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Original Article

Comparing the Outcomes and Side Effects of Administration of a Single Preoperative Dose of Vaginal Misoprostol With Intraoperative Oxytocin Infusion in Blood Loss During Abdominal Myomectomy

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Abstract
Objectives: This study aimed to compare the effectiveness of a single preoperative dose of misoprostol with intraoperative oxytocin infusion in abdominal myomectomies.
Materials and Methods: Patients undergoing abdominal myomectomies were divided into 2 groups. An hour before the operation, women in the misoprostol group (n = 35) received a single dose of vaginal misoprostol (400 μg); those in the oxytocin group (n = 35) received oxytocin (intravenous infusion of normal saline solution [30 units in 1000 mL] during myomectomy).
Results: Blood loss, operation time, and need for blood transfusion were significantly reduced in the group administered with vaginal misoprostol. No difference was observed between patients in term of the period of hospitalization and complications. The results of oxytocin in abdominal myomectomy showed no significant difference.
Conclusion: Administration of a single preoperative dose of misoprostol could be a simple and reliable method for reducing intraoperative blood loss and need for postoperative blood transfusion in abdominal myomectomies.
Keywords: Misoprostol, Oxytocin, Uterine myomectomy

Introduction

Uterine fibroids are the most common female pelvic tumors occurring in about 15% to 30% of women in the reproductive age. In an epidemiologic study published in 2003 in the United States, 80% of black and nearly 70% of white women were demonstrated to have ultrasound evidence of leiomyomas (1). When fibroids are associated with symptoms such as menorrhagia, congestive dysmenorrhoea, urinary frequency, infertility, and recurrent pregnancy losses, surgical intervention is often indicated (2). To date, there have been many fertility sparing procedures which have been used to alleviate the symptoms and enhance the fertility in women with uterine fibroids. Procedures such as uterine artery embolization (3), myolysis (4), and laparoscopic myomectomy (5,6) have been used in the treatment of uterine fibroids.

A number of trials have been carried out to assess the effectiveness and safety of interventions in reducing the blood loss during myomectomy (7). Such interventions include intramyometrial vasopressin (8), intravenous oxytocin (9), tourniquets (10), chemical dissection with sodium-2-mercapto ethane sulfonate (mesna) (11), and intramyometrial bupivacaine plus epinephrine (12).

A study was conducted by Ragab and colleagues in 2014 in Saudi Arabia on 69 patients undergoing abdominal myomectomy. It was shown that the use of 400 μg of vaginal or oral misoprostol 60 minutes before myomectomy reduced intraoperative bleeding and operation time (13).

Vasopressin has already been shown to decrease blood loss at the time of myomectomy (8,10). Misoprostol is now being used by obstetricians and gynecologists worldwide for the evacuation of the uterus for missed abortions, intrauterine deaths, induction of labor, and the prevention of postpartum hemorrhage (14,15). Its popularity especially in developing countries such as Jamaica may be accounted for the fact that it is able to produce powerful uterine contractions and lead to a reduction in myometrial hemorrhage, while being inexpensive and easy to store. Contrary to a previous study in Turkey (14), we chose to investigate the use of misoprostol in a larger subset of patients in conjunction with oxytocin in a Persian population with a high incidence of myomectomies (8).

This surgical procedure (myomectomy) involves a significant risk of hemorrhage (16). Different treatments have been proposed to reduce hemorrhage during myomectomy (17). Oxytocin administration reduces blood loss after delivery and this hormone is widely used to prevent postpartum hemorrhage (9).

In this study, we compared the effectiveness of a single preoperative dose of misoprostol with intraoperative oxy-

tocin infusion for the reduction of blood loss at the time of myomectomy.

Materials and Methods

We enrolled 70 volunteer married women in the study. In this randomized clinical trial, a simple non-probability sampling was used. Seventy women with uterine fibroid were referred to the Alzahra hospital, Tabriz, between January 10, 2014 and February 30, 2015, who were scheduled to undergo myomectomy. They were classified into 2 groups of 35 as below: Group A, receiving 400 µg of vaginal misoprostol (2 tablets of 200 µg, High Wycombe Pharmaceutical Co.) (single dose, 1 hour before surgery, and intravenous infusion of 1000 mL of normal saline solution at a rate of 120 mL/h, 20 minutes before the start of anesthesia until completely removing the myoma from the pelvic cavity); Group B, receiving oxytocin (3 vials of 10 units, Tamin Pharmaceutical Co.) (30 units in 1000 mL of normal saline solution at a rate of 120mL/h, 20 minutes before the start of anesthesia until completely removing the myoma from the pelvic cavity).

