The effect of misoprostol on intra-operative blood loss during myomectomy operation : Randomized controlled trial

Original Article

Sabry El Sayed Mohamed, Dina Yahia Mansour, Ahmed Nagy Shaker

Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

ABSTRACT

Introduction: Uterine myomas are most prevalent benign tumors in reproductive-aged women. Myomectomy is a surgical treatment for symptomatic uterine myomas for women who want to preserve fertility. Uncontrolled intraoperative bleeding with others life-threatening complications make the surgery risky even more than the hysterectomy and require a skilled surgeon, several methods have been developed to reduce this complications. Misoprostol PE1 analogue, which is recently used as treatment and prophylaxis of postpartum hemorrhage, may reduce intra-operative blood loss during abdominal myomectomies when bleeding constitutes a major problem.

Aim of the work: Was to assess the effect part of a single dose of Misoprostol (400 microgram) given rectally one hour preoperative on the amount of blood loss during open Myomectomy.

Patients and Methods: In a prospective randomized double-blind placebo-controlled trial which was conducted at Ain shams maternity Hospital in Cairo from October 2017 to May 2018, 50 women undergoing abdominal myomectomy for symptomatic uterine myomas were randomly divided into 2 groups : Group I (control group) consisted of 25 patients, each patient was given 2 tablets of placebo trans-rectally one hour preoperatively and without any intervention to reduce blood loss and Group II (study group) consisted of 25 patients, each patient was given 400 micrograms of misoprostol trans-rectally one hour preoperatively. The primary outcome was intraoperative blood loss. This clinical trial was registered in clinicaltrial.gov registry with number: NCT03483142.

Results: Intra-operative blood loss was significantly lower in those women randomized to receive rectal misoprostol versus the placebo group (460.8- 155.2 mL vs. 815.4 - 187.7 mL). Misoprostol group showed lower mean blood loss (*P<0.01*) ; additionally, there was a highly significant statistical difference between Misoprostol group and placebo group as regards the postoperative hemoglobin, hematocrit concentration, operative time and IV fluid infusion during surgery (*P<0.01*) as Misoprostol group showed a higher postoperative hemoglobin and hematocrit concentration, and less operative time and infused IV fluid. There was no statistical significant difference between both groups as regards the blood transfusion.

Conclusion: Preoperative single dose of rectal misoprostol (400 micrograms) is an effective simple method for reducing intra-operative bleeding, operative time, mean post-operative HB and Hct drop.

Key Words: Intra-operative blood loss, misoprostol, myomectomy operation.

Received: 15 November 2018, **Accepted**: 21 November 2018

Corresponding Author: Ahmed Nagy Shaker**,** MSc.**,** Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, Cairo, Egypt, **Email:** dr_nagy.ahmed@yahoo.com

ISSN: 2090-7265, February 2019, Vol.9, No.1

INTRODUCTION

Uterine myoma is the most prevalent pelvic tumors which arise from myometrial smooth muscle cells and occurred in about 20-40% of reproductive-aged women[1]. These tumors are hormonal (estrogen) dependent and grow within the reproductive period. Myomas are predominately asymptomatic, but become symptomatic in 20-50% of affected cases, presenting with abnormal uterine bleeding mainly menorrhagia, pelvic pain radiating to back, or urinary symptoms. The severity of symptoms depend on size, number and location of the tumors[2]. The standard method for treating uterine fibroids is hysterectomy for women who have completed their childbearing and myomectomy for those who want to preserve their fertility[3]. However, bleeding is one of the most prevalent complications in cases subjected to myomectomy[4]. Literature shows that about 20% of the cases who underwent myomectomy need blood transfusion[2]. Different methods are used to reduce bleeding during myomectomy including GnRH agonist before surgery or intraoperative vasopressin, intravenous oxytocin, intramyometrial bupivacaine plus epinephrine, tourniquet methods and preoperative uterine artery embolization and clamping of the uterine and/or ovarian arteries[5]. As well-known prostaglandins increase contractions of myometrium and lead to decrease myometrial bleeding. In recent years, Misoprostol a synthetic PGE1 analogue is commonly used for cervical

 DOI: 10.21608/EBWHJ.2019.28641

ripening, medical abortion, management of miscarriage, induction of labor and management of postpartum hemorrhage. It can be given vaginally, orally, buccally or rectally[6]. In a previous study, Celik and Sapmaz investigated that a single dose of misoprostol before myomectomy would reduce intraoperative bleeding and the need for blood transfusion postoperatively in women who underwent myomectomy[7]. As there are few studies assessing the effect of misoprostol for decreasing blood loss during myomectomy, the goal of this study was to assess the effect of a single rectal dose of Misoprostol (400 microgram) given one hour preoperatively on the amount of bleeding during abdominal Myomectomy.

