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ORIGINAL

Comparison of Rectal and Sublingual Misoprostol Prescription to Reduce Bleeding During and After Cesarean Section: double blind, randomized clinical trial

Comparación de la prescripción de misoprostol rectal y sublingual para reducir la hemorragia durante y después de la cesárea: ensayo clínico aleatorio doble ciego

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Abstract

Introduction: Postpartum hemorrhage is an important cause of mortality and morbidity in pregnant women. There are various ways to control bleeding during and after childbirth. The aim of this study was to compare the rectal and sublingual misoprostol administration in reducing bleeding during and after cesarean section.
Materials and methods: This double-blind clinical trial study was performed on 80 pregnant women who referred to Shahid Sadoughi Hospital in Yazd for elective cesarean section. Mothers were randomly divided into two groups. Immediately after the birth of the infant, 20 units of oxytocin were infused in 500 ml ringer serum in both groups. In the first group 400 µg rectal misoprostol was administered after spinal anesthesia and in the second group 400 µg sublingual misoprostol. The data were collected by a questionnaire and the data were analyzed by SPSS 22 software.
Results: The results of the study showed that intraoperative hemorrhage was 393.37 ml in the rectal misoprostol group and 404.25 ml in the sublingual misoprostol group (p = 0.73). Also, there was no significant difference in the amount of bleeding in recovery between the two groups (p = 0.91). Mean preoperative hemoglobin level was 12.86 in rectal group and 12.26 in sublingual group (p = 0.07). Postoperative mean hemoglobin was 11.85 in rectal group and 11.4 in sublingual group (p = 0.18). None of the patients needed transfusions during the study and the side effects such as shivering, nausea and vomiting were not different between the two groups (p>0.05).
Conclusion: The findings of this study showed that sublingual misoprostol is as effective as rectal misoprostol and that sublingual form may be used as a drug in the prevention of postpartum hemorrhage rather than rectal form.

Key words: Postpartum hemorrhage, misoprostol, sublingual administration, rectal administration, cesarean section.

Resumen

Introducción: La hemorragia posparto es una causa importante de mortalidad y morbilidad en las mujeres embarazadas. Existen varias formas de controlar la hemorragia durante y después del parto. El objetivo de este estudio fue comparar la administración de misoprostol rectal y sublingual en la reducción de la hemorragia durante y después de la cesárea.
Materiales y métodos: Este ensayo clínico doble ciego se realizó en 80 mujeres embarazadas que fueron remitidas al Hospital Shahid Sadoughi de Yazd para realizar una cesárea electiva. Las madres fueron divididas aleatoriamente en dos grupos. Inmediatamente después del nacimiento del bebé, se infundieron 20 unidades de oxitocina en 500 ml de suero ringer en ambos grupos. En el primer grupo se administraron 400 µg de misoprostol rectal tras la anestesia espinal y en el segundo 400 µg de misoprostol sublingual. Los datos se recogieron mediante un cuestionario y los datos se analizaron con el software SPSS 22.
Resultados: Los resultados del estudio mostraron que la hemorragia intraoperatoria fue de 393,37 ml en el grupo de misoprostol rectal y de 404,25 ml en el grupo de misoprostol sublingual (p = 0,73). Tampoco hubo diferencias significativas en la cantidad de sangrado en la recuperación entre los dos grupos (p = 0,91). El nivel medio de hemoglobina preoperatoria fue de 12,86 en el grupo rectal y de 12,26 en el grupo sublingual (p = 0,07). La hemoglobina media postoperatoria fue de 11,85 en el grupo rectal y de 11,4 en el grupo sublingual (p = 0,18). Ninguno de los pacientes necesitó transfusiones durante el estudio y los efectos secundarios como escalofríos, náuseas y vómitos no fueron diferentes entre los dos grupos (p>0,05).
Conclusión: Los resultados de este estudio demostraron que el misoprostol sublingual es tan eficaz como el rectal y que la forma sublingual puede utilizarse como fármaco en la prevención de la hemorragia posparto en lugar de la forma rectal.

Palabras clave: Hemorragia posparto, misoprostol, administración sublingual, administración rectal, cesárea.

Introduction

One of the leading causes of maternal mortality in the world is postpartum hemorrhage. According to WHO reports, 585,000 maternal deaths are reported annually, the leading cause of postpartum hemorrhage as a result of active birth control in a way that reduces this serious risk[1]. Due to the increased rate of cesarean section, the risk of postpartum hemorrhage is more common with moderate bleeding during cesarean section. Post-cesarean hemorrhage control prevents morbidity from blood transfusion[1]. Postpartum hemorrhage is defined as loss of more than 500 cc after normal delivery and 1000 cc after cesarean section[2].