The amount of blood accumulated in the aspiration equipment, and number of gauze pads used in the surgery for absorbing the blood were considered as the basis for calculating the patient's blood loss during the operation. To evaluate the effect of blood loss on hemoglobin and hematocrit values, the patient's hemoglobin (g/dL) and hematocrit (%) values were measured 1 day before, and 6 and 24 hours after the operation. Abdominal incision in 2 groups was made with equal consideration. The operation was performed by the same team and hemostasis rules were observed closely. An anesthesiologist was responsible for monitoring and recording the information.

Individuals excluded from the study were: patients with cardiac, renal and pulmonary diseases, coagulopathy, and those known to be allergic to misoprostol. None of the patients had received preoperative hormonal therapy (such as a GnRH analogue or oral contraception pills) that could affect intraoperative bleeding.

Randomization

Misoprostol and oxytocin were administered randomly (using a randomized number table) by 1 nurse. The misoprostol administration was performed 60 minutes before the operation and the oxytocin administration was performed before the anesthesia until completely removing the myoma from the uterus. The operation team were not informed which of the treatments were administered the patients (misoprostol or oxytocin). The following information were recorded for patients: all of the patients' socio-demographic characteristics, as well as the size and number of preoperative myoma; uterus size in pelvic examination; operation time; preoperative and postoperative hemoglobin and hematocrit values (10); intraoperative blood loss; need for intraoperative and postoperative blood transfusion; preoperative, intraoperative and postoperative blood pressure and pulse values; complications; need for postoperative additional analgesic, and period of

hospitalization.

The number and localization of myomas and the myoma diameter were established by ultrasonography. Preoperative, intraoperative, and postoperative average systolic/diastolic blood pressures and pulse values were used to calculate changes in blood pressure (mm Hg) and pulse (beat/minute). Complications were defined as an increase to over 38°C in body heat (febrile morbidity), nausea and vomiting, diarrhea, headache, arthralgia, paresthesia, dizziness, spasm, cardiac arrest, cough, blurred vision, hearing disorders, hypotension, tachycardia, and ST depression in electrocardiogram (ECG) from the intervention time up to discharge from hospital and finally, myomectomy leading to hysterectomy.

All data were matched in terms of socio-demographic variables.

Statistical Method

Continuous and ordinal data were established as mean standard deviation (SE) and other data as nominal scale (present 1; absent 0). To analyze the data, SPSS version 16.0 was used. Quantitative variables as mean ± standard deviation (SD) and qualitative data were reported as number and percentage. For comparison of quantitative variables in three groups, one-way analysis of variance (ANOVA) was used. And if the test result was significant, to compare the 2 groups, Tukey HSD test was used. Paired samples t test was used to compare the groups separately before, during, and after myomectomy. P value less than 0.05 was considered statistically significant.

Results

Our study indicated that compared to oxytocin, a single preoperative dose of misoprostol in myomectomies resulted in a statistically significant reduction in intraoperative blood loss and in the need for postoperative blood transfusion.

The comparison between the study and control groups did not show any significant differences for socio-demographic data, preoperative clinical data, location of myoma, and laboratory parameters ($P < 0.05$) (Tables 1 and 2).

The mean hemoglobin and hematocrit in the group receiving misoprostol were 12.3±1.4 mg/dL and 37±4.4%, respectively, before treatment. After treatment, 6 hours after surgery, mean hemoglobin and hematocrit were 11.5±1.4 mg/dL and 34.6±4.2%, and 24 hours after surgery, they declined to 10.8±1.5 mg/dL, and 32.5±4.7%, respectively. In oxytocin group, the mean preoperative hemoglobin and hematocrit were 12.7±1.2 mg/dL, and 38±3.9%, respectively. After treatment, 6 hours after surgery, they declined to 10.1±1.1 mg/dL, and 30.6±3.2%, and 24 hours after surgery, to 9.8±0.7 mg/dL, and 29.9±2.4%, respectively ($P < 0.05$, paired samples t test).

