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Randomised Controlled Trial

Prophylactic effect of rectal and sublingual misoprostol on postpartum hemorrhage in mothers with preeclampsia following cesarean section surgery; a double-blind randomized controlled trial

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ABSTRACT

Background: Postpartum hemorrhage is one of the three major causes of maternal morbidity and mortality, so delay in the diagnosis and proper management of postpartum hemorrhage is of great importance. The present study aimed to determine the prophylactic effect of misoprostol on postpartum hemorrhage in patients with preeclampsia.

Methods: This was a double-blind randomized controlled clinical trial performed on 128 pregnant women with preeclampsia undergoing cesarean section in Kamali hospital in Karaj. After cesarean delivery, immediately after clamping the umbilicus, the first group was administered 400 μg of rectal misoprostol and the second group was given 400 μg of sublingual misoprostol. The third group (control) was given 30 units of oxytocin during surgery and within 12 h after surgery, respectively. Hemoglobin and hematocrit were measured 24 h later. The estimated bleeding rate by the physician, the need for additional medication to control bleeding, and the amounts of hemoglobin and hematocrit in the first 24 h were compared in the three groups. Finally, the obtained information was entered into SPSS version 21 and analyzed using statistical tests.

Results: The mean hemoglobin and hematocrit levels 6 and 12 h after cesarean section were significantly lower in the oxytocin group than in the sublingual and rectal misoprostol groups (Hemoglobin level (mg/dl) for oxytocin group 10.39 ± 0.73 and 9.53 ± 1.09 vs. sublingual misoprostol 11.05 ± 0.71 and 10.39 ± 0.84 vs. rectal misoprostol 10.92 ± 0.85 and 10 ± 1.01; hematocrit level for Hemoglobin level (%) for oxytocin group 31.27 ± 2.29 and 28.64 ± 2.93 vs. sublingual misoprostol 33.09 ± 2.20 and 31.05 ± 2.37 vs. rectal misoprostol 32.54 ± 2.7 and 29.92 ± 2.86) ($p < 0.005$). The mean estimation of visual bleeding in the oxytocin group was higher than the other three groups, followed by the rectal and the sublingual groups, respectively. However, there was no significant difference between the three groups regarding visual bleeding. There was no significant difference in hemoglobin and hematocrit between the two groups of sublingual and rectal misoprostol before and 6 and 12 h after the surgery ($P > 0.05$).

Conclusion: It seems that sublingual or rectal misoprostol administration along with oxytocin is associated with a reduction in postpartum cesarean section bleeding compared to oxytocin administration alone.

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1. Introduction

Postpartum hemorrhage (PPH) is one of the five leading causes of maternal mortality, especially in the developing countries [1]. Postpartum hemorrhage refers to the blood loss of 500 ml or more in a normal delivery and 1000 ml or more in a cesarean section after the end of the third stage [2]. The risk of PPH increases in the presence of risk factors such as multiple births, polyhydramnios, grand multi-parity (more than five parities), severe preeclampsia, prepartum hemorrhage, prolonged labor, labor induction, obesity, and anemia [3,4]. Among the mentioned causes, preeclampsia is an important issue. The association between preeclampsia and postpartum hemorrhage has been shown in various studies [5]. Studies show that careful use of clinical protocols to control PPH not only prevents uterine atony and improves the conditions of preeclamptic women, but also it prevents dangerous complications such as hysterectomy [6].

One of the pharmacological methods in this field is the use of synthetic misoprostol from the prostaglandin E1 analog, which was first used in the active management of the third stage of labor (AMTSL) in the developing countries in 1996. It is rapidly absorbed orally and sublingually, and vaginal or rectal use is preferred in some cases because it is believed to reduce gastrointestinal side effects [7]. The use of misoprostol to control postpartum hemorrhage has been included in several hemorrhage control protocols worldwide [8]. Youssef et al. used 400 μg of misoprostol to prevent PPH in mothers undergoing cesarean section. The prophylactic administration of misoprostol, especially before cesarean section, had a good and significant effect on the prevention of PPH [9]. However, some placebo-controlled trials have reported the opposite. In some studies, the effect of misoprostol in the treatment of bleeding has been compared with other drugs. A study on the prophylactic effect of misoprostol showed that the addition of either misoprostol and Tranexamic acid to oxytocin had better effects on reducing bleeding than the oxytocin group alone [10].