There are various ways to control bleeding during and after childbirth. Although routine use of oxytocin may reduce blood loss, in preeclampsia, heart failure and cesarean section in the long term are not appropriate due to hypotension, tachycardia and antidiuretic effect[3]. Misoprostol is a synthetic analogue of prostaglandin E1 whose benefits over other prostaglandins include its stability in high temperature, low cost and availability. It has been shown to be rapidly absorbed and its effect on the uterus has been shown to be rapid, as well as concerns about the misoprostol administration before the birth of the baby did not have a detrimental effect on the studies[4].

Many studies have shown the beneficial role of oral or rectal misoprostol in preventing or controlling postpartum hemorrhage[5]. But proving its usefulness in rectal consumption as compared to oral consumption needs further investigation. Since the sublingual type is better for the patient than the rectal, it is easier for the patient to use and also reaches the highest plasma concentration in a shorter time, so this study we aimed to investigate the effect of sublingual and rectal misoprostol administration on reducing bleeding during and after cesarean section.

Materials and Methods

This prospective, randomized, double-blinded trial was conducted at shahid sadoughi hospital, Yazd, Iran. Approval was obtained from ethical committee of department of obstetrics and gynecology, shahid sadoughi university of Yazd.

This study was performed on 80 pregnant women who were candidates for elective cesarean section. Pregnant women (gestational age 37 weeks and older), and pregnant women with preeclampsia and eclampsia, polyhydramnios hypersensitivity to misoprostol, asthma, coagulopathy, myomectomy history, macrosomia, Placenta Previa, post-partum history, uterine fibroids, fetal distress and Placental abruption were excluded.

The recruited women were divided into two groups using random number table. Immediately after the birth of the infant, 20 units of oxytocin were infused in 500 ml ringer serum in both groups. The first group received 400 µg rectal misoprostol after spinal anesthesia and the second group 400 µg sublingual misoprostol. The researcher and the patient did not know the type of medication and the groups. In the sublingual group, the study drug was given sublingual and placebo was prescribed retally, but in the rectal group, the study drug was given rectal and placebo was prescribed sublingually. If there is excessive uterine bleeding due to atony, the uterus is initially massaged, and if the bleeding continues, the rate of oxytocin infusion is increased and then intramuscular methergine (0.2 mg) is given.

The primary outcome was the estimation of the intraoperative blood loss. The volume of bleeding was estimated by weighting blood gases, which Each gram of overweight equals 1cc of bleeding and the amount of blood aspirated in the suction bag. Other outcomes were: the hemodynamic variables, the change of hematocrit and hemoglobin values, need for transfusion and uterotonic drugs and occurrence of side effects related to misoprostol such as fever, chills and nausea and vomiting.

Vital signs (systolic, diastolic and mean arterial pressure and heart rate) were measured every 5 minutes during cesarean section and every 15 minutes at recovery time. Hemoglobin and hematocrit were measured before and 6 hours after cesarean section. Intraoperative adverse events up to two hours later and fever up to 1 hour postpartum were recorded at 20, 40 and 60 minutes. Finally, Statistical analysis of the data was performed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY).

Results

In this study 80 women were randomly divided into two group. All groups were demographically homogenous with no statistical significance, as shown in **table I**.

There was no significant difference in intra-operative blood loss between the two groups. Similarly, there was no significant difference in the amount of bleeding in recovery room between the two groups (**table II**).

The results showed that there was no significant difference between hemoglobin and hematocrit after surgery. Accordingly, there was no significant difference between groups regarding hemoglobin and hematocrit changes. It can therefore be said that sublingual misoprostol administration is as effective as rectal misoprostol (**table III**).

There was no significant difference regarding any of side effects such as fever, chills and nausea/vomiting between group. Also, the need for oxytocin and methergine in two group was similar (**table IV**).

The mean of systolic, diastolic, heart rate and mean arterial blood pressure were not significantly different between the two groups at the time of surgery and recovery.

Table I: Demographic and preoperative Hb and Hct of patients.

	Rectal group N=40	Sublingual group N=40	p-value
Age (year)	32.07 ± 4.5	30.2 ± 5.8	0.11
BMI (kg/m^2)	29.77 ± 3.27	30.58 ± 3.57	0.29
Pre Hb (g/dL)	12.86 ± 1.22	12.26 ± 1.71	0.07
Pre Hct (%)	38.38 ± 3.32	37.11 ± 4.28	0.14

Table II: Comparison the estimated blood loss between groups.