PATIENTS AND METHODS

This prospective comparative randomized double-blinded placebo controlled clinical trial aimed to assess the effect of a single preoperative dose of 400 microgram of misoprostol given rectally on intraoperative blood loss during abdominal myomectomy operation. The trial was registered in ClinicalTrials.gov registry with clinical trial registration number: NCT03483142. The study was conducted in Ain Shams University Maternity Hospital, Cairo, Egypt from October 2017 to May 2018. The Ethical Research Committee, Obstetrics and Gynecology Department, Ain Shams University, Cairo, Egypt approved the protocol of the study. All patients who attended the outpatient gynecological clinic, looking for treatment for their symptomatic myomas, in the period between October 2017 and May 2018 were invited to participate in the clinical study. Seventy-five women were screened to ensure that they fulfilled the inclusion criteria of the study. Inclusion criteria included (1) age between 20 and 39 years; (2) five or less symptomatic uterine fibroids; (3) maximum diameter of the largest fibroid 6 cm; (4) all fibroids classified as intramural or subserous by ultrasound and (5) uterine size <24 weeks' of gestation on bimanual examination. Exclusion criteria included (1) history of previous pelvic or abdominal surgery (laparotomy), this excluded caesarean section; (2) history of endometriosis; (3) allergy to misoprostol; (4) hypertension; (5) cardiac or pulmonary diseases; (6) bleeding or coagulation disorders; (7) anemia (Hb < 10 g/dL); (8) chronic endocrinal or metabolic diseases such as diabetes; (i) obesity (body mass index > 30 kg/m2). Twenty-five women were excluded from the clinical study as they had one or more of the exclusion criteria. A total of 50 women were included to the clinical study after counselling about possible other surgical treatments such as hysterectomy. All were counselled about the study and written informed consent was obtained from participants. Before the surgery, the patients signed a written consent to participate in the study after presenting an explanation about the nature and possible consequences of the clinical study in an easy way. A detailed history was taken from all women and all were examined clinically to exclude any general medical disorders. Body mass index (BMI) was calculated for each woman. Vaginal and abdominal examinations were done. Pelvic and abdominal ultrasound examination was done for all women to assess the number and location of fibroids and the largest fibroid diameter. A pre-operative full blood count and coagulation profile were done for all women. The patients were randomized into two groups:

Group I: Control group including 25 patients who received placebo. Two rectal placebo tablets of vitamin B6 have the same size and shape as the misoprostol one hour before the surgery and without any intervention method to decrease blood loss.

Group II: Study group including 25 patients; each woman was given 400 micrograms (two tablets 200mcg of Misotac® SIGMA pharmaceutical industries) misoprostol rectally one hour before operation.

The randomization was performed by computer (SPSS Random Number Generator; SPSS Inc., Chicago, IL, USA) using randomization sequence 1:1). Computer generated randomization cards were produced and saved in sealed, sequentially opaque numbered envelopes. The packages were made by the hospital pharmacy and their contents were kept unknown to the physicians and nurses. All study personnel and participants were blinded to treatment assignment for all duration of the study.

In all operations, the abdomen is entered by a laparotomy incision. The surgeries were performed by the same surgical team to avoid any bias related to surgical skills. In both groups, Myomectomy was done by enucleating all myomas and clamping of large blood vessels was performed. The uterine defect was closed with vicryl and no other interventions like tourniquets or ligation were used. The total volume of blood loss during the surgery was evaluated by measuring the amount of blood cumulated in the container of suction apparatus at the end of surgery and the amount of blood on the surgical towels by towel weighting. The surgical towels are weighted before and after surgery using a scale accurate to 1 gram and the weight difference will be calculated. The weight of 1 gram is taken as 1 ml blood. Calculating blood loss in theatre: (1) weigh a dry swab, (2) weigh blood soaked swabs as soon as they are discarded and subtract their dry weight (1ml of blood weighs approximately 1gm), (3) subtract the weight of empty suction bottles from the filled ones, (4) estimate blood loss into surgical drapes together with the pooled blood beneath the patient and onto the floor, (5) the volume of irrigation fluids, subtract this volume from the measured blood loss to estimate the final blood loss. Vital data during operation and the duration of the operation are recorded, time from opening of the peritoneum until its closure, to assess the effect of blood loss on hematocrit and hemoglobin values, the patient hematocrit (%) and hemoglobin (g/dL) values will be measured 1 hour preoperative and 1 and 24 hours postoperative. Intra or post-operative blood transfusion for any case in both

