Intravaginal misoprostol reduces intraoperative blood loss in minimally invasive myomectomy: a randomized clinical trial

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Summary

Purpose of investigation: We performed a randomized clinical trial to estimate whether preoperative use of misoprostol may reduce intraoperative blood loss of patients treated by minimally invasive surgery (MIS), such as laparoscopic (LM) or laparoscopically assisted myomectomy (LAM). *Methods:* Sixty-seven menstruating patients with three or less myomas of a maximum diameter of 90 mm, scheduled for MIS, 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 (I) and 34 in the placebo group (II). Estimated blood loss (EBL), decline of postoperative hemoglobin (Hb) and side-effects of administered agent were the outcomes of main interest. *Results:* The EBL was significantly higher in the placebo versus misoprostol group (217 ± 74 vs 126 ± 41, respectively). Similarly, the decline of postoperative Hb was significantly higher in group II (1.6 ± 0.43) compared to group I (1 ± 0.33). The operative time was comparable in both groups, while the rate of side-effects was similar between groups. *Conclusion:* The preoperative use of misoprostol in patients with uterine fibroids managed by minimally invasive surgery significantly reduces intraoperative blood loss. Misoprostol might be useful for the prevention of postoperative anemia in more extended minimal invasive interventions, such as myomectomy of large fibroids or laparoscopic hysterectomy.

Key words: Laparoscopy; Myomectomy; Misoprostol; Prostaglandin E1.

Introduction

Fibroids are the most common benign tumors of the uterus. It was estimated that almost 20% of the females will be diagnosed with uterine fibroids or myomas during their lives [1]. Abnormal uterine bleeding is the principal symptom of uterine fibroids, while the severity of this symptom depends on the location, the number and the size of the myomas. Historically, abdominal or vaginal hysterectomy was the standard treatment. Although, less radical surgical approaches were introduced thereafter in the management of fibroids, offering a conservative approach in cases of women wanting to preserve their fertility, the problem of intraoperative blood loss exists [2-4].

Misoprostol or prostaglandin E1 (PGE1), which was introduced as an agent with gastro-protective properties, was widely used in obstetrics for early abortion, early pregnancy failure, termination of second trimester-pregnancy, labor induction and uterine atony in case of postpartum hemorrhage (PPH) [5, 6]. Additionally, PGE1 has been used successfully in gynecology for cervical ripening before operative hysteroscopy, as well as to reduce intraoperative blood loss in patients with uterine fibroids treated with classical abdominal myomectomy [7].

The aim of the present study was to evaluate intraoperative blood loss in patients with uterine myomas, managed by minimally invasive surgery such as laparoscopic myomectomy (LM) or laparoscopically assisted myomectomy (LAM), after a single dose of intravaginal misoprostol or placebo which were administered preoperatively.

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Materials and Methods

A prospective, randomized study was performed among women scheduled and operated from February 2007 to February 2009 by minimally invasive surgery LM or LAM. Techniques of the former surgical approaches have been described in a previous report [4]. The population was randomly allocated in two groups: Group I received misoprostol intravaginally one hour before surgery, while Group II received placebo intravaginally at the same time. The same surgeon was involved in every type of myomectomy. The Institutional Review Board approved the study, and informed consent was given by all patients.

Inclusion criteria were menstruating women aged ≤ 45 years old, with three or less myomas of diameter ranging between 30 mm and 90 mm. Patients with cervical or endometrial pathology (pathologic PAP smear, hyperplasia with or without atypia, respectively), as well as with adnexal masses were excluded from the study. Preoperative ultrasonographic evaluation of the number and location of the myomas were routinely performed in all patients one month earlier and the day of the surgery.

For the purpose of the study the patients were randomly assigned to receive either a single intravaginal dose of misoprostol 400 mcg (Cytotec 200 mcg, Pfizer) (group I) or placebo (appearance of the placebo was similar to the active drug) (group II), using the SNOSE (sequentially numbered opaque sealed envelopes) system [8]. The randomization using closed and numbered envelops with PGE1 or placebo was prepared before the beginning of the study. Neither the patient nor the medical and paramedical staff involved in the surgery were aware of patient assignments A physician blinded to the results of the study surveyed the patients postoperatively. The randomization assignment was revealed when the study was completed and all the data were collected.

Patient characteristics of the two study groups such as mean age ± standard deviation (SD), body mass index (BMI; kg/m^2) and parity (nulliparous or multiparous) were calculated. The number and mean diameter of the myomas (± SD), the indica-

tions of the operation, and history of previous abdominal surgery were collected as well. Concerning the indications for the operation three subgroups of patients were created such as infertility, abnormal uterine bleeding, and rapidly growing myoma (duplication of the maximum diameter of myoma during the last six months). Patient characteristics are shown in Table 1.