A cohort study in three hospitals showed that 800 μg of sublingual misoprostol was effective in stopping bleeding within 20 min of use in women with PPH [11]. However, most studies on misoprostol have focused on its role in controlling PPH and in fact its therapeutic effect, and there are few studies on its possible prophylactic role. Ibrahim and Saad showed that the rate of heavy PPH (more than 1500 ml) was twice as high in women with preeclampsia as in women with normal blood pressure. Postpartum hemorrhage was also 1.6 times higher in women with preeclampsia than in women with normal high blood pressure [12]. According to the above mentioned issues and the contradictory results in the mentioned studies, this study was performed to determine the prophylactic effect of misoprostol on PPH in preeclampsia patients.

2. Methods

This study was a double-blind randomized clinical trial carried out on 128 pregnant women undergoing cesarean section referred to Kamali hospital in Karaj and randomization list provided by sealedenelop.com. This trial is fully compliant with the CONSORT criteria [13]. The inclusion criteria were gestational age over 35 weeks, having a healthy and live fetus, cephalic fetus, history of maximum of two previous cesarean deliveries, lack of coagulopathy or any dyscrasia in the mother, lack of hypertension, no placental adhesion such as placenta previa and increta, the absence of placental abruption (overt and covert), complete removal of the placenta after cesarean section, and the absence of emergency midwifery complications during the operation. After coding, the subjects were randomly assigned to the three treatment groups of rectal misoprostol (N = 42), sublingual misoprostol (N = 43), and only oxytocin (control group) (N = 43) (Fig. 1). After spinal anesthesia with the same protocol and cesarean section, immediately after the umbilical cord clamp, the first group was administered 400 μg of rectal misoprostol and the second group 400 μg of sublingual misoprostol. The first and second groups (intervention groups) and the third (control group)

