Role of Administration of Sublingual Misoprostol Before Open Myomectomy

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Abstract

Background: Uterine fibroids are considered the most prevalent benign tumors in women. open myomectomy is the conventional management for large or numerous fibroids. However, hemorrhage is one of the most prevalent consequences in open myomectomy cases. Misoprostol, an analog of prostaglandin E1, is widely used in obstetrics and is capable of increasing uterine contraction and decreasing hemorrhage. Our aim was to assess the impact of sublingual intake of Misoprostol before myomectomy to minimize blood loss during surgery.

Methods: A randomized controlled clinical trial was conducted on 150 women within their reproductive age with symptomatic fibroids who are planned for open myomectomy. They were randomized into "study" and "control" groups to receive either one dose of Misoprostol sublingually (400 mcg) or placebo before myomectomy. The operative time, intraoperative blood loss and the effect of blood loss on hematocrit and hemoglobin levels were assessed.

Results: The operative time among the Misoprostol group was significantly shorter than the placebo group (58.80±4.51 vs 71.08±10.62 minutes,$p<0.001$). Additionally, the blood loss in the suction apparatus and the total blood losses among the Misoprostol group were significantly reduced compared to the control group (279.16±44.61 vs 340.55±66.71 ml , $p<0.001$).

Conclusion: A sublingual dose of Misoprostol (400 mcg) one hour before surgery significantly reduces the intraoperative blood loss and the operation time during myomectomy.

Keywords: Myomectomy; Misoprostol; Blood loss.

INTRODUCTION

Uterine fibroids, "leiomyomas" or "myomas", are the most prevelant benign uterine tumors, occurring in >70% of women (1). Fibroids consist of smooth muscle, fibroblasts, and a significant quantity of fibrous extracellular matrix, all contributing to the pathogenetic process (2).

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In 20–50 % of affected cases, uterine fibroids are asymptomatic. The most prevalent symptom reported by women with fibroids is heavy menstrual bleeding; however, other gynecological symptoms include pelvic pressure and discomfort, extended menstrual bleeding, and bleeding outside of menstrual cycles. Anemia could be developed due to excessive bleeding. Increased frequency, incontinence, and hesitation are among the urinary symptoms that may be associated with fibroids (3).

It could be diagnosed clinically by recognizing a solid, multilobular uterus or solid, palpable lumps protruding from the uterus (1). However, transvaginal ultrasonography achieves higher sensitivity (90%) and specificity (87%) for diagnosis, which increased up to 100% and 98%, respectively, with adding sonohysterography (4).

Myomectomy on laparotomy or "open myomectomy" has been the conventional form of conservative surgical management for large uterine myomas in women who wish to preserve their uterus or fertility. Indeed, it has been the only conservative surgical option for treating fibroids until the development of laparoscopic and hysteroscopic techniques (5,6).

Blood loss associated with myomectomy is the most frequent adverse consequence. The need for blood transfusion ranges between 4 and 20% of myomectomy patients. To prevent blood loss during open myomectomies, several techniques have been developed, including ligating the uterine arteries temporarily, infiltrating vasopressin inside the myomas, applying Misoprostol or dinoprostone intravaginally, using pro-fibrin/thrombin agents, or using tourniquet around the cervix or infundibulopelvic ligaments (7).

Misoprostol is a prostaglandin E1 analog. It is widely used in obstetrics for cervical ripening, induction of labor, management of postpartum hemorrhage and termination of second-trimester pregnancies. Misoprostol is capable of increasing uterine contraction and decreasing hemorrhage (8,9). Recently, it has been tested in randomized controlled studies to reduce blood loss during myomectomy. Therefore, we conducted our study to assess the role of sublingual intake of Misoprostol before myomectomy in reducing blood loss during surgery.

METHODS

A randomized controlled clinical trial was conducted in the Obstetrics and Gynecology Department at Kasr El Aini Hospitals, Cairo University and the Obstetrics and Gynecology Department at EL-Menshawy General Hospital. It included 150 women at reproductive age with symptomatic fibroids who are planned for open myomectomy. The Research Ethics Committee (REC), Faculty of Medicine, Cairo University has approved this study under registration number (MS-70-2022). The included women had signed written informed consent before participating in the study after being informed of its purpose. All participants had the right to withdraw from the study without being adversely impacted regarding the medical care they should receive.

