ORIGINAL ARTICLE

Pre-operative Rectal Misoprostol before Myomectomy affect Bleeding in Patients with Intramural Myoma

SEYEDEHHAJAR SHARAMI, FOROZAN MILANI, FATEMEH HOSSEINI, FERESHTEH FAKOOR[1*]
Reproductive Health Research Center, Department of Obstetrics & Gynecology, Azzhra Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran; 2-Lung Diseases and Allergy Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran
Correspondence to Fereshteh Fakoor, Email: Iranianmedicine90@gmail.conm, Fax: +98 1333472206

ABSTRACT

Background: Myomectomy is a treatment of choice in patients who intend to achieve pregnancy in future. One of the important challenges in myomectomy is intra and post-operative bleeding.
Aim: To assess the efficacy of pre-operative rectal administration of misoprostol on the intra and post-operative bleeding in patients with intramural myoma.
Methods: A total of 94 women who were candidate for myomectomy were randomly enrolled in this clinical trial. The intervention group received 400 µg misoprostol rectally one hour before myomectomy.Hemoglobin and hematocrit were assessed in both intervention and control groups 4 and 24 hours after surgery. Furthermore, bleeding volume, duration of surgery, duration of admission, complications, need for transfusion and hysterectomy were assessed for both groups.
Results: The findings of this study revealed that pre-operative administration of 400 µg misoprostol resulted in a significant reduction in bleeding ($p<0.001$) but did not affect duration of surgery and admission, as well as complications, transfusion requirement, hysterectomy or hemoglobin and hematocrit levels 4 and 24 hours after surgery ($p>0.05$).
Conclusions: pre-operative rectal administration of 400 µg misoprostol resulted in reduction in intra-operative bleeding in patients with intramural myoma.
Keywords: Bleeding; Myomectomy; Misoprostol

INTRODUCTION

Uterine myomas are the most common benign tumors, which originate from smooth muscle cells in the myometrium[1]. The prevalence of myoma has been reported to range between 5.4 to 77% based on different diagnostic techniques[2,3]. Majority of myomas are asymptomatic but in 20 to 50% cases of myoma menorrhagia, pelvic pressure, pelvic pain or urinary symptoms may occur[4,5].

The standard treatment method for symptomatic myoma is patients who do not intend to become pregnant in the future is hysterectomy while in patients who pan to have children in future, myomectomy is the treatment of choice. Myomectomy can be performed through laparotomy, laparoscopy or hysteroscopy[6]. Intra or post-operative bleeding is one of the most important challenges in myomectomy[7]. It is reported that blood transfusion due to excessive bleeding may be required in up to 20% of trans-abdominal myomectomy cases[5] and in 5% of transabdominal myomectomies, excess blood loss might result in hysterectomy[6]. Furthermore, poorly managed bleeding might result in elongation of admission and increased costs of care in medical sectors.

Several clinical trials have been conducted to assess the effectiveness of medical treatments, including intramyometrial vasopressin[8], intravenous oxytocin[9], and intramyometrial bupivacaine plus epinephrine[10], in reduction of bleeding during myomectomy. The non-pharmacological methods to reduce intra-operative bleeding include using tourniquet or clamp[11,12]. But there are few clinical trial studies that assess the effects of medications in reducing intra-operative bleeding in myomectomy[13].

Misoprostol, a prostaglandin E1 antagonist, is being widely used in ripening of the cervix, labor induction, control of post-partum bleeding and pregnancy termination after second trimester[14,15]. The mechanism of action for misoprostol in reducing bleeding is mainly due to the increase in the contractility of myometrium[16]. Misoprostol can be administered sublingually or through oral, vaginal or rectal application[17].

Several studies assessed the effectiveness of various doses of misoprostol in reducing intra-operative bleeding in myomectomy and revealed controversial findings. Furthermore, the ideal dosage for misoprostol administration has not yet been determined[11,12]. On the other hand, the myomas were not categorized based on type and location, knowing that intramural myomas are accompanied with more extensive intra-operative bleeding compared to sub-serosal myomas[18]. To the best of our knowledge, no study has yet been conducted on the effect of the effectiveness of misoprostol administration on intra-operative bleeding in intramural myomectomy. Therefore, this study was conducted to assess the effect of pre-operative rectal administration of misoprostol on intra and post- myomectomy bleeding in patients with intramural myoma.