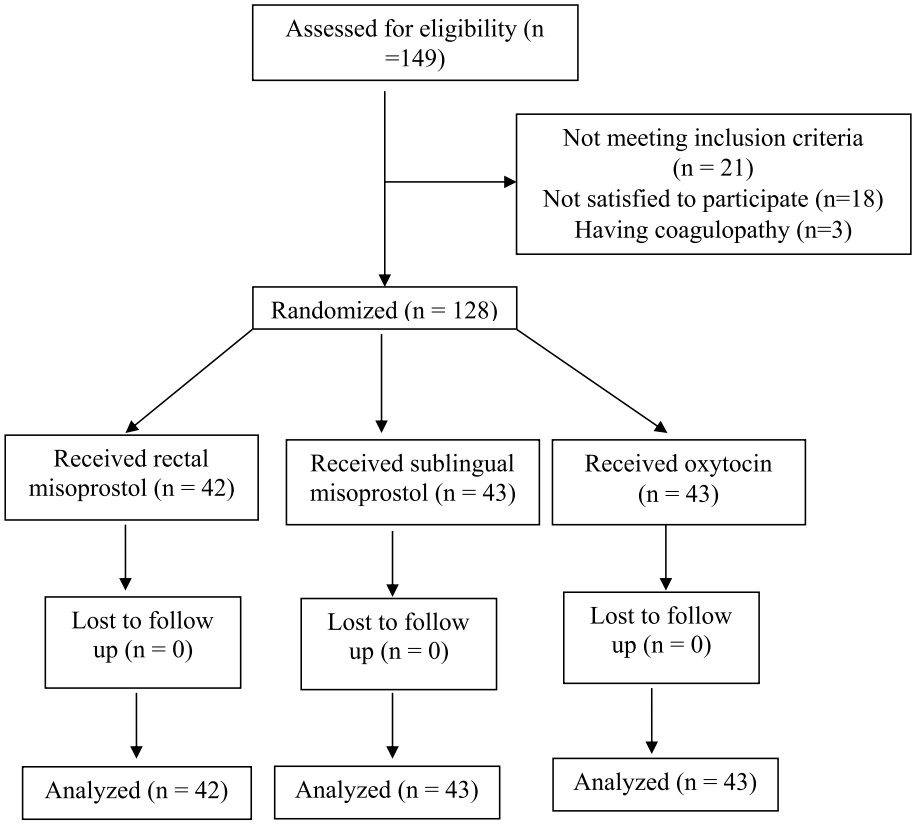

Fig. 1. CONSORT flow chart of participants.

were administered 30 units of oxytocin during surgery and within 12 h after surgery, respectively. Gauze pad count was performed after the operation, and hemoglobin and hematocrit were measured 24 h later. The required sample size in this study was 42 individuals per group. Data analyzer and the patients were unaware of the allocated groups.

2.1. Statistical issue

The results were analyzed for descriptive and analytical objectives. In this study, Chi square, independent-test and ANOVA were run in SPSS.

2.2. Ethical issues

The research followed the Tenets of the Declaration of Helsinki 2013. To keeping ethical principles, names of the patients were not pointed in the checklists. Ethics approval was also obtained from ethic committee of Karaj University of Medical Science (IR.ABZUMS.REC.1399.186). This trial register at https://www.researchregistry.com and now is available at: https://www.researchregistry.com/register-now#home/registrationdetails/62caa17f0b2b1e001f3e693d/) as well. In addition, the patients received a consent form.

3. Results

The mean age of women in the rectal misoprostol, sublingual, oxytocin groups was 31.19, 30.7, and 31.35 years, respectively without significant difference between the three groups. The two groups were similar in terms of some confounding variables such as gestational age, body mass index, history of hemorrhage in previous pregnancies, number of abortions, history of anemia, gravidity, parity, history of previous deliveries, and employment (Table 1).

Regarding intrapartum characteristics, 64% of the participants in the rectal misoprostol group, 67.4% in the oxytocin group, and 67.4% in the sublingual group had severe preeclampsia. There was no significant difference between the three groups in this regard. Induction during labor was performed in 19%, 39.5% and 30.2% of the cases in the rectal, oxytocin and sublingual groups, respectively, which did not differ significantly. The most common cause of cesarean section was uncontrollable hypertension in the rectal and sublingual groups and labor pain in the oxytocin group. There was a significant difference in the cause of cesarean delivery between the three groups ($P < 0.001$) (Table 2).

Table 1
Mean and standard deviation of quantitative variables in the three groups.

Variable		Rectal misoprostol	Oxytocin	Sublingual misoprostol
Age (years), Mean (SD)		31.19 (5.29)	31.35 (5.61)	30.7 (5.97)
Gestational age (years), Mean (SD)		37.91 (0.58)	38 (0.62)	37.95 (0.60)
Body mass index (kg/m^2), Mean (SD)		26.21 (2.47)	27.51 (2.48)	26.81 (2.48)
History of bleeding, No. (%)		2 (4.8)	4 (9.3)	9 (20.9)
Abortion No. (%)		13 (31)	11 (26.2)	12 (27.9)
History of anemia (%)		3 (7.3)	3 (7.1)	7 (16.3)
Gravidity, No (%)	1	6 (14.3)	8 (18.6)	9 (20.9)
	2	26 (61.9)	18 (41.9)	19 (44.2)
	3	10 (23.8)	17 (39.5)	15 (34.9)
Parity, No (%)	0	14 (33.3)	11 (25.6)	14 (32.6)
	3	23 (54.8)	17 (39.5)	20 (46.5)
	2	5 (11.9)	15 (34.9)	9 (20.9)
Previous delivery history, No (%)	No	4 (9.5)	8 (18.6)	9 (20.9)
	Cesarean section	19 (45.2)	16 (37.2)	20 (46.5)
	Normal delivery	19 (45.2)	19 (44.2)	14 (32.6)
Employment, No (%)		26 (61.9)	5 (11.6)	9 (20.9)