The inclusion criteria were women within their reproductive age with symptomatic fibroids and planned for open myomectomy. Women were excluded in case of age younger than 20 years, history of previous pelvic or abdominal surgery excluding cesarean section, bleeding or coagulation disorders, allergy to Misoprostol, medical disorders such as hypertension, diabetes, cardiac or pulmonary diseases, liver diseases or ischemic heart disease, and anemia (Hemoglobin [Hb] < 8 g/dL).

The participants were randomized to receive either a single dose of sublingual Misoprostol (400 mcg) or placebo using identical sealed envelopes prepared by the investigator. After enrollment, each participant was allowed to choose one envelope to determine the assigned group.

All women were subjected to detailed medical history and clinical examination to ensure adherence to inclusion criteria. On the day of the operation, the medication, either a single dose of sublingual Misoprostol (400 mcg) or placebo, was given one hour before the procedure. The primary outcome is to assess the role of receiving a single dose of sublingual Misoprostol (400 mcg) one hour before open myomectomy in reducing the estimated intraoperative blood loss.

We estimated the intraoperative blood loss by measuring the blood volume in the suction machine reservoir and calculating the weight difference of the surgical swabs. The difference of the surgical swabs (in grams) was translated to ml by using the blood density formula (1.050g/ml). To assess the impact of blood loss on hematocrit (Hct) and Hb levels, the patient's Hct and Hb were measured preoperatively and 24 hours postoperatively.

Sample size: Sample size was calculated by comparing intraoperative total blood loss between women undergoing myomectomy treated with sublingual Misoprostol or placebo. As reported in a previous publication by Alhalaby (2021), the mean±SD of total intraoperative blood loss in the Misoprostol group was 308±33 ml, while in the control group, it was 404.4±49.1 ml (10). Accordingly, the proper sample size was 75 women in each group to detect a real difference in blood loss of 30 ml with 95% power and α error of 0.05 using Student's t-test for independent samples. The sample size was calculated using "PS: Power and Sample Size Calculation" software, version 3.0.11 for Microsoft Windows "William D. Dupont and Walton D., Vanderbilt University, Nashville, Tennessee, USA".

Statistical methods: Data was analyzed using the statistical package for the Social Sciences (SPSS) version 25 "IBM Corp., Armonk, NY, USA". Numerical data were presented in mean ± standard deviation or median and range. Categorical data were presented in frequencies and percentages. P-values < 0.05 were considered statistically significant.

RESULTS

Our study included two groups of patients; the "Control Group" included 75 women who underwent myomectomy without pre-operative intake of sublingual Misoprostol, and the "Study Group" included 75 women who had sublingual Misoprostol given prior to myomectomy. Demographic characteristics of all participants in both groups showed no statistically significant differences "Table 1".

The pre-operative assessment showed no statistically significant differences between both groups regarding the following parameters: the number of myomas (P=0.080), the size of the largest myoma (P=0.373), the site of myoma whether intramural, subserous, or both (P=0.080), pre-operative Hct levels (P=0.121). However, pre-operative Hb levels were significantly higher among the placebo group than the Misoprostol group (p<0.001) "Table 2".

Regarding intra-operative assessment, the operative time was significantly shorter among the Misoprostol group than the placebo group (58.80±4.51 vs 71.08±10.62 minutes,p<0.001). In addition, the blood loss in suction and the total blood losses were significantly higher among the placebo group than the Misoprostol group (340.55±66.71 Vs 279.16±44.61 ml ,p<0.001 for suction and 483.21±76.06 Vs 420.39±53.49 ml, p<0.001 for total blood losses).

However, the weight of the surgical swabs showed no statistically significant differences between both groups "Table 3".

The post-operative assessment showed no significant difference between both groups regarding post-operative Hb level (P=0.601). However, the Hb deficit was significantly higher among the control group than the study group (1.30±0.59 Vs 0.45±0.36 g/dL p<0.001). Post-operative Hct percent was significantly higher among the study

group than the control group (p=0.028).The percentage of Hct deficit was significantly higher among the control group than the study group (2.27±1.15 Vs 0.49±0.33 p<0.001) "Table 4".

DISCUSSION

Uterine fibroids are considered the most prevalent benign tumors in women. Typically, they are asymptomatic; however, 20-50% of afflicted patients develop symptoms such as menorrhagia, pelvic discomfort or pressure, or urinary problems (11,12). In women who want to keep their fertility, open myomectomy is the conventional management for large or numerous fibroids. However, hemorrhage is one of the most prevalent consequences in open myomectomy cases (13).

