Effect of Use of Single Dose of Misoprostol on Blood Loss during Myomectomy

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ABSTRACT

Background: Uterine leiomyomas are the commonest benign tumours in women, which are estrogen-dependent and grow during the reproductive life. Standard treatment for leiomyoma is hysterectomy or myomectomy according to women's age and fertility. Prostaglandins and particularly PGE1 as misoprostol have an impact on uterine contractions and decrease blood loss.

Objective: To evaluate the effect of using a single dose of vaginal misoprostol (400 Microgram) one hour before abdominal myomectomy on intraoperative blood loss.

Materials and methods: This prospective randomized study was carried out postmenstrual upon 50 women with symptomatic uterine myoma who attended to Department of Obstetrics and Gynecology, Faculty of Medicine, Menoufia University during the period from October 2019 until October 2020. All subjects were divided into two equal groups: Misoprostol group included 25 women administered 400 mg misoprostol vaginally one hour before operation, and control group included 25 women underwent operation without misoprostol. Outcome variables included: intraoperative blood loss (ml), postoperative hemoglobin values, postoperative hematocrit values and operative time.

Results: there was statistically significant difference between the two studied groups according to amount of intraoperative blood loss (ml) as Misoprostol group showed less blood loss than control group [(308.0 ± 32.66 vs. 404.4 ± 87), with p = 0.001]. In addition, there was statistically significant difference between the two studied groups regarding operative time as Misoprostol group showed shorter duration than control group [(56.8 ± 3.12 vs. 78.6 ± 10.6), with p=0.001].

Conclusion: A single dose of preoperative vaginal misoprostol is an effective method for reducing blood loss and operative time during abdominal myomectomy operations.

Keywords: Abdominal myomectomy, Blood loss, Operative time, Uterine leiomyoma, Vaginal misoprostol.

INTRODUCTION

Leiomyomas are the most common benign tumors in women, which originate from myometrial smooth muscle cells. These tumors are estrogen-dependent and grow during the reproductive period. Leiomyomas are mostly asymptomatic, but become symptomatic in 20–50 % of affected cases, presenting with menorrhagia, pelvic pain or pressure, or urinary complaints [(1-3)].

The standard approach for treating leiomyomas is hysterectomy for women who do not want to have more children and myomectomy for those who want to preserve fertility [(4, 5)].

However, hemorrhage was one of the most common complications in cases underwent myomectomy. Literature showed that, about 20 % of the cases who underwent myomectomy needed blood transfusion [(6)].

Because hemorrhage is an important problem in myomectomies, methods have been developed to reduce hemorrhages. These methods include use of preoperative GnRH agonist, tourniquet methods, clamping of the bilateral uterine and/or ovarian artery and injection of intraoperative vasopressin into the myometrium [(7)]. As is well known, prostaglandins increase myometrial contractions and lead to a reduction in myometrial hemorrhage.

It has been shown that misoprostol, a PGE1 analogue, apparently reduces uterine artery blood flow when used in early pregnancies [(8)].

Misoprostol, which is employed in the induction of birth and abortus and the treatment and prevention of postpartum hemorrhages in obstetrics, may decrease intraoperative hemorrhage in myomectomies when hemorrhage constitutes an important problem [(9)]. This property of misoprostol can facilitate every surgical operation on myometrium, limiting blood loss to minimum. In recent years, misoprostol has been used for reducing bleeding during myomectomy. Misoprostol (prostaglandin E1 analogue) is used widely for cervical ripening, labor induction, postpartum hemorrhage and second trimester terminations. It could increase myometrial contraction and decrease hemorrhage [(10)].

In a previous study, **Celik and Sapmaz** [(11)] reported that a single dose of vaginal misoprostol before myomectomy reduced blood loss and the need for postoperative blood transfusion in women who underwent myomectomy.

The aim of the current study was to evaluate the effect of using a single dose of vaginal misoprostol (400 Microgram) one hour before abdominal myomectomy on intraoperative blood loss.

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PATIENTS AND METHODS

This prospective randomized study was carried out postmenstrual upon 50 women with symptomatic

uterine myoma who attended to Department of Obstetrics and Gynecology, Faculty of Medicine, Menoufia University during the period from October 2019 until October 2020.

Ethical consideration: After obtaining approval from the Local Ethics Committee, Faculty of Medicine, Menoufia University, women who agreed to participate gave their signed informed consent after explanation of the trial benefits and hazards. also, the confidentiality of the patient's data was guaranteed. All procedures were carried out in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The trial was registered with Local Ethics Committee of the Faculty of Medicine, Menoufia University. Patients included in this study were randomly divided into 2 equal groups as misoprostol group that included 25 women who were administered vaginal misoprostol 400 mcg one hour before abdominal myomectomy. Control group that included 25 women with myomas underwent myomectomy without administration of misoprostol.