Overall, 90.5% of the patients in the rectal group and 97.6% in the sublingual group did not need blood transfusion, while 65.1% in the oxytocin group did not need blood transfusion, showing that the need for blood transfusion in the oxytocin group was significantly higher ($P < 0.001$). The number of gauze pads used in the three groups was not significantly different ($P > 0.05$). The mean hemoglobin level before surgery was not significantly different between the three groups. However, 6 h after cesarean section, hemoglobin level was significantly lower in the oxytocin group (10.39 mg/dl) than in the sublingual (11.05 mg/dl) and rectal (10.92 mg/dl) groups. The same trend was observed after cesarean delivery, and the mean hemoglobin level was lower in the oxytocin (9.5 mg/dl), rectal (10 mg/dl) and sublingual (10.39 mg/dl) groups, respectively. The mean hematocrit did not show a significant difference in the three groups before the intervention. However, 6 h after the intervention, it was lower in the oxytocin group (31.27%) than the other two groups. Also, it was lower in the rectal group (32.54%) compared to the sublingual group (33.09) ($P < 0.001$). The mean hematocrit 12 h after the intervention was lower in the oxytocin group (28.64%) compared to the other two groups, and it was lower in the rectal group (29.92%) compared to the sublingual group (31.05%) was lower ($P < 0.001$). The mean estimation of visual bleeding in the oxytocin group was higher than the other two groups, followed by the rectal group and the sublingual group. However, there was no significant difference between the three groups in terms of visual bleeding estimation. There was no significant difference between the sublingual and rectal misoprostol groups in terms of the number of drapes, blood transfusion, additional drugs, hemoglobin and hematocrit levels before and 6 and 12 h after the study ($P > 0.05$) (Table 3). The trend of hemoglobin and hematocrit changes was shown in Figs. 2 and 3.

4. Discussion

Bleeding, hypertension and infection are the three leading causes of maternal mortality. Hemorrhage after childbirth is still one of the causes of maternal death in the developing countries. Most gynecologists use intravenous oxytocin as the first-line agent to prevent uterine atony and reduce bleeding during cesarean section. However, 10–42% of women receiving oxytocin need additional oxytocic agents such as ergot alkaloids and prostaglandins. Misoprostol, as an analogue of prostaglandin E1, causes uterine contractions and, unlike other prostaglandins, it is cheap and stable at room temperature. It is well absorbed when administered sublingually, vaginally, or rectally [14]. However, the findings regarding the effects of misoprostol versus oxytocin on reducing PPH have been different in published studies [15]. The effect of misoprostol on reducing blood loss has been confirmed in several studies [16–18].

A study by Samimi showed that the effect of 600 μg of rectal misoprostol was associated with a lower decrease in mean hemoglobin in the misoprostol group compared with the Syntocinon group [19]. Another study by Ahmed et al. showed that the injection of 20 units of oxytocin immediately after delivery was associated with less blood loss during surgery. Blood transfusion and additional uterine treatment were significantly higher in the oxytocin group compared with the misoprostol group [20]. In a study by Eftekhari on 100 pregnant women who underwent cesarean delivery under general anesthesia, one group received 200 μg of sublingual misoprostol and the second group received 20 units of oxytocin. The rate of blood loss in the misoprostol group was significantly lower compared to the oxytocin group [21].

Also, in a study by Sweed et al. evaluating the effect of misoprostol and oxytocin adjuvant in reducing intraoperative bleeding during cesarean delivery, the study revealed that sublingual misoprostol significantly reduced the estimated intraoperative bleeding compared to rectal administration [21]. Vimala also showed that sublingual administration of misoprostol 400 or intravenous injection of 20 units of oxytocin immediately after cesarean delivery had the same effect on hemoglobin changes and concluded that sublingual misoprostol was as effective as

Table 2
Intrapartum characteristics of the participants in the three groups of rectal misoprostol, sublingual misoprostol and oxytocin.