As few studies evaluated the role of Misoprostol in reducing blood loss during myomectomy, we conducted this study to assess the impact of sublingual Misoprostol on reducing blood loss and the operation time during open myomectomy. This study is a randomized controlled clinical trial on 150 women who underwent open myomectomy and randomly received either a single dose of sublingual 400 mcg Misoprostol (75 patients) or placebo (75 patients). We found that a single sublingual 400 mcg dose of Misoprostol one hour before myomectomy significantly reduces blood loss and operation time.

In agreement with the current study, Alhalaby et al. (2021) performed a study on 50 Egyptian women to assess the impact of receiving a single dose of vaginal Misoprostol preoperatively. They reported that the blood loss in the Misoprostol group was less than in the placebo group (308±32.66 vs. 404.4±87; P<0.001). In addition, the Misoprostol group showed a shorter operative time than the control group (56.8±3.12 vs. 78.6±10.6; P<0.001). The post-operative Hb and Hct levels were lower among the placebo group when compared to Misoprostol. Hb and Hct deficits were significantly higher among the placebo group than the Misoprostol group (10).

The beneficial effect of Misoprostol was also evaluated by two randomized controlled studies: Ragab et al. (2014), who studied the effect of the intra-vaginal administration and Abbas et al. (2019), who studied the effect of the sublingual administration. In both studies, it was observed that the larger dose of Misoprostol decreased blood loss and operative time much more than the lesser dose, with no rise in post-surgical fever, concluding that higher doses of Misoprostol (400 mcg twice, 1 and 3 hours before surgery) were more beneficial (14,15).

In a recent study by Sharami et al. (2020), Hb and Hct were evaluated 4 and 24 hours after myomectomy in the study and placebo groups. They also assessed the amount of blood loss, duration of operation, complications, and need for transfusion or hysterectomy. The study revealed that receiving a rectal dose of 400 mcg of Misoprostol before the operation significantly reduces blood loss (P<0.001). However, it did not affect the operative time, incidence of complications, need for transfusion or hysterectomy, or post-operative Hb and Hct levels at 4 and 24 hours after surgery (P>0.05) (16).

Mohamed et al. (2019) studied 94 randomly enrolled female candidates for myomectomy. The study group received a dose of Misoprostol (400 mcg) rectally one hour before surgery. The blood loss during surgery was significantly lower in women who received rectal Misoprostol than in the placebo group (460.8±155.2 mL vs. 815.4±187.7 mL). Additionally, the Misoprostol group showed a significantly higher post-operative Hb and Hct and a significantly shorter operative time. There was no significant difference between groups regarding the need for blood transfusion (17).

Abdel-Hafeez et al. (2015) also came in concordance with the current study. In their randomized trial, intra-operative blood loss was significantly lower in women receiving

rectal Misoprostol than in the control group (574±194.8 mL vs. 874±171.5 mL). Additionally, the deficit in post-operative Hb was significantly lower in the Misoprostol group than in the control group (1.7±0.4 g/dL vs. 2.1±0.5 g/dL). Abdel-Hafeez et al.also found that operation time in the Misoprostol group was 76.8±15.8 minutes compared to 94.8±22.8 minutes in the placebo group (18).

Niroomand et al. (2015) also assessed intraoperative blood loss, the post-operative need for blood transfusion, and the pre-operative and post-operative Hb levels. His results revealed that the mean pre-operative and post-operative Hb levels were not significantly different between the Misoprostol and the placebo groups. However, the mean operative time and estimated blood loss were significantly higher in the placebo group. In addition, about 9 patients (22.5 %) in the placebo group needed a blood transfusion, while there was no need for a blood transfusion in the Misoprostol group (P=0.001) (19).

Another study by Vahdat et al. (2015) confirmed the efficacy of sublingual Misoprostol during abdominal myomectomy. Post-operative Hb level (6 hours after surgery) was significantly higher in the Misoprostol group (9.8±0.8 vs. 9.1±0.9, P=0.003), while the Hb level after 24 hours showed no significant difference between both groups (10.50±0.56 vs. 10.24±0.58, P=0.066). Additionally, no significant difference was found between both groups regarding anemia and the need for blood transfusion after surgery (20).

Wali et al. (2021) performed a meta-analysis (including eight studies) about using Misoprostol for open myomectomy. They concluded that using Misoprostol prior to surgery was significantly linked to a reduction in blood loss, a decrease in Hb drop, a decrease in the need for blood transfusion, and a reduction in operating time. The duration of the post-operative stay and post-operative pyrexia did not differ (21).