Cytotec ® is a brand of misoprostol in the form of white tablets. Each tablet contains either 100 mcg or 200 mcg of misoprostol. Misoprostol (15-dexy-16-hydroxy-16-methyl PGE1) is a synthetic prostaglandin El analogue. The drug substance is a clear, colorless or yellowish oil that is practically insoluble in water. There are British pharmacopeia (BP), European (ph. Eur) and US pharmacopeia (USP) monographs for misoprostol.

Exclusion criteria:

Patients with any contraindications or allergy to misoprostol. Patients with medical disorders as history of hypertension, chronic endocrine or metabolic diseases such as diabetes, liver disease, angina or ischemic heart disease, cardiomyopathy, congestive heart failure, asthma, chronic obstructive pulmonary disease and dyslipidemia. Acute or recent vascular thrombosis, sickle cell anemia, patients on aspirin, patients on anti-diabetic drugs and severe anemia.

All participants were subjected to preoperative assessment including detailed history about age, obstetric history, fertility state, menstrual history and symptoms of the myoma like (pelvic pain, menorrhagia or pressure symptoms). Also, past history of any medical diseases or surgical operation. Any medication that has been taken before operation. Vital data (blood pressure, pulse, respiratory rate, temperature and body mass index). Transabdominal and transvaginal ultrasonographic assessments of the myoma size and site, presence of any ultrasonographically documented changes in the leiomyoma (e.g., calcification), and the size of the uterus. Laboratory workup included routine pre-operative complete blood count, liver functions, renal functions, fasting, post-prandial blood sugar, coagulation profile, blood group and Rh factor.

Outcomes: Intraoperative blood loss, postoperative hemoglobin, postoperative hematocrit and operative time.

Statistical Analysis

Our data were tabulated and analyzed statistically using microsoft excelo 2019 and SPSS v. 25 (SPSS Inc., Chicago, IL, USA)**.** Statistical analysis was done using descriptive and analytical tests. Descriptive included percentage (%), mean and standard deviation. Analytical included Chi-square (χ^2), Fischer exact test, student t test, Paired t-test and Mann-Whitney test. Considering P-value ≤ 0.05 is statistically significant.

RESULTS

In the current study, there was no statistically significant differences between the misoprostol group and controls regarding age ($p = 0.497$), gravidity ($p = 0.077$), parity ($p = 0.054$), number of abortions ($p = 0.768$), type of previous delivery ($p = 0.488$), body mass index ($p = 0.0997$) and diameter of myoma ($p=0.822$) as shown in Table (1).

Table (1): Clinical characteristic data of the two studied groups

	Misoprostol Group (n = 25)	Control Group (n = 25)	P Value
Age in years			
Range	30.0 – 40.0	30.0-48.0	0.497
Mean ± SD	32.88 ± 3.73	34.64 ± 4.10	
Gravidity			0.077
Mean ± SD	1.60 ± 1.04	2.32 ± 1.57	
Parity			0.054
Mean ± SD	1.0 ± 0.87	1.60 ± 1.04	
Number of abortions	**(N =8)**	**(N = 10)**	
Mean ± SD	1.75 ± 0.89	1.70 ± 1.06	0.768
Type of previous delivery			
No previous delivery	8(32%)	5(20%)	0.488
Normal vaginal	7(28%)	6(24%)	
Caesarean delivery	10(40%)	14(56%)	
BMI kg/m^2			
80 - <25	10(40%)	9(36%)	
25 - <30	8(32%)	7(28%)	0.0997
30 – 35	7(28%)	9(36%)	
Mean ± SD	25.60 ± 4.11	27.60 ± 4.30	
Diameter of myoma (cm):			
Mean ± SD	6.72 ± 1.06	6.64 ± 1.41	0.822

BMI: body mass index SD: stander deviation

As regards to intraoperative blood loss, there was statistically highly significant difference between the two studied groups, as misoprostol group showed less blood loss (308 ± 32.66 ml) comparing with control group (404 ± 87.18 ml), with p < 0.001 as shown in **Table (2).**

Table (2): Comparison between the two studied groups regarding the estimated amount of Intra-operative blood loss (ml).