groups was recorded and the transfused units were mentioned. Any postoperative side effects including febrile episode, increase to or over 38.5°C in body temperature within 24 h postoperative, were recorded. In both groups, the number and size of fibroid were rerecorded after removing all fibroids. The primary outcome for this clinical study was the estimated intra-operative blood loss. Secondary outcomes measures were the difference between the pre-operative and postoperative hemoglobin (HB) and hematocrit, postoperative febrile morbidity, the duration of the operation, the need for intra-operative or postoperative blood transfusion and the duration of hospital stay. In previous study where using a = 0.05 and power = 0.90 and standard deviation of the amount of blood loss = 121 mL, a sample size of at least 15 women per group was required to detect a difference of at least 121 mL of blood. The sample size calculation is done by STATA program V14. Statistical analysis was performed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). Categorical data were presented as number and percentage and intergroup differences were compared using the Pearson chi-square test or Fisher's exact test, when appropriate. Ordinal data were compared using the chi-squared test for trend. Continuous numerical variables were presented as mean and standard deviation and between-group differences were compared using the unpaired t-test. *P*-value <0.05 is considered statistically significant.

RESULTS

During the duration of the study, 75 women were assessed for study eligibility. Twenty five women were excluded from the clinical study as they had one or more of the exclusion criteria: 5 had a history of pelvic/ovarian endometriosis confirmed by previous laparoscopic examination, 6 had BMI > 30 kg/m2 and 4 women had previous cesarean section, 6 had uncontrolled diabetes and 4 had hypertension SBP above 150 mmHg. The remaining 50 women were divided into : 25 randomized to the misoprostol (study) group and 25 to the placebo (control) group and were included in the final analysis (Fig. 1). The comparison between the study and control groups did not show any significant differences for the baseline demographics characteristics including age, BMI, parity, preoperative HB, number, site and size of myoma as presented in Table 1. By contrast, there was a significant difference in all parameters related to intra-operative blood loss, operation duration and IV fluid infused between the two groups. Intraoperative blood loss was significantly lower in the study (misoprostol) group than in the control (placebo) group and was, respectively, 460.8 ± 155.2 mL vs. 815.4 ±187.7 mL; $P < 0.00001$. The duration of the operation was significantly shorter in the study (misoprostol) group compared with the control (placebo) group (70.84 ± 11.3 vs. 87.6 ± 21.2 min; $P = 0.001$, Table 2). There was a highly significant statistical difference between misoprostol and control group as regards the postoperative hemoglobin (10.6 ± 0.96 vs. 9.76 ± 0.78, $P<0.001$). Misoprostol group showed a higher postoperative hemoglobin concentration. There was a highly significant statistical difference between misoprostol and control group as regards the postoperative hematocrit (33.46 ± 3 vs. 31 ± 2.3 $P<0.001$). Misoprostol group showed a higher postoperative hematocrit concentration. The drop in hemoglobin concentration and hematocrit percentage was significantly lower in the study (misoprostol) group compared with the control (placebo) group (1.16 ± 0.5 vs. 1.7 ± 0.5 g/dL; $P = 0.0005$ and 3.5 ± 1.5 vs. 5.6 ± 1.6; P = 0.00001, respectively) (Table 3). There were no significant differences between both groups with respect to postoperative febrile morbidity, the requirement for blood transfusion or the length of hospital stay (Table 3).

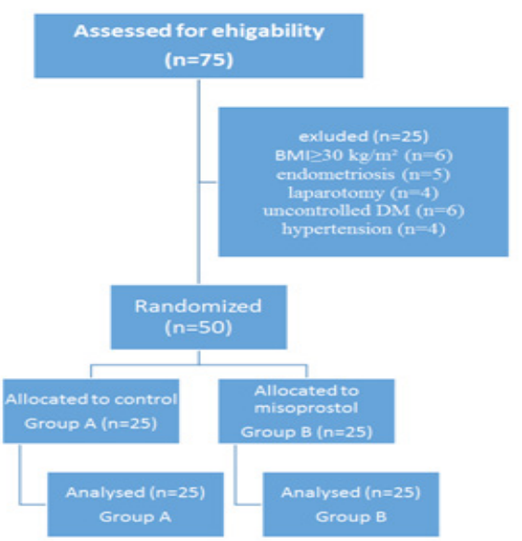

Fig. 1: Flowchart of the participant through the study.