METHODS

Study population: This clinical trial was conducted on 94 patients who were referred to a tertiary hospital for myomectomy from during 2018.
Ethical approval: The study protocol was approved by the Guilan University of Medical Sciences Ethical Committee (Ethics code: IR.GUMS.REC.1396.257) and was registered

in the Iranian Registry of Clinical trial (Code: IRCT20080826001096N5). A written informed consent was obtained from all patients before participation in the study.

Inclusion and exclusion criteria: Inclusion criteria were being within the age range of 18 to 50 years old, negative history for hormone therapy before surgery, existence equal or fewer than five intramural myomas with the size of at least 4 cm based on the ultrasound examination.

Exclusion criteria were anemia (hemoglobin level below 10 mg/dl), allergy to misoprostol, based on questions including the experience of skin eruptions, urticaria, rash, shortness of breath, cough, chest pain in prior misoprostol administrations. Patients were also excluded if they had hemorrhagic conditions, obesity (body mass index higher than 35 kg/m^2), uterine size larger than 24 weeks, severe adhesion during surgery,severe endometriosis, malignancy or chronic diseases, including chronic heart or lung diseases, diabetes mellitus, or metabolic or endocrine diseases.

Data collection method: Patients who were eligible for the study based on inclusion criteria were randomly assigned into intervention and control groups using random block sampling. In this method patients were divided into 4 blocks (aabb, abab, baba and bbaa) and two blocks were randomly selected as intervention and two remaining blocks as control group. The serum hemoglobin and hematocrit of all patients were assessed at baseline. The intervention group received 400 µg misoprostol (Misoglandin ©, Samisaz Inc. Iran) rectally one hour before myomectomy while the control group received placebo with similar appearance. Drug administration was performed by midwives. Data were collected from patients' medical records. All myomectomies were performed trans-abdominally using the Pfannenstiel incision. Intra-operative bleeding was measured based on the blood volume collected in the suction bottle and counting bloody surgical gauzes. Each 10.16 cm gauze was estimated to absorb 15 ml of blood and each 30.48 cm gauze was estimated to absorb 60 ml of blood. Surgery duration was timed for all patients from the initiation of skin incision till the end of suturing the skin.Similar surgical technique and resuscitation, reanimation and blood transfusion protocols were used for all patients. Blood transfusion was performed in case of measured bleeding of more than one litter or hemoglobin drop by at least 2 mg/dduring the surgery. The number of transfused blood products and hysterectomy were recorded. All patients were assessed for surgery complications, including fever and chills and diarrhea, after surgery. Hemoglobin and hematocrit were rechecked after 4 and 24 hours of surgery. All the laboratory tests were performed by the same laboratory. Data collection and analysis were performed in a double-blind setting by two obstetrics and gynecology residents.

Statistical analysis: Study variables were presented using descriptive statistics. Comparison of study variables between groups was performed using independent t-test, chi-square, repeated analysis of variance, Pearson correlation coefficient and Fisher exact test. For non-normally distributed variables the Mann-Whitney test was used for comparison. Data analysis was performed using the statistical package for social sciences (SPSS) software version 21. The level of statistical significance was determined as $p<0.05$.

RESULTS

A total of 94 patients with symptomatic intramural myomas were assigned into intervention and control groups (47 patients in each group).

There was no significant difference between groups in terms of age, body mass index, gravida, parity, number of abortions, number and size of myomas. There was a significant difference in myoma location (location of the largest myoma) between groups ($p<0.001$) while there was no significant difference in terms of the location of other myomas between groups ($p>0.05$) (Table1).

There was no significant difference in terms of hemoglobin and hematocrit between study groups at baseline and after 4 and 24 hours. In both groups hemoglobin and hematocrit levels decreased from baseline to 24 hours post-myomectomy ($p<0.001$) but there was no significant time*group effect on hemoglobin and hematocrit. Similarly, no significant time and group effects were observed for hemoglobin and hematocrit. The effect size for the analysis based on eta squared was very low (Table 2).

The comparison of hemoglobin between study groups at different time points are shown in Figure 1. There was only a significant difference in hemoglobin between intervention and control groups at 4- and 24-hours post-myomectomy ($p=0.017$). The hemoglobin reduction in the intervention group (0.41 ± 0.24 mg/dl) was significantly lower than hemoglobin reduction in the control group (0.58 ± 0.43). There were no significant difference between intervention and control groups in terms of hematocrit.

This study findings revealed that the mean intra-operative bleeding volume in the intervention group was significantly lesser than the control group ($p<0.001$). the effect size based on ETA squared was medium (0.35). based on the myoma location, posterior myoma was associated with a significantly less bleeding in the intervention group compared to the control group. The statistical analysis also revealed no statistically significant difference between study groups in terms of the duration of surgery and admission (Table 3).