	Rectal group N=40	Sublingual group N=40	p-value
Intra-operative Blood loss (mL) Mean ± SD	393.37 ± 143.69	404.25 ± 145.88	0.73
Recovery Blood loss (mL) Mean ± SD	78 ± 35.67	77.25 ± 26.21	0.91

Table III: comparison between groups regards postoperative Hb, Hct and their changes (ΔHb, ΔHct).

	Rectal group N=40	Sublingual group N=40	p-value
Post Hb (g/dL) Mean ± SD	11.85 ± 1.21	11.4 ± 1.72	0.18
Post Hct (%) Mean ± SD	34.96 ± 3.1	34.57 ± 4.2	0.64
ΔHb (g/dL) Mean ± SD	1.01 ± 0.7	0.86 ± 0.65	0.34
ΔHct (%) Mean ± SD	3.41 ± 2.7	2.54 ± 2.3	0.12

Table IV: Comparison of outcome variables among the groups.

	Rectal group N=40	Sublingual group N=40	p-value
Need for oxytocin patients (%)			
20 unit 40 unit	34 (85%) 6 (15%)	30 (75%) 10 (25%)	0.4
Need for methergine patients (%)			
Yes No	5 (12.5%) 35 (87.5%)	8 (20%) 32 (80%)	0.36
Fever (%)			
Yes No	0 (0%) 0 (0%)	0 (0%) 0 (0%)	Not available
Chills (%)			
Yes No	9 (22.5%) 31 (77.5%)	11 (27.5%) 29 (72.5%)	0.6
Nausea/vomiting (%)			
Yes No	4 (10%) 36 (90%)	7 (17.5%) 33 (82.5%)	0.33

Discussion

Bleeding, hypertension, and infection are the three leading causes of maternal mortality. In developing countries, postpartum hemorrhage is still one of the causes of maternal mortality[13]. Active control of bleeding using a uterotonic drug reduces postpartum hemorrhage[13]. But despite the fact that researchers agree on the use of uterotonic drugs to prevent postpartum hemorrhage, the choice of the best drug is still under discussion[14].

Misoprostol is a synthetic analogue of prostaglandin E1 that can be used to treat uterine atony and prevent postpartum hemorrhage. Unlike methergine and carboprost, misoprostol is also prescribed for women with hypertension and asthma[15]. Various type and doses of misoprostol have been used in various studies to control bleeding including 400 micrograms rectal[16,17], 200, 400 or 600 micrograms oral[20-18,15], 400 micrograms sublingual[21,22], 400 micrograms of oral powder misoprostol (23 micrograms) or 400 micrograms in rectal enema[24]. Studies have shown that misoprostol is effective in reducing bleeding but there is controversy regarding the dosage and method of administration.

In this study Patients were similar in both groups, and gravidity, age and BMI were not significantly different between the two groups. None of the patients in the two groups needed transfusions during the study. There was also no difference between the two groups in the amount of oxytocin and methergine needed. The findings of the present study showed that there was no significant difference in the amount of intraoperative bleeding and the bleeding in the recovery room between the two groups. Therefore, sublingual misoprostol administration may be as effective as rectal misoprostol. In addition to confirming the effect of sublingual misoprostol, the results showed that the mean hemoglobin and hematocrit were not different between the two groups before and after the surgery. Side effects were not observed in any patients. Also, the hemodynamic variables in this study were not significantly different between the two groups during surgery and recovery.

The study of Beigi et al. Was conducted on 542 nulliparous mothers in one group receiving 400 µg of sublingual misoprostol and in the other group receiving 20 units of intravenous oxytocin immediately after the birth of the newborn, the results of which showed postnatal hemorrhage in the misoprostol group 96.3 ml and in the oxytocin group was 395.78 ml. In the present study, postpartum hemorrhage in recovery was 77.25 ml. Unlike the Beigi study, all subjects received 20 units of oxytocin after birth in the present study. Also, in the Beigi study, fever and body temperature, headache, diarrhea, chills, vomiting, nausea and hiccups were significantly higher in the misoprostol group, which is inconsistent with the present study, which may be due to the sample size and type of drug comparisons[22]. Because Beigi study compared the sublingual misoprostol study with oxytocin and the present study sublingual misoprostol with rectal misoprostol. In another study by Soleimani et al, who evaluated the effect of sublingual misoprostol on the prevention of bleeding in cesarean section, 186 pregnant women who volunteered for cesarean section were evaluated. One group received 400 µg of sublingual misoprostol with oxytocin and one group received placebo and oxytocin. Their findings, similar to those of Beigi's study, showed that mean fall in hemoglobin and

hematocrit level were significantly lower in the misoprostol group than in the placebo group, and the need for additional uterine contraction factors was significantly lower in the misoprostol group. Similar to the present study, unlike other studies, there were no significant differences between the two groups in case of side effects. There was no significant difference between the two groups in the need for blood transfusion[25].