Variable		Rectal misoprostol	Oxytocin	Sublingual misoprostol	*P*-value
Induction during labor, No (%)		8 (19)	17 (39.5)	13 (30.2)	0.12
Preeclampsia	Severe	27 (64.3)	29 (67.4)	29 (67.4)	0.93
Severity, No (%)	Mild	15 (35.7)	14 (32.6)	14 (32.6)	
Cause of cesarean section, No (%)	lack of progress	8 (19)	11 (25.6)	6 (14)	<0.001
	Uncontrollable high blood pressure	15 (37.5)	7 (16.3)	19 (44.2)	
	FHR drop	14 (33)	3 (7)	7 (16.3)	
	Excretion of meconium	3 (7.1)	3 (7)	5 (11.6)	
	Delivery pain	2 (4.8)	17 (39.5)	4 (9.3)	
	Abruption	0 (0)	2 (4.7)	2 (4.7)	

Table 3
Comparison of the hematological variable among the three groups of rectal misoprostol, sublingual misoprostol and oxytocin.

Variable		Rectal misoprostol group	Oxytocin group	Sublingual misoprostol group	*P*-value
Number of drape, No (%)	1	36 (85.7)	26 (60.5)	40 (93)	<0.001
	2	6 (14.3)	17 (39.5)	3 (7)	
Blood transfusion, No (%)	No	38 (90.5)	28 (65.1)	40 (97.6)	<0.001
	1 pack cell unit	2 (4.8)	8 (18.6)	0 (0)	
	2 pack cell units	2 (4.8)	7 (16.3)	1 (2.4)	
Additional drug, No (%)		10 (23.8)	22 (51.2)	4 (9.3)	<0.001
Type of drug additional, No (%)	No	32 (76.2)	21 (48.8)	39 (90.7)	0.006
	1 g of misoprostol	1 (2.4)	3 (4)	0 (0)	
	800 μg of misoprostol	6 (14.3)	10 (23.3)	3 (7)	
	Misoprostol + oxytocin	3 (7.1)	7 (16.3)	1 (2.3)	
	1600 misoprostol	0 (0)	2 (4.7)	0 (0)	
Number of gauze pads, No (%)		7.1 (1.63)	7.26 (1.59)	7.05 (1.17)	0.73
Hemoglobin before surgery (mg/dl), Mean (SD)		12.33 (0.84)	12.54 (1.03)	12.40 (0.86)	0.53
HB 6 h (mg/dl), Mean (SD)		10.92 (0.85)	10.39 (0.73)	11.05 (0.71)	<0.001
HB 12 h (mg/dl), Mean (SD)		10 (1.01)	9.53 (1.09)	10.39 (0.84)	0.001
HCT before surgery (%), Mean (SD)		36.55 (3.35)	36.79 (3.28)	36.78 (3.48)	0.93
HCT 6 h (%), Mean (SD)		32.54 (2.7)	31.27 (2.29)	33.09 (2.20)	<0.001
HCT 12 h (%), Mean (SD)		29.92 (2.86)	28.64 (2.93)	31.05 (2.37)	0.001
Estimation of bleeding, Mean (SD)		302.38 (126.85)	361.63 (161.03)	277.91 (88.84)	0.07

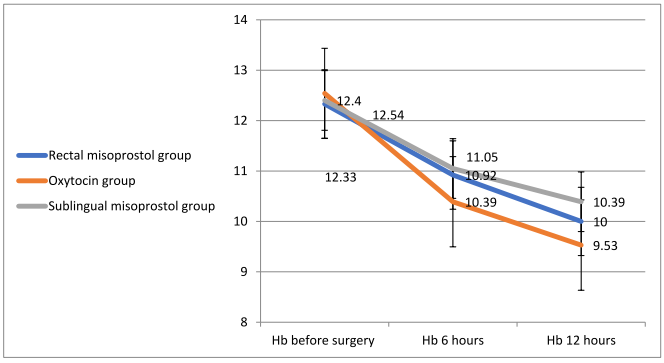

Fig. 2. Hemoglobin changes at three different times.

