

# The Use of Single Versus Double Dose of Intra-vaginal Prostaglandin E<sub>2</sub> "Misoprostol" prior to Abdominal Myomectomy: A Randomized Controlled Clinical Trial

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## Abstract

**Background:** The study aimed to investigate the effectiveness of a single versus double dose of prostaglandin E<sub>2</sub> "misoprostol, 400 microgram" prior to myomectomy for multiple uterine fibroids.

**Methods:** This was a prospective randomized controlled trial comprised of 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 2 doses, 3 and 1 hr prior to surgery (group B, 35 cases). Operation time, intra and post-operative blood loss, hemoglobin concentration, blood pressure and body's temperature were estimated and compared in both groups. The data were statistically analyzed using chi-square test. The  $p < 0.05$  was considered significant.

**Results:** In group B, the mean operative time was significantly ( $p < 0.001$ ) shorter than in group A ( $25.8 \pm 4.14$  vs.  $35.4 \pm 5.6$  min respectively). The mean value for operative blood loss was significantly ( $p < 0.001$ ) smaller in group B ( $101.4 \pm 25.5$  vs.  $200.16 \pm 18.8$  ml). There was a significant ( $p < 0.01$ ) rise of the body temperature in group B ( $38.5 \pm 0.7$  vs.  $37.18 \pm 0.84$  °C). There were no differences between the two groups regarding hemoglobin levels, post-operative febrile morbidity or length of hospital stay.

**Conclusion:** In this study, two doses of pre-operative intra-vaginal misoprostol were more effective than one dose in reducing intra and post-operative blood loss and shortening of operation time during abdominal myomectomy.

**Keywords:** Abdominal myomectomy, Double dose, Misoprostol.

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## Introduction

Uterine leiomyomas are the most common benign tumors among women. Although most of them are asymptomatic, 20% to 50% of them cause menorrhagia, pelvic pain or pressure, colorectal and or urinary complaints (1). Uterine leiomyomas are essentially the most frequent indication for abdominal hysterectomy (2). Fertility-preserving operations such as myomectomies have become more imperative because older women are willing to have children, the use of

assisted reproductive techniques has increased, and the incidences of dyspareunia and sexual dysfunction following hysterectomy have also escalated (3).

Myomectomy can be accomplished by laparotomy, laparoscopy or hysteroscopy. Substantial blood loss associated with the dissection of huge fibroids renders myomectomy a more technically challenging procedure. It was reported in abdominal myomectomy that up to 20% of patients

need blood transfusion and up to 2% might need hysterectomy (4). Number of interventions have been introduced to reduce bleeding during myomectomy. Despite these actions, prevention of excessive hemorrhage during myomectomy remains a major task for surgeons (5-8).

It is well known that prostaglandins such as misoprostol prostaglandin E<sub>2</sub> analog, not only increases myometrial contractions but also reduces uterine artery blood flow and may decrease intra-operative hemorrhage in myomectomies (9). In this prospective randomized controlled trial, an attempt was made to examine the effectiveness of two doses of pre-operative vaginal misoprostol for reduction of blood loss and the operative time during abdominal myomectomy.

### Methods

This study comprised of 69 patients among those attending the gynecology outpatient clinic at Mansoura University Hospital during the period from January 2011 to January 2013 (Clinical Trials.gov Identifier: NCT02154932). All patients had multiple symptomatic uterine fibroids (abnormal vaginal bleeding, dull aching lower abdominal pain and pelvic heaviness, subfertility or recurrent abortion) and were scheduled for abdominal myomectomy according to the hospital guidelines. The excluded patients were the ones who had hypertension, cardiac and pulmonary disease, chronic endocrine or metabolic diseases such as diabetes, obesity (body mass index >30 kg/m<sup>2</sup>), all cases of single myoma and those known to be allergic to prostaglandin preparations. None of the patients had received pre-operative hormonal therapy (such as a GnRH analogue or oral contraceptive pills) that could affect intra-operative bleeding or the duration of operation. The protocol of this study was approved by the Departmental Ethics Committee. All participants were provided with patient information sheet and were counseled before being considered eligible for inclusion in the study and a written consent was obtained from each participant.