ETA>0.4 (large), ETA 0.25-0.4 (medium), ETA<0.25 (small)

Comparison of the frequency of blood transfusion, hysterectomy and complications between study groups are presented in Table 4. There was no significant difference between intervention and control groups in terms of blood transfusion, hysterectomy and complications.

Table 1: Comparison of the demographic and anthropometric characteristics of study subjects as well as the number and size of the myomas between intervention and control groups

Variable		Study group		Total	p*
		Intervention (n=47)	Control (n=47)		
		Mean ± SD	Mean ± SD		
Age (years)		39.34±6.38	38.00±4.89	38.67	0.225
BMI (kg/m^2)		25.82 ± 2.89	25.99 ± 3.26	25.90	0.768
Gravida		1.09±0.95	1.23±0.94	1.16	0.447
Parity		0.85±0.91	1.00±0.98	0.93	0.446
Number of abortions		0.17±0.56	0.11±0.37	0.14	0.520
First myoma size (mm)		46.00±18.86	53.11±16.66	49.55	0.056
Second myoma size (mm)		31.54±11.44	32.17±8.33	31.84	0.878
Third myoma size (mm)		33.33±11.55	35.00±21.21	34.00	0.913
First myoma location	Anterior	28 (59.6%)	19 (40.4%)	<0.001**	
	Posterior	15 (31.9%)	8 (17.0%)		
	Fundus	4 (8.5%)	20 42.6%)		

* Independent t-test ** Chi-square test

Table 2. Distribution and comparison of hemoglobin and hematocrit at the study time points between intervention and control groups

Variable		Intervention (n=47)	Control (n=47)	p value of analysis				Effect size	Power
				p	Time effect*	Group effect	Time*group effect		
Hb	Baseline	11.42±1.10	11.31±1.23	0.678	0.001	0.679	0.307	0.002	0.07
	4 hours post-operation	10.34±1.25	10.32±1.41	0.926					
	24 hours post-operation	9.94±1.29	9.74±1.47	0.490					
HCT	Baseline	34.27±3.30	33.89±3.77	0.742	0.001	0.555	0.962	0.004	0.09
	4 hours post-operation	31.05±3.79	30.58±4.14	0.571					
	24 hours post-operation	29.80±3.88	29.26±4.67	0.541					

* P<0.05

Table 3. comparison of mean bleeding volume, duration of surgery and admission between intervention and control groups

Variable		Study group		P value
		Intervention (n=47) Mean ± SD	Control(n=47) Mean ± SD	
Intra-operative bleeding volume (cc)	Regardless of myoma location	371.60±239.35	503.7±272.4	<0.001 ETA=0.36
	First myoma location-Anterior	380.5±278.6	503.7±272.4	0.091
	First myoma location-Posterior	355.3±178.7	713.8±361.1	0.003**
	First myoma location-Fundus	370.0±170.1	609.5±343.4	0.210
Surgery duration (m)		17.63±85.13	68.51±17.41	0.143
Admission duration (days)		2.15±0.36	2.19±0.4	0.585

* Mann-Whitney U test ** p<0.05

Table 4: Comparison of the frequency of blood transfusion, hysterectomy and complications between intervention and control groups

Variable		Study group		Total	p*
		Interventionn (%)	Control n (%)		
Transfusion	Yes	4 (8.5%)	5(10.6%)	9 (9.6%)	0.50
	No	43 (91.5%)	42 (89.4%)	85 (90.4%)	
Hysterectomy	Yes	1 (6.4%)	3 (6.4%)	4 (4.2%)	0.308
	No	46 (97.9%)	44 (93.6%)	90 (95.8%)	
Complications (fever and chills and diarrhea)	Yes	5 (110.6%)	2 (4.3%)	7 (7.4%)	0.217
	No	42 (89.4%	45 (95.7%)	87 (92.6%)	