Fazel et al.'s study comparing rectal misoprostol and oxytocin showed that 400 µg of rectal misoprostol were as effective as 10 units of oxytocin and there was no significant difference between intraoperative bleeding and hemoglobin differences before and after the operation. However, the bleeding rate was lower in the misoprostol group. The rate of intraoperative bleeding was 578 ml in the misoprostol group and 620 ml in the oxytocin group. In the present study, bleeding rate was 393.3 ml in the misoprostol group and 404.25 ml in the sublingual group. Similar to the present study in Fazel et al., None of the patients needed transfusion and side effects such as nausea, vomiting and chest pain were not significantly different between the two groups and shivering was higher in misoprostol group[12].

Another study by Nasr et al, comparing rectal misoprostol and oxytocin, showed that 800 mg of rectal misoprostol compared to 5 units of oxytocin were equally effective in controlling hemorrhage. There was no significant difference between the two groups in terms of hemoglobin before and after surgery and postoperative bleeding. Hemodynamic variables were also examined in this study, but there was no difference between the two groups. Similar to other studies, only shivering and fever were higher in the misoprostol group than in oxytocin[26].

In the study of Uncu et al., 248 pregnant women were studied (in one group 400 mg oral misoprostol; second group 400 mg oral and one 400 mg vaginal dose; third group 400 mg rectal and fourth group 400 mg vaginal). The results of their study showed that there was no significant difference between hemoglobin and postpartum hematocrit levels. However, the difference between their study and the present study was the type of delivery and the sample size. In their study, the effect of drugs on normal delivery and in the present study was cesarean delivery. Finally, their study showed that although misoprostol is useful in the treatment of postpartum hemorrhage, it has no significant effect on the prevention of atony causing postpartum hemorrhage[11].

Studies of the effect of misoprostol on postpartum hemorrhage have examined the efficacy of this drug over other drugs. One study showed that the combination of misoprostol and oxytocin was better in controlling bleeding than misoprostol alone (26). In a study by Singh et al. In India, the results showed that 600 µg of sublingual misoprostol had a greater and more effective effect on reducing bleeding than 400 micrograms of misoprostol, oxytocin, and even syntometrine[27]. However, a meta-analysis study by Hofmayer et al. found that administration of oxytocin and ergot products during the third stage of labor had a greater effect than misoprostol on preventing postpartum hemorrhage as well as maternal mortality[28]. In another study by NG et al., The results showed that 400 µg of oral misoprostol had a similar effect on post-operative hemoglobin compared to muscular syntometrine but shivering was higher in the misoprostol group (19). Also, the findings of various studies showed that nausea, fever and chills were common findings for oral misoprostol administration[31-29].

In a study in 2018 by Sweed et al., A comparative study of the sublingual and rectal misoprostol was performed. Results of their study showed that intraoperative bleeding was 457.5 ml in rectal group, 357.8 ml in sublingual group and 641.7 ml in control group. In the present study bleeding rate was 393.37 cc in rectal group and 404.25 cc in sublingual misoprostol group. In contrast to the present study, the results of the Sweed study showed that there was a significant difference between the two groups in bleeding and the rate of bleeding was lower in the sublingual group. The prescribed dose of misoprostol in Sweed et al. Was similar to the present study, but the dose of oxytocin was different, probably due to the large sample size and lack of brand equity in the Sweed study. In the Sweed study, hemoglobin and hematocrit changes in the pre- and postoperative were also lower in sublingual group compared to the rectal group[32].

Limitations of this study include failure to evaluate other drugs, different doses of misoprostol, and lack of sample size. But the strengths of the study were the matched study groups for age, BMI, and pregnancy gravid and double blind. According to the results of this study and the same effect of misoprostol with other drugs and also the effect of sublingual form of misoprostol compared to rectal form, also because of the easier storage method at room temperature, no need for injections, cheaper and Easier consumption sublingual form Compared to rectal one, misoprostol sublingual form can be used to control bleeding during and after delivery. If there are any side effects, they are not dangerous and may be temporary and can be resolved within a maximum of 12 hours and in addition to their many benefits, these side effects can be neglected. However, there are still disagreements in various studies on the dosage used and its forms, and more extensive studies with larger sample sizes are recommended.

Interests conflict

The researchers declare that they have no conflict of interest.

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