Intra-operative blood loss (ml)	Misoprostol group (n=25)	Control Group (n=25)	U	P value
Mean ± SD	308.0 ± 32.66	404.4 ± 87.18	14.50*	<0.001*

U: Mann-Whitney SD: standard deviation *: significant

Also in this study, there was statistically significant difference between the two studied groups regarding operative time as misoprostol group showed significantly shorter duration of myomectomy (56.8 ± 3.12 min), as compared to control group (78.6 ± 10.6 min), with p = 0.001) as shown in table (3).

Table (3): Comparison between the two studied groups according to duration of myomectomy operation

Duration of myomectomy operation (min)	Misoprostol Group (n=25)	Control Group (n=25)	t	P
Mean ± SD	56.8 ± 3.12	78.6 ± 10.6	3.873*	0.001*

SD: standard deviation t: Student t-test *significant

Regarding hemoglobin and hematocrit concentrations pre- and post-operative among the studied groups. It was found that, misoprostol group had significantly increased hemoglobin (11.36 ± 0.59 gm/dL) than control group [(10.04 ± 0.35 gm/dL), (P < 0.001)]. While, Hb levels were improved post-operative (11.36 ± 0.59 qm/dL) than preoperative (11.0 - 13.0 qm/dL) but the difference was non-significant between them (P=0.055). Meanwhile in control group, hemoglobin level was statistically significantly decreased postoperative (10.04 ± 0.35 gm/dL) lower than preoperative (11.70 ± 0.52 gm/dL) with P < 0.001 as shown in table (4).

Regarding comparison between preoperative and postoperative hematocrit values in the two studied groups it was found that there was statistically significant difference in comparing postoperative hematocrit values between both studied groups. Misoprostol group showed significantly higher hematocrit levels (36.89 ± 2.66) as compared to control group [(32.60 ± 1.35), (P < 0.001)] as shown in table (4).

Table (4): Comparison between the two studied groups concerning hemoglobin and hematocrit concentration

	Misoprostol Group (n=25)	Control Group (n=25)	t	P value
Preoperative HB (gm/dL) Mean ± SD	0.77 ± 0.11	11.70 ± 0.12	0.447	0.636
Post-operative Hb (gm/dL) Mean ± SD	11.36 ± 0.59	10.04 ± 0.35	3.770	< 0.001*
#P value	0.055	< 0.001*		
Preoperative HCT (%) Mean ± SD	37.20 ± 2.60	37.73 ± 2.40	0.745	0.460
Post-operative HCT (%) Mean ±S D	36.89 ± 2.68	32.60 ± 1.35	2.996	< 0.001*
#P value	<0.001*	<0.001*		

Hb: hemoglobin HCT: hematocrit SD: standard deviation t: Student t-test # paired t test

DISCUSSION

Myomectomy performed open or with minimal invasive techniques (robotic/laparoscopic myomectomies) could be related with increased blood loss and need for blood transfusion. For this reason, different interventions have been developed to control heavy bleeding including peri-cervical mechanical tourniquet for uterine arteries, uterine artery ligation or embolization and chemical methods as GnRH agonists, vasopressin, ergometrine, oxytocin, dinoprostone and misoprostol [11, 12]. Misoprostol use for bleeding control during myomectomy is not widely used, but it seems to be easy to use and cost effective. Its cost is small compared to vasopressin and GnRH analogues. The mechanisms of action include uterine muscle contraction which leads to contraction of vascular structures and blood flow reduction as well as vasoconstrictive effect on uterine arteries [13].

The route of administration includes sublingual, oral, vaginal, and rectal route. Regarding the pharmacokinetics of misoprostol, after either oral or sublingual administration, the plasma concentration of misoprostol reaches its peak in less than 30 min, with a subsequent rapid decrease in blood concentration. As far as the vaginal administration, misoprostol reaches its peak in almost 1 h while the plasma concentration decreases progressively, even though it remains for at least 6 h at higher blood concentrations than when misoprostol is administered via sublingual or oral route [13]. Rectal route has a longer half-life than oral route [14].

Misoprostol use has several advantages including cost, and fewer side effects compared especially with the widely used GnRH agonists or vasopressin. Moreover, misoprostol can be administered even an hour preoperatively. The most common side effects include chills, nausea and vomiting, headache and vertigo, hypertension, abdominal pain and diarrhea, which are not associated with either the dosage or route of administration [14]. Therefore, one of the aims of this study was to clarify if there is clear evidence that misoprostol can reduce blood loss, need for blood transfusion, and postoperative morbidity during myomectomy.