Table 1: Demographic characteristics of the recruited women.

Variable	Misoprostol group (n = 25)	Control group (n = 25)	*P*-value
Age (years)	36.64 ± 3.7	36.7±2.8	0.966 $
BMI (kg/m2)	25.7±1.8	25.6±1.8	0.845 $
Parity (%)			
P0	7 (28%)	12 (48%)	0.424 #
P1	4 (16%)	3 (12%)	
P2	7 (28%)	5 (20%)	
P3	3 (12%)	4 (16%)	
P4	3 (12%)	0 (0%)	
P5	1 (4%)	1 (4%)	
Number of myomas (%)			
1	8 (32%)	5 (20%)	0.597 #
2	6 (24%)	7 (28%)	
3	4 (16 %)	8 (32%)	
4	4 (16%)	5 (20%)	
5	3 (12%)	3(12%)	
Site of myomas (%)			
Intramural	19 (76%)	22 (88%)	0.423 #
Subserous	5 (20%)	3 (12%)	
Subserous and intramural	1 (4%)	0 (0%)	
Uterus size (weeks)	9.66± 2.64	10.24 ± 3.4	0.5 $
Size of largest myoma (cm2)	110 ±39	112.5 ± 36.3	0.246 $
Pre-operative haemoglobin (g/dL)	11.8 ± 0.85	11.5 ± 0.77	0.216 $
Preoperative hematocrit (%)	36.6 ± 2.1	36.6± 2.1	0.999 $

Table 2: Intraoperative outcome measures.

Variable	Misoprostol group (n = 25)	Control group (n = 25)	P-value
Blood volume in suction (mL)	76.32± 44	76.32± 44	0.00001 $*
Blood volume extracted from swabs (mL)	384.5 ± 124.4	384.5 ± 124.4	0.00001 $*
Estimated blood loss (mL)	460.85 ± 155.2	460.85 ± 155.2	0.00001$*
Operation time (min)	70.84 ± 11.3	70.84 ± 11.3	0.001 $*

Table 3: Postoperative outcome measures.

Variable	Misoprostol group (n = 25)	Control group (n = 25)	*P*-value
Postoperative Haemoglobin (g/dL)	10.6 ±0.96	9.76 ± 0.78	0.001 $*
Postoperative Hematocrit (%)	33.46 ± 3	31 ± 2.33	0.001 $*
Change in haemoglobin (g/dL)	1.16 ± 0.5	1.72 ± 0.55	0.0005 $*
Change in haemoglobin (g/dL)	3.53 ± 1.47	5.6 ± 1.58	0.00001 $*
Length of hospital stay (days)	2.36 ± 0.42	2.58 ± 0.37	0.0564 $
Blood transfusion (%)			
Yes	1 (4%)	4 (16%)	0.5 #
No	24 (96%)	21 (84%)	
Adverse effects (%)			
Fever (>38.5°C on day 0/1)	0 (0%)	0 (0%)	0 no statistical difference #
Chills	0 (0%)	0 (0%)	
Diarrhea	0 (0%)	0 (0%)	
Nausea	0 (0%)	0 (0%)	

Data presented as mean +/- SD, or number of women (%), $ independent sample t-test, # chi-squared test, * significant value

DISCUSSION

Myomectomy is a treatment for symptomatic uterine myomas and preserve fertility. Uncontrolled intraoperative bleeding is the greatest operative risk which makes the surgery even higher in risk more than a hysterectomy and requires a skilled surgeon. Conservative surgery remains the main method for treatment of uterine myomas, however, hemorrhage is often a problem in this surgery and can result in postoperative anemia, intraoperative hypovolemic shock, adhesions with infertility and pelvic infection. Many studies have been done to decrease hemorrhage during myomectomy including Uterotonics such as misoprostol, ergometrine, hormonal, tourniquet, peri-cervical mechanical tourniquet and uterine artery dissection[8]. Misoprostol, a synthetic analogue of prostaglandin E1 that can be administered through different routes including vaginal, oral, sublingual and rectal[8]. Misoprostol acts by one of two mechanisms to decrease bleeding. First, like prostaglandins, prostaglandin analogs increase myometrial contractions. 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 myoma before reaching the myoma or myomas. Through this effect, vascular structures are contracted and blood flow is decreased[9]. The second mechanism may be the direct vasoconstrictive effect of misoprostol on arteries of the uterus[9].

This study is a double blinded prospective randomized clinical trial to assess the effect of a single preoperative dose of 400 microgram of misoprostol given trans-rectally on blood loss during abdominal myomectomy operation[7].