The average amount of bleeding in patients receiving misoprostol was 401±48 mL and in the group receiving oxytocin was 589±49 mL ($P < 0.05$, paired samples t test). Duration of surgery in the group receiving misoprostol was 82±3 minutes and in the group receiving oxytocin

Table 1. The Sociodemographical Characteristics of Cases

Characteristic	Misoprostol (n=35)	Oxytocin (n=35)	P Value
Age (y)	37.7 ± 5.3	38.4±4.6	NS[a]
Parity (number)	2.8±2	2.8±1.5	NS[a]
Gravida (number)	2±1.7	2±1.2	NS[a]
Body mass index (kg/m²)	26.4±2.9	25.7±3.4	NS[a]
Total myoma number (number)	3.6±1.6	4.3±1.6	NS[a]
Largest myoma diameter (mm)	91.6±35.2	88.4±29.7	NS[a]
Uterus size (pregnancy wk)	12.1±3.5	10.7±2.2	NS[a]
Location of myomas			
Intramural	80±15	74.3±16	NS[a]
Subserous	20±16	22.9±17	NS[a]
Abdominal incision			
Phannenstiel	50.65±5.3	48.47±4.2	NS[a]
Midline	54.35±6.5	56.53±6.1	NS[a]

Values are as mean ± SD.
[a] $P < 0.05$, statistically insignificant difference, Tukey HSD test.

Table 2. Preoperative and Postoperative Values for Patients

Characteristic	Misoprostol (n=35)	Oxytocin (n=35)	P Value
Preoperative Hb (g/dL)	12.3±1.4	12.7±1.2	NS[a]
Preoperative Hct (%)	37±4.4	38±3.9	<0.05[b]
Postoperative Hb 6 hours (g/dL)	11.5±1.4	105±1	<0.05[c]
Postoperative Hct 6 hours (%)	34.6±4.2	31.6±3.2	<0.05[d]
Postoperative Hb 24 hours (g/dL)	10.8±1.5	10.1±0.9	<0.05[e]
Postoperative Hb 24 hours (%)	32.5±4.7	30.5±2.9	<0.05[f]
Approximate blood loss (mL)	401±48	589±49	<0.05[g]
Operation time (min)	82±3	93±2	<0.05[h]
Need for blood transfusion	1 (3.2)	3 (9.7)	<0.05[i]
Hospitalization period (d)	2.1±0.4	2.2±0.8	NS[j]
Complication	4 (12.5)	4 (12.5)	NS[k]

Values are as mean ± SD.
[a,b] $P < 0.05$, statistically insignificant difference, Tukey HSD test.
[c,d,e,f,g,h,j] $P < 0.05$, statistically insignificant difference, paired sample t test.
[i,k] $P < 0.05$, statistically insignificant difference, chi-square test.

was recorded as 93 ± 2 minutes ($P < 0.05$, paired samples t test), and the need for blood transfusion was significantly lower in the misoprostol group. Blood transfusions were required for 1 patient in misoprostol group (1 of 35 patients, 3.2 ± 2.2%), and 3 patients in the oxytocin group (3 of 35 patients, 9.7 ± 2.1%) ($P < 0.05$, chi-square tests). Length of stay in hospital ($P < 0.05$, paired samples t test) and complications during and after surgery in the two group did not show a significant difference ($P < 0.05$, paired samples t test).

The comparison of the changes in 2 groups showed that misoprostol was effective in reducing the bleeding during abdominal myomectomy ($P = 0.005$).

Discussion

Our study revealed that compared to oxytocin, a single preoperative dose of misoprostol in myomectomies resulted in a statistically significant reduction in intraoperative blood loss and in the need for postoperative blood transfusion.

Myoma is the most frequent benign pelvic mass in premenopausal and postmenopausal women. In previous studies, 25% to 50% of women reported pelvic evidence of myoma. Some of the symptoms associated with myoma include the following: abdominal pain, vaginal bleeding, pelvic pain or pressure sensation, reduced bladder capacity, constipation and infertility. Treatments include watchful waiting, medical/surgical interventions, or uterine artery embolization techniques. Therefore, in most patients with asymptomatic myoma, only care and conservative treatment are considered. In women who desire to preserve fertility, conserving surgery such as myomectomy is performed. Abdominal hysterectomy as a surgical intervention is indicated for symptomatic myoma and is

associated with large or significant morbidity which may require blood transfusion, as excessive bleeding may occur during surgery. The main significant cause of morbidity during surgery is intraoperative bleeding that requires blood transfusion. Interventions to reduce blood loss during surgery can affect the need for blood transfusion and postoperative mortality (8).

Surgeries such as myomectomy can lead to significant blood loss during the operation, and surgical hemostasis in the patient ensures success. There are different methods for controlling bleeding and wound healing during myomectomy (17).