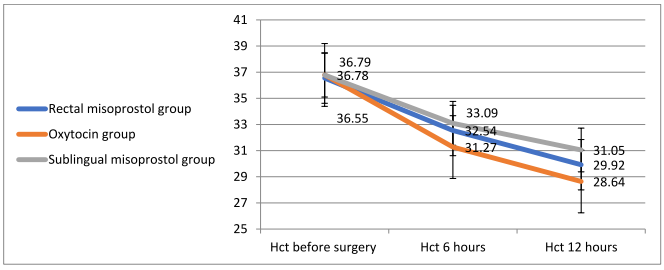

Fig. 3. Hematocrit changes at three different times.

intravenous oxytocin in reducing loss [22]. The results of the mentioned studies exhibited a difference between the rates of postpartum hemorrhage in the misoprostol group which was consistent with the findings of our study.

However, other findings have been reported inconsistent with the results of our study. A study by Vodouhe et al. comparing the administration of 600 μg of sublingual misoprostol during umbilical cord ligation with 20 units of intravenous oxytocin showed that there was no significant difference in the mean blood loss between the misoprostol and oxytocin groups [23]. In a multicenter randomized trial, 366 patients in the misoprostol group and 263 women in the oxytocin group had bleeding in the third stage of labor, and this difference was significant. In addition, 15% in the misoprostol group and 11% in the oxytocin study group required additional uterotonic drugs.

A double-blind trial by Chaudhuri et al. which included 200 participants undergoing cesarean delivery, examined the effect of 800 μg of rectal misoprostol and 40 units of intravenous oxytocin for the prevention of atonic uterus. This study showed that blood loss during surgery and after surgery was significantly higher in the oxytocin group than in the misoprostol group [24]. Discrepancy in findings may be due to differences in the study population, method of administration and dosages of misoprostol and oxytocin. In another study, Koch and Rattmann showed that the main cause of postpartum hemorrhage is uterine atony and about 15% needed blood transfusion. Misoprostol was effective and safe for treating postpartum hemorrhage in which treatment of postpartum hemorrhage was successful in about 85% of women [25].

5. Conclusion

The results of this study showed that the administration of misoprostol sublingually or rectally with oxytocin is associated with reduced bleeding after cesarean delivery compared with oxytocin alone. In

communities where access to health care systems is limited or in areas where injectable drug use is not available, the use of misoprostol can significantly reduce maternal mortality. Misoprostol can be a good option to prevent postpartum hemorrhage due to its cost-effectiveness, ease of use, greater effectiveness and accessibility, and faster absorption.

Ethical approval

Trial Registration: Present study was registered in the Iranian registration of clinical trials (#IRCT20201022049108N1; https://en.irct.ir/trial/51799,#ethicode:IR.ABZUMS.REC.1399.186).

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Author contribution

All authors had the same contribution with active participation in all steps of the study. MSA and MA searched the literature and prepared the primary draft. SES and MA conducted final edition. MSA performed statistical analysis. MA, MSA and SES have done the practical paraclinical parts of study, intervention and data collection. All authors wrote and signed the final paper.

Registration of research studies

Trial Registration: Present study was registered in the Iranian registration of clinical trials (#IRCT20201022049108N1; https://en.irct.ir/trial/51799,#ethicode:IR.ABZUMS.REC.1399.186).

Consent

Not applicable.

Guarantor

Mina Ataei.

Provenance and peer review

Not commissioned, externally peer reviewed.

Declaration of competing interest

The authors of this article declare that they have no conflict of interests.

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