In this study, there were no statistically significant differences between both groups regarding the sociodemographic data, age, body mass index, occupation, marital status, special habits, parity, uterine size and characteristics of the myomata which coincides with the results of study reported by Celik and Sapmaz[7]. As regard preoperative data of the patients, comparison between two groups was done including pulse, systolic blood pressure, diastolic blood pressure, temperature and preoperative hemoglobin and hematocrit values and no statistically significance difference was found which also coincides with the results of study reported by Celik and Sapmaz[7].

In our study, it was found that average blood loss in the control group was 815.5 ml and it was 461 in the study group which agrees with Chiang *et al.*[10] who stated that the average volume of blood loss for abdominal myomectomy varies across studies from approximately 200 to 800 ml.

The amount of intraoperative blood loss in our study was significantly lower in the study group, misoprostol led to reduction in blood loss by 354 ml.

This agreed with the results of study reported by Celik and Sapmaz[7] in which 25 patients underwent abdominal myomectomy, 13 in the study group and were given a single dose 400 microgram of vaginal misoprostol and 12 patients in the control group were given placebo. Misoprostol led to reduction in blood loss by 149 ml in the study group.

This also agreed with another study reported by Kalogiannidis *et al.*[11] in which 67 menstruating patients with three or less myomas of a maximum diameter of 90 mm, scheduled for minimally invasive myomectomy, were randomly allocated to receive a preoperative single dose of intravaginal misoprostol or placebo. Sixty-four patients remained in the final analysis, 30 in the misoprostol group and 34 in the placebo group. The average blood loss was significantly higher in the placebo group (217±74 ml) versus misoprostol group (126±41 ml). Misoprostol led to reduction in blood loss by 91 ml in the study group.

Another study agreed with our results by Abdel-Hafeez *et al.*[12] in which 50 women undergoing abdominal myomectomy for symptomatic uterine leiomyomas were randomly assigned to receive a single dose of pre-operative of rectal 400 microgram misoprostol (n = 25) or placebo (n = 25) 1 h before the operation. The primary outcome was intraoperative blood loss. Intra-operative blood loss was significantly lower in those women randomized to receive rectal misoprostol versus the placebo group (574 ± 194.8 mL vs 874 ± 171.5 mL). Additionally, the drop in postoperative hemoglobin was significantly less in the misoprostol group (1.7 ± 0.4 g/dL) compared with the placebo group (2.1 ± 0.5 g/dL). Misoprostol led to reduction in blood loss by 300 ml in the study group.

Another study also agreed with our results by Niroomand *et al.*[2], 80 women with myomas were randomly assigned to receive 200 microgram misoprostol or placebo (vitamin B6) 3 h before surgery. Blood loss during surgery was assessed in two groups. Intra-operative blood loss was significantly lower in those women randomized to receive vaginal misoprostol versus the placebo group (458 ± 287 mL vs 696 ± 411mL). Misoprostol led to reduction in blood loss by 238 ml in the study group.

Another study similar to ours shows the following by Ragab *et al.*[9], in which 69 patients with multiple myomas undergoing myomectomy. Patients received either an intra-vaginal single dose of 400 microgram misoprostol 1 hr pre-operatively (Group A, 34 cases) or two doses, and 1 hr prior to surgery (Group B, 35 cases). The mean value for operative blood loss was significantly (p<0.001) smaller in group B (101.4 ± 25.5 vs. 200.16 ± 18.8 ml). Misoprostol led to reduction in blood loss by 98 ml in Group B than Group A. Double dose of misoprostol was more effective in reducing intraoperative blood loss than single dose.

Another study supports our results by Shokeir *et al.*[13], in which 108 patients underwent abdominal myomectomy, 54 in the study group were given a single dose of intravaginal 20 mg dinoprostone 60 min before the operation and 54 patients in the control group were given

placebo. The average blood loss was significantly higher in the placebo group (485.7 ± 361.3 ml) versus dinoprostone group (364.1 ± 279.4 mL). Dinoprostone led to reduction in blood loss by 124 ml in the study group.

Another study also supports our results by Biswas *et al.*[14], in which 132 patients undergoing total abdominal hysterectomy with or without bilateral salpingo-oophorectomy for symptomatic myomas were randomly allocated to receive either 400 µg of sublingual misoprostol or placebo 30 minutes before surgery. The average blood loss was significantly higher in the placebo group (435 ml) versus misoprostol group (356ml). Misoprostol led to reduction in blood loss by 79 ml in the study group.