Contrary to the current study, Wetherell et al. (2022) conducted a similar study in Australia on two randomized groups to receive Misoprostol. Both groups were matched in age and uterine fibroid criteria regarding number and size. Wetherell et al. reported no significant difference between Misoprostol and placebo regarding total blood loss (306 ml±281 ml vs. 325±352 ml; P=0.83) (22). However, these results could be attributed to the fact that this study was exploratory and was performed on a much lower sample size.

Finally, the role of Misoprostol intake before myomectomy in reducing blood loss during surgery could be attributed to the decrease in the vascularity and perfusion of uterine myomas. Khalaf et al. (2020) depended on uterine Doppler to evaluate the effect of Misoprostol, and they found that Misoprostol significantly decreases the vascularity and perfusion of uterine fibroids whether administered rectally or sublingually one hour before open myomectomy (23).

CONCLUSION

Our study revealed that a single dose of Misoprostol (400 mcg) sublingually one hour before the operation is significantly effective in reducing blood loss and operation time during myomectomy. No study has yet been conducted to prove the best route for Misoprostol administration before abdominal myomectomy; therefore, we recommend further studies comparing the different routes of Misoprostol administration.

DECLARATIONS

Competing interests: The author has no financial or other conflicts of interest.

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Informed consent: All women gave their consent after being informed of the study's objective and design, and they were given the option to leave the study at any time.

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Table 1: Demographic characteristics of all participants

	Control Group "n=75"	Study Group "n=75"	P-value
Age (years)	34.40±4.72 34 (25 - 44)	33.45±4.83 33 (25 - 45)	0.227
Parity	1.55±0.81 1 (0 - 3)	1.65±1.05 2 (0 - 4)	0.486
Previous Cesarean section	1 (0 - 3)	1 (0 - 4)	0.738
Previous normal delivery	0 (0 - 3)	0 (0 - 3)	0.583
Number of abortions	1 (0 - 4)	1 (0 - 4)	0.939

Table 2: Pre-operative Assessment

	Control Group "n=75"	Study Group "n=75"	P-value
Number of myomas	1.73±0.78 2 (1 - 4)	1.97±0.88 2 (1 - 4)	0.080
Size of largest myoma (cm)	6.76±0.66 6.7 (5.6 - 8.3)	6.65±0.84 6.5 (5.4 - 8.4)	0.373
Type of fibroids **- Intramural** **- Subserous** **- Both**	 54 (72 %) 7 (9.33 %) 14 (18.67 %)	 45 (60 %) 12 (16 %) 18 (24 %)	0.268
Pre-operative hemoglobin (g/dL)	11.80±1.14 11.8 (9.4 - 13.8)	11.05±1.17 10.9 (9.2 - 14)	<0.001
Pre-operative Hematocrit (%)	41.18±2.80 41.6 (34 - 45.7)	40.43±3.12 40.4 (33 - 45.6)	0.122

Table 3: Operative Assessment

	Control Group "n=75"	Study Group "n=75"	P-value
Operation time (minutes)	71.08±10.62 70 (54 - 91)	58.80±4.51 59 (50 - 68)	<0.001
Blood loss in suction (mL)	340.55±66.71 330 (210 - 510)	279.16±44.61 280 (210 - 380)	<0.001
Weight difference of swabs (gm)	149.80±19.40 142 (137 - 212)	148.29±24.93 137 (132 - 207)	0.680
Total blood loss (mL)	483.21±76.06 475 (350 -712)	420.39±53.49 417 (336 - 577)	<0.001

Table 4: Post-operative Assessment

	Control Group "n=75"	Study Group "n=75"	P-value
Post-operative hemoglobin (g/dL)	10.50±1.15 10.6 (8 - 12.6)	10.60±1.22 10.3 (8.7 - 13.5)	0.601
Hemoglobin difference (g/dL)	1.30±0.59 1.3 (0.4 - 5.2)	0.45±0.36 0.4 (-2.1 - 1.1)	<0.001
Post-operative Hematocrit (%)	38.91±2.34 39.2 (32.4 - 42.8)	39.93±3.11 40 (32.3 - 45.1)	<0.001
Hematocrit difference (%)	2.27±1.15 2.4 (-5.7 - 3.9)	0.49±0.33 0.5 (-1.3 - 1.6)	<0.001