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Comparing the effects of sublingual misoprostol and oxytocin infusion in reducing hemoglobin level after cesarean delivery

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ABSTRACT

Postpartum hemorrhage still remains a leading cause of maternal death worldwide, especially in developing countries. The amount of bleeding after childbirth depends on the delivery type, as it is 500 and 1000cc in average for the normal vaginal delivery and cesarean delivery, respectively. Regarding the complications and necessary considerations in a routine infusion of oxytocin after delivery, the aim of this study was to compare the effects of sublingual misoprostol with oxytocin infusion. Controlling the bleeding after cesarean can be introduced as a substitute for oxytocin, as it has similar effects and fewer side effects. This clinical trial was conducted in Ali-ibn Abi-Talib hospital, Zahedan, Iran during 2013 on pregnant women candidate for cesarean section (C-section). The sample size was 60 pregnant women undergoing C-section out of which 30 were in sublingual misoprostol group and the rest in intravenous oxytocin group. Hemoglobin decrease and other side effects were studied in two groups. All study data were analyzed in SPSS 18 software using a Chi-square (χ^2) test. The results showed that hemoglobin decrease in the sublingual misoprostol group was significantly lower compared to that of the oxytocin group. Moreover, frequent side effects were seen in the misoprostol group; however, they were transient, reversible, and with a statistically insignificant incidence ($P>0.05$). According to the results obtained from this study, the use of sublingual misoprostol is suggested as a good alternative to intravenous oxytocin to reduce postpartum hemorrhage after cesarean delivery.

Keywords: bleeding, intravenous oxytocin, sublingual misoprostol.

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Introduction

Postpartum hemorrhage is a worldwide leading cause of maternal mortality, especially

in developing countries (1). According to the report of World Health Organization (WHO), more than 585,000 women annually lose their

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lives, 25% of which is due to excessive bleeding (2). Bleeding is different in various delivery methods. The average amount of bleeding in normal vaginal delivery and cesarean section (C-section) is 500 and 1000 cc, respectively (3). Severe bleeding (requiring blood transfusion or with 10% hematocrit drop) can be seen in approximately 4% of vaginal deliveries and 6% of C-sections (5-4). Obviously, effective interventions are necessary to reduce bleeding after C-section and normal deliveries due to postoperative complications and the risks associated with blood transfusion.

Since most of the postpartum hemorrhage occurs due to uterine atony, use of uterotonic drugs such as oxytocin and syntonins are regular treatment and first-line therapy for prevention of obstetric hemorrhage. The main reason for the use of these drugs is that they can reduce postpartum bleeding by irritation of myometrium tissue (7-6). Despite the frequent use of oxytocin in normal deliveries and caesarean consumption, it might not be suitable in some cases, such as pre-eclampsia, heart disease, and prolonged delivery, due to the oxytocin-induced tachycardia. Oxytocin has negative inotropic and antiplatelet effects and can increase heart rate (8-10). Due to the effects of oxytocin and the importance of uterotonic drugs, several studies have been conducted to identify suitable drugs with acceptable therapeutic effects and fewer side effects than oxytocin.

Misoprostol is a synthetic analog of prostaglandin E1 that is used in the treatment of peptic ulcers by the protecting the gastric mucosa and preventing acid secretion (11). Easy to use, low cost and stability at room temperature are the main benefits of misoprostol. Clinical and pharmacological studies have proved misoprostol as an uterotonic drug in the uterus myometrium tissue stimulation (12). Many clinical trials have been done to compare the effects of

misoprostol and oxytocin in reducing postpartum hemorrhage in order to find the best, most effective, and safest method of administration of the dose.

Some studies have shown that administering misoprostol orally or rectally can be a viable replacement for oxytocin in preventing postpartum hemorrhage (13-14). Although the effects of sublingual misoprostol to reduce the vaginal bleeding after vaginal delivery is studied in several clinical trials, a limited number of investigations have been performed on the effects of oxytocin in cesarean delivery. Nowadays, the majority of cesareans are done by regional anesthesia in spinal anesthesia. However, this method involves some consequences such as a drop in blood pressure during and after surgery. Moreover, the use of oxytocin can also lead to sympathetic blocks and drop in blood pressure, the precise infusion control of which a pump is difficult. Therefore, to reduce bleeding after the C-section and lower maternal mortality, it is critical to select the most appropriate dose of a drug with the least side effects and the high impact. The main objective of the present study is to compare the efficacy of sublingual misoprostol with oxytocin infusion in reducing bleeding after C-section and to introduce an alternative to oxytocin.