On contrary one study by Chai *et al.*[15], in which 64 patients undergoing total abdominal hysterectomy with or without bilateral salpingo-oophorectomy for symptomatic myomas were randomly allocated 32 patients received 400 µg of sublingual misoprostol and 32 patients received placebo containing 20mg vitamin B[6] both given 30 minutes before surgery. Women who had misoprostol were found to have similar operative blood loss to those who had placebo (570.9 ± 361.3 ml for misoprostol group versus 521.4 ± 297.4 ml for placebo group). This study differs from our study as regard the route of administration of misoprostol and the time between administration and beginning of the study.

Regarding the operative time in our study, it was significantly shorter in the study group (71±11.3) vs. (87± 21.2) min in control group as a result of the decrease in the blood loss and better surgical field and these results agreed with the results reported by Celik and Spamaz[7], in which operative time was decreased by 10 min in study group, which was (48.5±7.4) vs. (58 ± 8.8) in control group. Other study showed that the mean operative time was significantly (p<0.001) shorter in group B (receive double dose) than in group A (single dose) (25.8 ± 4.14 vs. 35.4 ± 5.6 min, respectively)[9]. Another study showed that the duration of the operation was significantly shorter in the study (misoprostol) group compared with the control (placebo) group (76.8 ± 15.8 vs. 94.8 ± 22.8 min; P = 0.002)[12].

The infused fluid volume in our study was significantly lower in the study group than control group (2412.32±549.3 vs. 3707.4±713.5 ml), respectively, because of the decrease in the blood loss.

In our study, we compared the preoperative and postoperative hemoglobin also the preoperative and postoperative hematocrit as secondary outcomes. We found that the change in hemoglobin and hematocrit was significantly lower in the study group. Also, the difference between pre and postoperative HB and Htc (1±.5 vs. 1.7±.55 g/dl) and (3.53%±.0146 vs. 5.7%±.0158), respectively, which confirms the effect of misoprostol in reducing blood loss during myomectomy.

These results agreed with the results reported by Celik and Spamaz[7]. This found that misoprostol group had postoperative hemoglobin values after 1 hour postoperative that was significantly higher than those found in the group given placebo (10.6±0.6 vs. 9.7±0.4)

This also agreed with the study reported by Kalogiannidis *et al.*[11] which found that the decline of postoperative Hb was significantly higher in control group (1.6 g/dL ± 0.43) compared to misoprostol group (1 g/dL ± 0.33).

In addition, the study by Shokeir *et al.*[13] supports our results as they found that the control group had a significant decrease in Hb level 24h after operation compared with the dinoprostone group.

Similarly, the study by Biswas *et al.*[14] stated that the postoperative drop in hemoglobin was smaller in the misoprostol group (1.1g/dL) than in the placebo group (1.9 g/dL).

On contrary, the study by Chai *et al.*[15] stated that there were no observed differences in the change in hemoglobin level after the operation between misoprostol and placebo group.

There were no statistically significant differences between both groups regarding intraoperative and postoperative vital data of the patients, which agrees with Celik and Spamaz[7].

Our study established that misoprostol lead to statistically insignificant reduction in need for blood transfusion when compared to control group which disagree with Celik and Spamaz[7] which stated that misoprostol resulted in a statistically significant reduction in need for postoperative blood transfusion when compared to placebo.

Neither the misoprostol group nor the placebo patients required transfusion of more than two units of blood per patient, which agrees with Celik and Spamaz[7].

Our study analyzed the risk of blood transfusion in both groups and we found that the absolute risk in treatment group was 0.04 with 95% confidence interval (0.02 to 0.30); while the absolute risk in control group was 0.16 with 95% confidence interval (0.17 to 0.55) and the absolute risk reduction (ARR) was 0.12 with 95% confidence interval (-0.04 to 0.44). We also found that the relative risk (RR) was 0.25 with 95% confidence interval (0.16 to 1.26) and the relative risk reduction was 0.75 with 95% confidence interval (-0.26 to 0.84). The number needed to treat (NNT) was 8 with 95% confidence interval (-27.20 to 2.29).

Larger studies are required for better assessment of the effect of misoprostol in reduction of blood transfusion.

In our study as regard the side effects of misoprostol, the side effect of febrile morbidity was not seen in the patients who had received misoprostol; the difference between the misoprostol and placebo groups was not statistically

significant. No statistically significant differences were observed for other side effects either (diarrhea, nausea).

This agree with the study by Celik and Spamaz[7], the study explained that the reason for the insignificant differences observed for the misoprostol side effects may be that patients administered a single dose of misoprostol and after surgery the patients were either still anesthetized or under the effect of an analgesic.