Fisher's exact test

DISCUSSION

The findings of this study support the effect of rectal administration of misoprostol on reducing the bleeding volume during intramural myomectomy. Furthermore, although in this study the frequency of posterior myoma was higher in the intervention group compared to the control group (31.9% vs 17%), the bleeding volume in the intervention group was less than the control group. Misoprostol is a cheap and relatively safe medication that can reduce bleeding by inducing myometrial contraction and thus contraction of myometrial blood vessels[19]. Previous studies also reported convincing results for the effect of rectal administration of misoprostol on bleeding volume in myomectomy. In a clinical trial on 60 patients who were candidate for myomectomy, the intervention group received 400 µg misoprostol rectally while the control group received placebo. The results revealed that the bleeding volume in the intervention group was significantly lower than the control group[11]. In another clinical trial, women who received 400 µg rectal misoprostol one hour before myomectomy had a significantly lower bleeding

volume compared to the control group[20]. The findings of the mentioned studies were in line with the findings of our study. To the best of our knowledge none of the previous studies assessed the effect of rectal misoprostol administration on intra-operative bleeding based on myoma location. Therefore, the results of our study can be better generalized compared to the previous studies due to the homogeneity of the studies cases, which yield a higher precision.

Although the bleeding volume in the misoprostol group was lower than the control group, there were no significant difference between groups in terms of hemoglobin and hematocrit at baseline and after 4 and 24 hours from myomectomy. In the study by Niroomand et al. on 80 women who were candidate for myomectomy, 40 women received 200 µg rectal misoprostol before surgery. The results revealed no significant difference in hemoglobin and hematocrit between groups at 6 and 12 hours after surgery, which were in line with the findings of our study[5]. In a clinical trial in India, 30 women received rectal misoprostol and intramyometrial vasopressin. They reported a significantly higher hemoglobin levels after surgery in the intervention group compared to the control group, who only received vasopressin[19]. In the study by Kalogiannidis et al. on 64 patients, among whom 30 received vaginal misoprostol, underwent laparoscopic myomectomy. They found that the hemoglobin decrease was significantly higher in the control group compared to the intervention group, which was in contrast to the findings of our study[21]. The reason for this difference might be due to the smaller sample size, different surgical method (laparoscopic vs trans-abdominal) and rout of administration (vaginal vs rectal) in the studies. Another reason for the differences in the findings of the studies might be the lower threshold for transfusion in our study compared to the previous studies.

In our study no significant difference was observed in blood transfusion between intervention and control groups. Similar to the findings of our study, in the study by Rashed et al. no significant difference in transfusion was observed between misoprostol and control group[20]. In contrast to the findings of our study, in the study by Celick et al. the need for transfusion in 13 women who received 400 µg misoprostol was significantly lower compared to the control group[16]. The reasons for the difference in the findings of our study and the study by Celick et al. might be due to the smaller sample size in the study by Celick et al. and difference in the rout of administration of misoprostol (rectal vs vaginal).

The findings of our study revealed no significant difference between misoprostol and control groups in terms of complications including fever and chills and diarrhea. This finding was in line with the findings of the previous studies by Hafeeze et al[11], Frederick et al[22] and Rashed et al[20]. This finding was predictable considering the lower rate of complications in rectal administration of misoprostol compared to oral administration of misoprostol. In contrast, in the study by Ragab et al. who assessed the effect of two different doses of misoprostol (400 and 800 µg vaginal misoprostol) prior to trans-abdominal myomectomy, high body temperature was reported in patients who received 800 µg misoprostol[17]. This finding is predictable regarding the high dose of misoprostol. One of the advantages of our study was the inclusion of patients with intramural myoma, which are accompanied with higher rates of bleeding. Furthermore, the sample size in our study was larger than the sample sizes of the previous studies. The main disadvantage of our study was that we did not compare the effects of misoprostol with other medications in reducing intra and post -operative bleeding.

CONCLUSION

The findings of this study revealed that rectal administration of 400 µg misoprostol is an easy and cheap method for reducing the intra-operative bleeding in myomectomy. The findings of this study provide evidence for the use of misoprostol as an effective, safe and cheap method for reducing bleeding in myomectomy surgery. There is a need for further studies to assess the efficacy of different doses of misoprostol with different routes of administration in reducing bleeding during myomectomy.

Conflict of Interest Disclosure: The author(s) declare(s) that there is no conflict of interest.

Funding: This study was extracted from a thesis of resident of Obstetrics & Gynecologyby financial support of Deputy of Research and Technology ofGuilan University of Medical Sciences.

Data Availability: No data were used to support this study.