Materials and Methods

Following the previous studies, this randomized clinical trial study involved 60 pregnant women undergoing cesarean section with spinal anesthesia in the hospital of Ali-ibn Abi-Talib, Zahedan. The age range of the subjects sampled according to ref was 19-35. To begin with, the cesarean patients with singleton cephalic term pregnancy with a normal status in the placenta, fetus, uterus, and amniotic fluid and natural supplements enrolled in this study. The exclusion criteria of the study included having anemia,

coagulation disorders, prolonged second stage of Labor, the use of anticoagulants, vaginal bleeding, a history of chronic disease, asthma, atonic uterus during surgery, duration of surgery more than 60 minutes, abnormal body mass index ($19 < \text{BMI} > 30$), the need for transfusion of blood products, parity more than four times, and a history of cesarean.

All patients were under the same spinal anesthesia. Before performing C-section, the complete and sufficient explanation was given about the objectives and their informed consent was gained. The study ethical code (ir.zaums.rec.1391.861) was also obtained IRCT. The patients were randomly (using permuted block) divided into two groups (A and B).

Group A) Immediately after the cesarean-section, 400 mcg sublingual misoprostol (2 tablets of 200 mcg) was administered to the patients.

Group B) Immediately after the cesarean-section, the patients of this group were administered 20 units of oxytocin in one liter of Ringer lactate solution at 20 drops per minute during the 8-hour infusion.

The type and amount of serum in both groups were the same and for a liter of intravenous infusion every 8 hours.

Care after the operation, including monitoring vital signs of the patient every 15 minutes to an hour, the second 4 hours, every 60 minutes, and then every 4 hours for 24 hours in both groups were similar. Also, during each control of vital signs, the consistency of the uterus and the vaginal bleeding was controlled. In case of abnormal bleeding and atonic uterus, cases were recorded on the information form and appropriate care was provided based on the patient's condition and doctor's supervision. Variables such as age and parity were tested. The group matching in these variables was also taken into account. Preoperative

hemoglobin was measured 6 hours after surgery. The main outcomes assessed in this study included hemoglobin reduction and comparison of hemoglobin before and after surgery, medical complications, the need for additional treatment, and the need for blood transfusion. The findings from the study were collected and analyzed at the end of the study by using SPSS 18 software, where in a p-value less than 0.05 was considered as statistically significant.

Results

The demographic data including age and parity in two groups is compared and shown in Table 1. The comparison of hemoglobin decrease average and the drugs side effects in the two groups are shown in Table 2. The hemoglobin decrease in the two groups was considerable. As shown in Table 3, in the oxytocin group, 12 patients (40%) had hemoglobin between 0.1 to 0.9 mg per deciliter, 10 patients (33.3%) between 1 to 1.9 milligrams per deciliter, 5 patients (7.16%) between 2 to 2.9 mg per deciliter, and 3 patients (10%) greater than 3 mg of hemoglobin per dL drop. In the misoprostol group, 17 patients (7.56%) had hemoglobin between 0.1 to 0.9 mg per deciliter, 10 patients (33.3%) between 1 to 1.9 milligrams per deciliter, and 3 patients (10%) between 2 to 2.9 mg of hemoglobin per dL drop, which are statistically significant ($P > 0.001$).

In the oxytocin group, 25 patients (83.4%) did not mention side effects while 1 patient (3.3%) had nausea and vomiting, 3 patients (10%) had hypotension and tachycardia and, 1 patient (3.3%) had fever and chills. Moreover, in the misoprostol group, 23 patients (7.76%) did not mention any side effects while 3 patients (10%) had nausea and vomiting, 2 cases (6.6%) had hypotension and tachycardia, and 2 patients (6.6%) had fever

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Table 1. Comparison of age and parity in the two groups

Group Variable	Oxytocin		misoprostol		total	p-value
	Frequency (percentage)	Frequency (percentage)	Frequency (percentage)	Frequency (percentage)		
Age	18-24	9(30%)	12(40%)	21(35%)	0.574	
	25-29	10(33.3%)	9 (30%)	9(31.7%)		
	30-35	11 (36.7%)	9(30%)	20(33.3%)		
Parity	1-2	22(73.7%)	17(56.6%)	39(65%)	0.216	
	3-4	8(26.3%)	13(43.4%)	21(35%)		

Table 2. Comparison of Hb declination and the frequency of complications in the two groups

Group Variable	Oxytocin	misoprostol	Total	p-value	
Hb decline	0.94±0.81	0.87±0.86	0.91±0.84	0.001	
Complications	Have	5(16.6%)	7(23.3%)	12(20%)	0.605
	Dose not have	25(83.4%)	23(76.7%)	48(80%)	

Table 3. Comparison of Hb declination and the frequency of complications in the two groups

Group	Hb decline	Frequency	Percentage
Oxytocin	0-0.9	12	40
	1-1.9	10	33.3
	2-2.9	5	16.7
	≥3	3	10
Misoprostol	0-0.9	17	56.7
	1-1.9	10	33.3
	2-2.9	3	10
	≥3	0	0

Table 4. Comparison of the frequency and percentage of complications in the two groups

Group Complications	Oxytocin		Misoprostol	
	Frequency	Percentage	Frequency	Percentage
Non Complications	25	83.4	23	76.7
Nausea & Vomiting	1	3.3	3	10
Hemodynamic disorder	3	10	2	6.6
Fever & Chills	1	3.3	2	6.6

and chills. The results indicated no significant difference between the two groups (P= 0.091) (Table 4).