The preoperative and postoperative values of Hb (mean ± SD; g/dl) for both groups of the study and the decline of Hb were estimated. The estimated blood loss (EBL; ml) was also evaluated and expressed as the volume difference between the irrigated and aspirated liquid from the peritoneal cavity during the operation (no gauze was used). Additionally, postoperative anemia, the need for blood transfusion and duration of the operation were analyzed. Side-effects related to pharmaceutical agents used in the study such as vomiting, chills, diarrhea, and fever were estimated postoperatively and during the hospitalization by a patient survey. Postoperative anemia was defined as the postoperative value of Hb of less than 8 g/dl or the decline between preoperative and postoperative Hb value of 4 g/dl. Fever was considered as the body temperature of more than 38°C in two consecutive measurements at least six hours apart postoperatively.

Statistical analysis

Performing a pilot study prior to the randomization, a difference of 0.5 (g/dl) of decline of Hb was found in five patients per group. The power analysis followed showed that a sample size of 25 patients per arm was needed to obtain a statistically significant result with power equal to 90%. The Student's t-test used for variables with continuous outcomes to compare the mean values of the different variables of the two study groups, while the chi-square and Fisher's exact test analysis were used to compare cross-tabulated data. All p values are 2-sided, while differences between groups were considered statistically significant at $p < .05$. Statistical analysis was performed by using the Statistical Package for Social Science version 15.0 (SPSS Inc., Chicago, IL).

Results

Sixty-seven patients were enrolled in the study. Three of these refused to participate in randomization. A total of 64 patients were thus included in the final analysis: 30 patients in group I (misoprostol group) and 34 patients in group II (placebo group). A flow chart of inclusion and randomization of patients treated is shown in Figure 1.

Patient characteristics are presented in Table 1. Patient age, BMI, parity, the mean number and diameter of myomas, and indications for the operation were similar between the two study groups. The rate of previous abdominal surgery was not significantly different between the two groups (Table 1).

The preoperative value of Hb (mean ± SD) was similar between group I and II (12.7 ± 11 vs 12.6 ± 0.8, respectively), while the postoperative value of Hb was significantly higher in the misoprostol group (11.6 ± 1.1) compared to the placebo group (11 ± 0.6). The decline of Hb between the preoperative and postoperative values (group I; 1 ± 0.33 vs group II; 1.6 ± 0.43, $p < .0001$), as well as the EBL (group I; 126 ± 41 vs group II; 217 ± 74, $p < .0001$) was significantly higher in the placebo group compared to the misoprostol group. No need for blood transfusion was necessary for either group. Duration of the operation did not differ between group I and II of the study (86 ± 23 vs 77 ± 20 min, respectively). The rate of side-effects related to the administered agents was not significantly different between the two groups (Table 2).

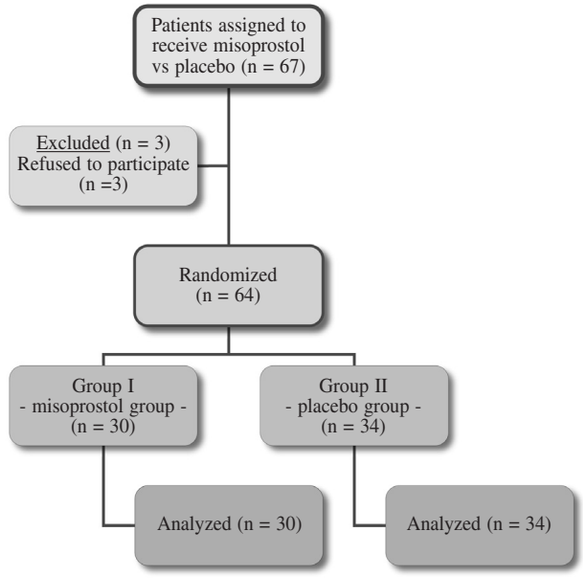

Figure 1. — Flow chart of the inclusion criteria and randomization of the study patients.

In the placebo group, a case of postoperative fever was observed without any signs of systematic or wound infection, which retired within 24 hours from the operation. Vomiting, chills and diarrhea were not observed in the present data.

Discussion

This study has demonstrated that preoperative intravaginal administration of 400 mcg of misoprostol (PGE1) compared to placebo in patients with uterine myomas managed by minimally invasive myomectomy significantly reduced intraoperative blood loss and the perioperative decline of Hb.

Myomectomy was first introduced in 1931 and was considered as a surgical approach with high perioperative morbidity [9]. Since then the technique has improved and today myomectomy via the abdomen or laparoscopy constitutes the standard care of women who desire to preserve their fertility. However, intraoperative blood loss during the enucleation of myomas remains a principal problem for every surgical technique. Mechanical and pharmaceutical methods have been introduced to reduce blood loss during myomectomy, especially those of large volume [10]. A tourniquet was used for mechanical vascular occlusion of the uterine and ovarian vessels [10, 11]. Vasoconstrictive agents such as vasopressin (antidiuretic hormone) and pitressin (synthetic vasopressin)

Table 1. — *Patient characteristics of the two study groups*.