Our study showed that, there was no statistically significant differences between misoprostol group and controls regarding age, gravidity, parity, number of abortions, type of previous delivery, body mass index and diameter of myoma. This agrees with **Rashed *et al.*** [15] who revealed that the comparison between the study and control groups did not show any statistically significant differences for socio-demographical data and preoperative clinical data (P > 0.05). Also, with **Celik and Sapmaz** [11] who found no statistically significant differences between both groups regarding age, parity, body mass index and uterine size in pregnancy weeks. Besides, **Mohamed *et al.*** [16] showed no statistically significant differences between both groups regarding the sociodemographic data, age, body mass index, occupation, marital status, special habits and parity.

The current study found high statistically significant low intraoperative blood loss among misoprostol group (308 ± 32.66 ml) than control group (404 ± 87.18 ml). This is consistent with **Rashed *et al.*** [15] who found that the amount of intraoperative blood loss was significantly lower in the study group where misoprostol led to reduction in blood loss by 122 ml. This also, agrees with the results reported by **Celik and Sapmaz** [11] who showed that misoprostol led to reduction in blood loss by 149 ml in the study group. In the same line, **Mohamed *et al.*** [16] found that, average blood loss in the control group was 815.5 ml and it was 461 ml in the study group. The amount of intraoperative blood loss in their study was significantly lower in the study group where

misoprostol led to reduction in blood loss by 354 ml. This also agrees with another study by **Kalogiannidis *et al.*** [17] in which the average blood loss was significantly higher in the placebo (control) group (217 ± 74 ml) versus misoprostol group (126 ± 41 ml). Moreover, another study by **Abdel-Hafeez *et al.*** [1] agrees with our results in which 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). Another study by **Niroomand *et al.*** [18] also is in accordance with our results where 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). On the contrary, one study by **Chai *et al.*** [19] showed that 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 differed from our study as regards the route of administration of misoprostol and the time between administration and beginning of the study.

This study demonstrated statistically significant difference between the two studied groups regarding operative time as misoprostol group showed significantly shorter duration of myomectomy (56.8 ± 3.12 min) than control group (78.6 ± 10.6 min). In accordance with this, **Mohamed *et al.*** [16] revealed that the operative time was significantly shorter in the study group (71 ± 11.3 min) vs. (87 ± 21.2 min) in control group because of the decrease in the blood loss and better surgical field. In addition, these results agree with the results reported by **Celik and Spamaz** [10], in which operative time was decreased by 10 min in study group than in control group. Another study by **Abdel-Hafeez *et al.*** [1] 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).

Regarding hemoglobin and hematocrit concentrations pre-and post-operative among the studied groups, our study found that misoprostol group had significantly increase in hemoglobin and hematocrit levels (11.36 ± 0.59 gm/dL and 36.89 ± 2.66%) than control group (10.04 ± 0.35 gm/dL and 32.60 ± 1.35%) postoperative. While, there was no significant difference between the two groups regarding Hb and HCL pre-operative. This is compatible with **Rashed** [15] as the laboratory parameters, preoperative hemoglobin and hematocrit values showed no statistically significant differences between both groups. While, postoperative hemoglobin and hematocrit values were significantly higher in the study group. This confirms the effect of misoprostol in reducing blood loss duringmyomectomy, and the differences between hemoglobin and hematocrit values from the pre to the post-operative status were significantly lower in the study group. Our findings are harmonious with those reported by **Mohamed *et al.*** [16] who 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 ± 0.5 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 agree with that reported by **Celik and Spamaz** [10] who 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 gm/dl). This also agrees with the study reported by **Kalogiannidis *et al.*** [17] who found that the decline of postoperative Hb was significantly higher in control group (1.6 ± 0.43 g/dl) compared to misoprostol group (1 ± 0.33 g/dL). In addition, the study by **Shokeir *et al.*** [20] supports our results as they found that the control group had a significant decrease in Hb level 24 h after operation compared with the dinoprostone group. Similarly, the study by **Biswas *et al.*** [21] stated that the postoperative drop in hemoglobin was smaller in the misoprostol group (1.1 g/dl) than in the placebo group (1.9 g/dl). Our findings are contradictory with those reported by **Chai *et al.*** [19] who stated that there were no observed differences in the change in hemoglobin level after the operation between misoprostol and placebo group.

CONCLUSION

From our results, it was found that a single dose of 400 mcg vagina misoprostol one hour before abdominal myomectomy could significantly decreases intraoperative estimated blood loss, operating time, reduces postoperative hemoglobin decrease and so decreases the need for postoperative blood transfusion.

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