None of the subjects needed an extra dose of oxytocin. Also, none of them needed to receive blood products.

Discussion

According to the results of this study, the use of misoprostol tablets for sublingual instead of oxytocin infusion after C-section leads to a significant reduction in hemoglobin loss after the cesarean procedure. Although the frequency of its

use compared to oxytocin infusion reactions is higher, there is no statistically significant difference in complications between the two groups. Many investigations conducted in this field in Iran and around the world have reported mixed results. For example, a clinical trial by Vimala et al. (2006) was performed to compare the efficacy of sublingual misoprostol and oxytocin intravenously for bleeding after C-section. The study included 112 pregnant women with indications for C-section. At the end of the study, researchers reported that sublingual misoprostol is more effective compared to intravenous

oxytocin in the C-section postpartum bleeding (15). This issue was also observed in our study probably due to the similarity of conditions. In another study, Lapaine et al. (2006) reported a lower bleeding after the C-section when taking oral misoprostol compared with the oxytocin infusion. Thus, it is recommended that oral misoprostol can be an effective alternative for oxytocin (16). However, unlike the results of this work, our study shows that hemoglobin declination in the misoprostol group was lower. The reason for this difference could be related to differences in the use of misoprostol. In another work, clinical trials were done by Kola et al. (2011) in Nigeria with the aim of comparing the effect of sublingual misoprostol with intravenous oxytocin to prevent bleeding after C-section. In this study, 1000 pregnant women who underwent elective and emergency C-section were divided in two groups and treated with 400 mcg sublingual misoprostol or 20 IU oxytocin infusion, respectively. Since patients treated with sublingual misoprostol were bleeding less during and after the operation, it was reported that sublingual misoprostol is an effective alternative to intravenous oxytocin in the prevention of bleeding after C-section (17). This study has the same conditions as our study, and the effectiveness of misoprostol for bleeding after cesarean was proved to be consistent with our study. Eftekhari et al. (2009) in Kerman compared the effect of sublingual misoprostol with intravenous oxytocin to prevent bleeding after cesarean section by testing 100 pregnant women who were undergoing elective cesarean section. Their results showed that the bloodshed and hemoglobin declination in the misoprostol group were less than the group receiving intravenous oxytocin. The researchers mentioned that due to the lack of side effects and long-term impact of sublingual misoprostol, sublingual misoprostol is a more attractive alternative compared to intravenous oxytocin (18). Consistent with this work, in our study, the rate of bleeding was lower in the misoprostol group. The study states that the

misoprostol group has fewer side effects, but in our case the results were opposite: although the frequency of side effects was higher in the misoprostol group, there was no statistically significant difference between the two groups. A review and meta-analysis study conducted by Conde-Agudelo et al. (2013) showed that misoprostol combined with oxytocin is far more effective than oxytocin alone. This meta-analysis study presents the results of some similar studies that ultimately demonstrated the effectiveness of misoprostol in bleeding control (19). A review and meta-analysis study by Hua et al. (2013) conducted with the aim of comparing misoprostol and oxytocin in bleeding during cesarean revealed that the size of oxytocin and misoprostol is effective in controlling bleeding during a C-section (20). Our study also showed results consistent with those of this meta-analysis. Fakoor et al. (2011) compared the effect of intravenous oxytocin and sublingual misoprostol in reducing postpartum hemorrhage in 200 pregnant women. The results showed that sublingual misoprostol has a better effect than intravenous oxytocin in reducing bleeding after childbirth (21). Similar to what observed in our study, both of these studies show the possibility of replacing oxytocin sublingual with misoprostol. Given that some studies have examined the form of oral and rectal misoprostol, it is recommended to conduct similar studies and finally a comprehensive meta-analysis to compare various forms of misoprostol. Due to patient awareness during C-section with the spinal method, different doses of misoprostol in the form of rectal and sublingual or rectal and oral simultaneously are recommended. Thus, by choosing the optimum dose and application method, the best alternative should be selected for oxytocin infusion. Considering that the frequency of side effects was higher in the misoprostol group, similar studies with larger sample size are recommended for evaluation of drug effects.

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Conflict of Interests

Authors have no conflict of interests.

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