The volume of blood lost during abdominal myomectomy depends on the size and the location of myoma. Consecutive bleeding in the context of myoma after myomectomy is justified by the distribution of blood vessels. In numerous studies, the average amount of intraoperative bleeding during abdominal myomectomy for uterine size larger than 14 weeks have been reduced by non-mechanical techniques (10).

The major problem in abdominal myomectomy is excessive blood loss which can lead to blood transfusion, febrile morbidity, and potential loss of fertility due to hysterectomy. Identifying effective interventions to reduce bleeding in abdominal myomectomy is essential for clinical decision making based on scientific evidence. A number of safe and effective interventions to reduce bleeding during myomectomy have been proposed, including intramyometrial vasopressin, intramyometrial bupivacaine plus epinephrine, misoprostol, removal of myoma with unencrypted and close bilateral uterine and ovarian arteries (16).

Misoprostol acts through one of the 2 mechanisms to reduce blood loss. First, like prostaglandins, these prostaglandin analogs increase myometrial contractions (18). This increase in contraction is the effect of prostaglandins on vascular structures, which stem from both uterine artery and utero-ovarian anastomosis and supply blood to leiomyoma before reaching the myoma or myomas. Through this effect, vascular structures are contracted and blood flow is reduced.

The second mechanism may be the direct vasoconstrictive impact of misoprostol on uterine arteries. This effect of prostaglandin analogs was demonstrated in vitro by Baxter et al (19). Similarly, fetal anomalies have been attributed to misoprostol, reducing blood flow in uterine artery during uterine contractions (20).

The results of studies, reporting the changes in cervical resistance due to the use of misoprostol in non-pregnant patients are inconsistent (21).

The first advantage is the cost-effectiveness. Presently the most popular method for reducing hemorrhage in myomectomy is GnRH analogs (22). Although this is not their primary use, these GnRH analogs were the first treatment to be employed for myomas. However, the growth of myomas after the treatment has been noted, as well as developing the osteoporosis in long-term use; thus, GnRH analog use has been restricted only to decrease the

myoma volume preoperatively and to reduce intraoperative blood loss (22,23). Cost concerns are partially valid for vasopressin treatment as well (although not so great a concern as GnRH analogs). Some side effects have been reported as arisen from the use of intraoperative vasopressin: temporary increase in blood pressure during local vasopressin injection, bleeding at injection site, and intravascular infiltration by mistake (24). In addition, Tulandi et al (25) reported pulmonary edema after the use of local vasopressin, and Martin and Shenk (26) reported myocardial infarction. Nezhat et al (27) reported that vasopressin administered intravascularly may cause life-threatening hypotension.

The oxytocin receptor is a heptahelical membrane receptor, 389 amino acids long, which consists of 7 transmembrane helices, a short N-terminal extracellular domain, and a longer C-terminal intracellular domain (28). The effects of oxytocin on the uterus are principally mediated by the direct effects on myometrial smooth muscle cells. Oxytocin receptors are expressed in the human endometrial epithelium (29) and oxytocin stimulation of deciduous endometrium induces prostaglandin production (30). The presence of oxytocin receptor has been demonstrated in microvascular endothelial cells isolated from human myometrium (31).

Investigators have reported that the most common side effects after administration of 400 µg of vaginal or oral misoprostol are chills (17.3%), nausea and vomiting (10.2%), headache and vertigo (7.1%), abdominal pain (79.6%), and diarrhea (4.1%) (14). In addition to these side effects, some studies have reported a slight increase or decrease in blood pressure. In a striking case, a 71-year-old woman who took high doses (3 mg) of misoprostol by mistake experienced fever, tremor, tachycardia, hypertension, nausea, and abdominal cramp, but recovered with supportive treatment (32).

In our study, there were observed no important side effects in the patients who had received misoprostol. The difference between the misoprostol and oxytocin groups was not statistically significant. This is possibly because we administered a single dose of misoprostol, and after surgery the patients were either still anesthetized or under the effect of an analgesic. In the literature, all side effects of misoprostol were appeared 90 minutes after misoprostol administration in patients who were not anesthetized (33).

Other methods for reducing hemorrhage in myomectomy include mechanical vascular occlusion techniques known as tourniquet or uterine artery embolization, which have also become popular in recent years (34). All these methods require additional interventions or a separate procedure during the operation. The difficulty of access to the uterine artery with large and laterally placed myomas (such as ligamentum latum myomas) and difficulty of placing the tourniquet are significant disadvantages (35). While our method does not entail any additional intraoperative procedures.

Ethical Issues

Conflict of Interests

The authors declare no conflict of interests.

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