Characteristics	Group I (n = 30)	Group II (n = 34)	*p* value
Age (years; mean ± SD)	37.2 ± 6.5	34.8 ± 4.6	ns
> 35 years, n (%)	15 (50)	14 (41.2)	
BMI (kg/m^2; mean ± SD)	24 ± 4	25 ± 4.8	ns
Parity			
Nulliparous, n (%)	21 (70)	24 (71)	ns
Multiparous, n (%)	9 (30)	10 (29)	
Number of myomas (mean ± SD)	1.5 ± 0.7	1.4 ± 0.6	ns
Mean diameter of the myomas (mm; mean ± SD)	50 ± 16	52 ± 18	ns
Indication for operation, n (%)			
Infertility	16 (53)	19 (55)	ns
Abnormal uterine bleeding	8 (27)	13 (39)	
Rapid myoma growth	6 (20)	2 (6)	
Previous abdominal operation, n (%)	5 (17)	9 (26)	ns

BMI = body mass index, SD = standard deviation, NS = non significant, group I = misoprostol group, group II = placebo group.

Table 2. — *Peroperative outcomes of the two study groups*.

Characteristics	Group I (n = 30)	Group II (n = 34)	*p* value
Decline of Hb* (mean ± SD; g/dl)	1 ± 0.33	1.6 ± 0.43	< .0001
Preoperative Hb	12.7 ± 1	12.6 ± 0.8	ns
Postoperative Hb	11.6 ± 1.1	11 ± 0.6	.02
EBL (mean ± SD)	126 ± 41	217 ± 74	< .0001
Postoperative anemia	0	0	ns
Blood transfusion	0	0	ns
Duration of the operation	86 ± 23	77 ± 20	ns
Rate of side-effects, n (%)	0	1 (3)	ns
Vomiting	0	0	
Chills	0	0	
Diarrhea	0	0	
Fever	0	1	

Hb = hemoglobin, EBL = estimated blood loss, SD = standard deviation, group I = misoprostol group, group II = placebo group, * decline of Hb between pre- and postoperative values.

were also used successfully to reduce perioperative blood loss, constricting the smooth muscles of small vessels of the myometrium [10-12]. Ginsburg *et al*. in a prospective randomized study showed no difference in blood loss and need of postoperative transfusion when pharmaceutical vasoconstriction or mechanical occlusion in cases of uterine fibroids treated by myomectomy were used [10]. Others showed less operative blood loss intraoperatively when vasopressin was used during myomectomy compared to a mechanical tourniquet [11]. However, vasopressin is a drug with significant complications and high economical cost [13]. Severe hypotension and cardiopulmonary complications such as pulmonary edema, bradycardia and cardiac arrest have been published in gynecology, especially after intramyometrial injection in patients with uterine fibroids treated by myomectomy [14, 15]. Misoprostol, because of its uterotonic and vasoconstrictive effect, is used in obstetrical practice and is widely accepted because of its low cost and acceptable rate of side-effects [5, 6, 16]. Furthermore, it has been used in gynecology for cervical ripening before operative hysteroscopy [17]. Recently a placebo-controlled randomized prospective study investigated the effectiveness of preoperative use of misoprostol (n = 13) versus placebo (n = 12) in patients with uterine fibroids managed by abdominal myomectomy [7]. The authors concluded that PGE1 is a reliable method to reduce intraoperative hemorrhage and postoperative need for blood transfusion. The postoperative Hb in a group of patients with vaginal administration of PGE1 was significantly higher compared to the placebo group. Our data showed similar results of decline of Hb between preoperative and postoperative values. Furthermore, the EBL in the present study was significantly higher in the placebo group, which is in accordance with the previous report [7], although the figures of blood loss in the published report by Celik and Sapmaz (misoprostol group, 472 ± 77 ml vs placebo group, 621 ± 121 ml) were higher compared to our results (126 ± 41 ml vs 217 ± 74 ml, respectively). This could be due to the different surgical approach between the two studies (abdominal myomectomy in the published report vs minimally invasive surgery in the present trial). Previous reports confirmed that minimally invasive myomectomy is a less hemorrhagic procedure compared to myomectomy by laparotomy or minilaparotomy [18, 19].

Cramping, chills, fever and vomiting are the most common side-effects reported after the use of misoprostol, with nausea and diarrhea occurring less often [20]. These symptoms are often resolved during the first 24 hours. These side-effects were not different between the compared groups in the present study. We observed only one case of fever postoperatively in the placebo group, while no case of chills, vomiting, or diarrhea were observed in either group. It is already known from obstetrical practice, that side-effects are observed mainly during the first two hours after the oral or vaginal administration of PGE1 [21]. In surgical gynecology it is obvious that side-effects such as cramping, chills and vomiting can not be clearly observed because of the effect of general anesthesia.

Conclusion

The present study demonstrated that a single dose of intravaginal misoprostol is effective in reducing intraoperative hemorrhage and postoperative decline of Hb in patients with uterine fibroids managed with LM or LAM. Misoprostol might be further useful in more extended surgical approaches such as myomectomy of large fibroids or in laparoscopic hysterectomy. Prospective clinical studies are needed to confirm the alleviation of postoperative anemia by use of misoprostol in such operations.

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