In the study by Kalogiannidis *et al.*[11], the rate of side effects was similar between groups, which agree also with the studies by Shokeir *et al.*[13] and Biswas *et al.*[14].

Misoprostol may be used at different dosages and administered by different routes. Our study used 400 microgram of rectal misoprostol. We chose this method because the rectal route has the advantage of easy administration, rapid absorption, no risk for patients under general anesthesia, particularly useful in cases of severe bleeding when the oral and vaginal routes are not practical and may be associated with a lower incidence of side effects. The dosage chosen as it is commonly used in second trimester abortion. Recently excellent results after misoprostol rectally for the treatment of postpartum hemorrhages was reported Prata and Weidert[16].

In comparison with the results of some previous studies on different methods used to reduce bleeding in myomectomies, misoprostol could be simple, cheap and easy method to be used before myomectomy, however, researches on misoprostol compared to any of those methods as an active control have not been conducted till now.

Although our study made no comparison with other methods used to reduce intraoperative bleeding, some advantages of misoprostol over some of those methods could be monitored.

Misoprostol has the advantage of the cost compared to GnRH analogs and is considered the most popular method for reducing hemorrhage in myomectomy. However, the growth of myomas after treatment has been noted, as well as the development of 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. Misoprostol seems cheap when compared to the limited benefits derived from using GnRH analogs only for these purposes[7].

Another advantage over GnRH analogs is that the effect of GnRH analogs attained only after a long time while misoprostol can be administered an hour before the operation and significantly reduces intraoperative blood loss.

In comparison between misoprostol and vasopressin, cost concerns are partially valid for vasopressin treatment as well as safety concerns. Side effects have been reported to arise from the use of intraoperative vasopressin: temporary increase in blood pressure during local vasopressin injection, bleeding at injection site and intravascular infiltration by mistake[17]. In addition, Butala *et al.*[18] reported pulmonary edema after use of local vasopressin, and Park and Yoo[19] reported myocardial infarction. Side effects reported from misoprostol are chills, nausea and vomiting, headache and vertigo, abdominal pain and diarrhea. In addition to these side effects, some studies reported a slight increase or decrease in blood pressure[20].

Other methods for reducing hemorrhage in myomectomy, mechanical vascular occlusion techniques known as tourniquet or uterine artery embolization, also have become popular in recent years. 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 broad ligamentary myomas) and difficulty of placing the tourniquet are significant disadvantages[5].

Previous studies conducted with misoprostol and this study indicates that the use of misoprostol before myomectomies reducing hemorrhage is both reliable and effective. Our study involved a small number of cases, but still larger than the similar study done by Celik and Spamaz[7].

Investigation of misoprostol use in larger populations and with different dosages and administration routes together with comparison to other methods used to reduce bleeding during myomectomy are required.

CONCLUSION

Despite the small number of patients included in this study, it clearly showed that the use of single preoperative dose of rectal misoprostol (400 mcg) is easy to use, minor or no side effects, low cost, good clinical outcomes and a simple applicable method for reducing intraoperative blood loss, operative time and postoperative drop in hemoglobin and hematocrit values in abdominal myomectomy operations.

RECOMMENDATIONS

This study recommends the use of a single preoperative dose of rectal misoprostol (400 mcg) for all patients undergoing abdominal myomectomy operation.

Other studies comparing between misoprostol and other methods used to decrease bleeding during abdominal myomectomy (eg: intramyometrial injection of vasopressin, or preoperative GnRh agonists) is also recommended.

Further researches with large number of patients and with different dosage and administration routes to compare the efficacy of each route.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Khan, A. T, Shehmar, M, and Gupta, J. K. (2014): Uterine fibroids: Current perspectives. International Journal of Women's Health. https://doi.org/10.2147/IJWH.S51083

2. Niroomand, N, Hajiha, S, Tabrizi, N. M, and Ghajarzadeh, M. (2015): A single dose of misoprostol for reducing hemorrhage during myomectomy: a randomized clinical trial. Archives of Gynecology and Obstetrics, 292(1): 155–158.

3. Vilos, G. A., Allaire, C., Laberge, P. Y., Leyland, N., Vilos, A. G., Murji, A., and Chen, I. (2015).: SOGC Clinical Practice Guideline: The management of uterine leiomyomas. Journal of Obstetrics and Gynaecology Canada, 37(2), 157–178.

