation is similar in two groups.

Conclusion

The results of this study demonstrated that total bleeding was significantly lower after administration of sublingual misoprostol as compared to the TA during and after the lower segment CS, without adverse hemodynamic effects. Furthermore, sublingual misoprostol group had more hemodynamic stability compared to TA group. Thus, sublingual misoprostol could be prescribed as a treatment in addition to standard therapy (as an adjunct to oxytocin) and significantly leads to better control of bleeding in the short term and increases the quality of surgery with spinal anesthesia and outcomes for a long time.

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Compliance with Ethical Standards

Conflict of interest The authors declared no conflict of interest. The authors have no financial conflict of interest to declare.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1975 Declaration of Helsinki, as revised in 2008 (5).

Informed consent Informed consent was obtained from all patients for being included in the study.

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