Author Disclosure: The authors declare no conflict of interest

REFERENCES

1. S. BJ. Berek & Novak's Gynecology. . Edition t, editor. Philadelphia: Lippincott Williams & Wilkins; 2012. 1066-89 p.
2. Cheng M-H, Wang P-H. Uterine myoma: a condition amendable to medical therapy? Expert opinion on emerging drugs. 2008;13(1):119-33.
3. Haney A. Clinical decision making regarding leiomyomata: what we need in the next millenium. Environmental health perspectives. 2000:835-9.
4. Buttram Jr VC, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. Fertility and sterility. 1981;36(4):433.
5. Niroomand N, Hajiha S, Tabrizi NM, Ghajarzadeh M. A single dose of misoprostol for reducing hemorrhage during myomectomy: a randomized clinical trial. Archives of gynecology and obstetrics. 2015;292(1):155-8.
6. Lethaby A, Vollenhoven B, Sowter M. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids (Cochrane review). The Cochrane Library. 2001;4.
7. Parker WH. Uterine myomas: management. Fertility and sterility. 2007;88(2):255-71.
8. Frederick J, Fletcher H, Simeon D, Mullings A, Hardie M. Intramyometrial vasopressin as a haemostatic agent during myomectomy. BJOG: An International Journal of Obstetrics & Gynaecology. 1994;101(5):435-7.
9. Agostini A, Ronda I, Franchi F, Bretelle F, Roger V, Cravello L, et al. Oxytocin during myomectomy: a randomized study. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2005;118(2):235-8.
10. Zullo F, Palomba S, Corea D, Pellicano M, Russo T, Falbo A, et al. Bupivacaine plus epinephrine for laparoscopic myomectomy: a randomized placebo-controlled trial. Obstetrics & Gynecology. 2004;104(2):243-9.

11. Abdel-Hafeez M, Elnaggar A, Ali M, Ismail AM, Yacoub M. Rectal misoprostol for myomectomy: A randomised placebo-controlled study. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2015;55(4):363-8.
12. Fletcher H, Mrcog JF, Mrcog MH, Simeon D. A randomized comparison of vasopressin and tourniquet as hemostatic agents during myomectomy. Obstetrics & Gynecology. 1996;87(6):1014-8.
13. Kongnyuy EJ, Van Den Broek N, Wiysonge C. A systematic review of randomized controlled trials to reduce hemorrhage during myomectomy for uterine fibroids. International Journal of Gynecology & Obstetrics. 2008;100(1):4-9.
14. Tanha FD, Golgachi T, Niroomand N, Ghajarzadeh M, Nasr R. Sublingual versus vaginal misoprostol for second trimester termination: a randomized clinical trial. Archives of gynecology and obstetrics. 2013;287(1):65-9.
15. Tanha FD, Salimi S, Ghajarzadeh M. Sublingual versus vaginal misoprostol for cervical ripening before hysteroscopy: a randomized clinical trial. Archives of gynecology and obstetrics. 2013;287(5):937-40.
16. Celik H, Sapmaz E. Use of a single preoperative dose of misoprostol is efficacious for patients who undergo abdominal myomectomy. Fertility and sterility. 2003;79(5):1207-10.
17. Ragab A, Khaiary M, Badawy A. The Use of single versus double dose of intra-vaginal prostaglandin E2 “misoprostol” prior to abdominal myomectomy: a randomized controlled clinical trial. Journal of reproduction & infertility. 2014;15(3):152.
18. Martinez MEG, Domingo MVC. Size, Type, and Location of Myoma as Predictors for Successful Laparoscopic Myomectomy: A Tertiary Government Hospital Experience. Gynecology and minimally invasive therapy. 2018 Apr-Jun;7(2):61-5. PubMed PMID: 30254939. Pubmed Central PMCID: PMC6113999. Epub 2018/09/27. eng.
19. Srivastava S, Mahey R, Kachhawa G, Bhatla N, Upadhyay AD, Kriplani A. Comparison of intramyometrial vasopressin plus rectal misoprostol with intramyometrial vasopressin alone to decrease blood loss during laparoscopic myomectomy: Randomized clinical trial. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2018;228:279-83.
20. Rashed MR. Effct of Rectal Adminstration of Misoprostol in Myomectomy. Al_Azhar Assiut Medical Journal. 2014 SUPPL - 2 12(4):270-80.
21. Kalogiannidis I, Xiromeritis P, Prapas N, Prapas Y. Intravaginal misoprostol reduces intraoperative blood loss in minimally invasive myomectomy: a randomized clinical trial. Clinical and experimental obstetrics & gynecology. 2011;38(1):46-9.
22. Frederick S, Frederick J, Fletcher H, Reid M, Hardie M, Gardner W. A trial comparing the use of rectal misoprostol plus perivascular vasopressin with perivascular vasopressin alone to decrease myometrial bleeding at the time of abdominal myomectomy. Fertility and sterility. 2013;100(4):1044-9