4. Adesina, K. T, Owolabi, B. O, Raji, H. O, and Olarinoye, A. O. (2017): Abdominal myomectomy: A retrospective review of determinants and outcomes of complications at the University of Ilorin Teaching Hospital, Ilorin, Nigeria. Malawi Medical Journal. https://doi.org/10.4314/mmj.v29i1.8

5. Wright, K, Louie, M, and Siedhoff, M. (2018): Hemostasis Techniques in Myomectomies. Current Obstetrics and Gynecology Reports, 7(2), 58–65.

6. Tang, O. S, Gemzell-Danielsson, K, and Ho, P. C. (2007): Misoprostol: Pharmacokinetic profiles, effects on the uterus and Side effects. International Journal of Gynecology and Obstetrics. https://doi.org/10.1016/j.ijgo.2007.09.004

7. Celik, H, and Sapmaz, E. (2003): Use of a single preoperative dose of misoprostol is efficacious for patients who undergo abdominal myomectomy. Fertility and Sterility, 79(5), 1207–1210.

8. Kongnyuy, E. J, and Wiysonge, C. S. (2011): Interventions to reduce haemorrhage during myomectomy for fibroids. In E. J. Kongnyuy (Ed.), Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley and Sons, Ltd. https://doi.org/10.1002/ 14651858.CD005355.pub4

9. Ragab, A, Khaiary, M, and Badawy, A. (2014): The use of single versus double dose of intra-vaginal prostaglandin E 2 "misoprostol" prior to abdominal myomectomy: A randomized controlled clinical trial. Journal of Reproduction and Infertility, 15(3), 152–156.

10. Chiang, K. J, Lai, H. C, Yu, M. H, and Wang, Y. C. (2014): Reducing blood loss during laparoscopic myomectomy by temporary uterine artery clamping using bulldog clamp. Journal of Medical Sciences (Taiwan), 34(4), 190–192.

11. Kalogiannidis, I, Xiromeritis, P, Prapas, N, and Prapas, Y. (2011): Intravaginal misoprostol reduces intraoperative blood loss in minimally invasive myomectomy: A randomized clinical trial. Clinical and Experimental Obstetrics and Gynecology.

12. Abdel-Hafeez, M, Elnaggar, A, Ali, M, Ismail, A. M, and Yacoub, M. (2015): Rectal misoprostol for myomectomy: A randomised placebo-controlled study. Australian and New Zealand Journal of Obstetrics and Gynaecology, 55(4), 363–368.

13. Shokeir, T, Shalaby, H, Nabil, H, and Barakat, R. (2013): Reducing blood loss at abdominal myomectomy with preoperative use of dinoprostone intravaginal suppository: A randomized placebo-controlled pilot study. European Journal of Obstetrics Gynecology and Reproductive Biology, 166(1), 61–64.

14. Biswas, J, Chaudhuri, P, Mandal, A, Bandyopadhyay, S. N, Dasgupta, S, and Pal, A. (2013): Effect of a single preoperative dose of sublingual misoprostol on intraoperative blood loss during total abdominal hysterectomy. International Journal of Gynaecology and Obstetrics, 122(3), 244–247.

15. Chai, J, Hon, E, Li, C. F, Pun, T. C, Yeung, S. B, and Ho, P. C. (2011): A pilot study of pre-operative misoprostol in reducing operative blood loss during hysterectomy. European Journal of Obstetrics Gynecology and Reproductive Biology, 158(1), 72–75. https://doi.org/10.1016/j.ejogrb.2011.03.023

16. Prata, N, and Weidert, K. (2016): Efficacy of misoprostol for the treatment of postpartum hemorrhage: Current knowledge and implications for health care planning. International Journal of Women's Health. https://doi.org/10.2147/IJWH.S89315

17. Mostafa-Gharabaghi, P, Alizadeh, S, Atashkhoye, S, Sayyah-Melli, M, Jafari-Shobeiri, M, Ouladsahebmadarek, E, Aghdam, Y. H. (2017): 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. International Journal of Women's Health and Reproduction Sciences, 5(4), 306–311. https://doi.org/10.15296/ijwhr.2017.52

18. Butala, B, Shah, V, Parikh, B, Jayaprakash, J, and Kalo, J. (2014): Bradycardia and severe vasospasm caused by intramyometrial injection of vasopressin during myomectomy. Saudi Journal of Anaesthesia, 8(3), 396. https://doi.org/10.4103/1658-354X.136630

19. Park, K. S, and Yoo, K. Y. (2017): Role of vasopressin in current anesthetic practice. Korean Journal of Anesthesiology. https://doi.org/10.4097/kjae.2017.70.3.245