All patients were randomly allocated into two treatment groups using a computer-generated random table in sealed envelopes. Group A included 34 cases and received 400 microgram prostaglandin E<sub>2</sub> analog, misoprostol, (Misotac<sup>®</sup>, 200 microgram, by SIGMA pharmaceutical industries, Alexandria, Egypt), intra-vaginally, 1 hr before operation. Group B included 35 cases received 800 microgram prostaglandin E<sub>2</sub> analog intra-

vaginally in two doses, 3 and 1 hr before surgery. The tablets were mixed with lubricant gel and inserted in the posterior fornix and the patient was asked to rest in bed for at least 1 hour after insertion. Abdominal myomectomy was performed according to the standard technique through transverse lower abdominal incisions in all patients by consultant level without use of intra-operative tourniquet. Blood loss during and after surgery was estimated by suction and towel collection and weighing.

The outcome measures in both groups included the operative time, intra and post-operative blood loss, post-operative hemoglobin concentration, intra and post-operative blood pressure and body temperature over the post-operative 7 days.

**Statistical analysis:** The data obtained from this study were statistically analyzed using SPSS software (SPSS 11 Inc., Zonguldak Karaelmas University, Zonguldak, Turkey) and using chi-square test to compare differences in rates and student t-test to compare means and standard deviations. The p<0.05 was considered significant.

### Results

Table 1 for patients' characteristics showed no statistically significant differences between both groups. Menorrhagia was the main presenting symptom for both groups (22/34, 64.7%, in group A and 24/35, 68.6%, in group B). All patients had multiple uterine fibroids in different locations of

**Table 1.** Patients' demographic criteria in the myomectomy study groups (single vs. double pre-operative intra-vaginal prostaglandin E<sub>2</sub> dose)

| Variables                                | Group A    | Group B    |
|--|------------|------------|
| Age (year)                               | 29.83±7.07 | 30.08±9.89 |
| Gravidity                                | 1.83±2.12  | 1.90±2.82  |
| Parity                                   | 1.51±2.12  | 1.41±1.28  |
| <b>Main complaint (number of cases)</b>  |            |            |
| Menorrhagia                              | 22         | 24         |
| Mass                                     | 5          | 5          |
| Recurrent abortion                       | 4          | 4          |
| Infertility                              | 3          | 2          |
| Total                                    | 34         | 35         |
| <b>Type of fibroid (number of cases)</b> |            |            |
| Sub-mucous                               | 20         | 19         |
| Combined                                 | 14         | 16         |
| Total                                    | 34         | 35         |
| <b>Number of fibroid</b>                 | 2.91±4.24  | 3.33±4.2   |
| <b>Size of the uterus in weeks</b>       | 15.33±8.48 | 13.14±5.65 |

Data shown as mean±SD

**Table 2.** Patients characteristics, blood loss, operative time, pre- and post-operative hemoglobin, and length of hospital stay after myomectomy in the study groups (single vs. double pre-operative intra-vaginal prostaglandin E<sub>2</sub> dose)

| Variables   | Group A<br>(single dose) (n=24) | Group B<br>(double dose) (n=24) |
|---|---------------------------------|---------------------------------|
| <b>HB (M±SD)</b>                                      |                                 |                                 |
| Pre-operative   | 10.9±1.06                       | 11.08±0.9                       |
| Post-operative  | 10.2±1.4                        | 10.35±0.7                       |
| <b>Mean blood loss (M±SD)</b>                         | 200.16±18.8 <sup>a</sup>        | 101.4±25.5 <sup>a</sup>         |
| <b>Need for blood transfusion</b>                     | no need                         | no need                         |
| <b>Mean intra-operative blood pressure S/D (M±SD)</b> | 114.16±7.07/ 73.3±21.23         | 114.13±14.14/ 72.58±21.25       |
| <b>Mean time of the operation in minutes (M±SD)</b>   | 35.4±5.6 <sup>a</sup>           | 25.8±4.14 <sup>a</sup>          |
| <b>Mean body temperature (M±SD)</b>                   | 37.18±0.84 <sup>b</sup>         | 38.5±0.7 <sup>b</sup>           |
| <b>Length of Hospital stay (hr)</b>                   | 48                              | 48                              |

Data shown as mean±SD; a: p<0.001; b: p<0.01

the uterus (submucous, intramural and subserous).

In group B, the mean operative time was significantly (p<0.001) shorter than group A (25.8±4.14 vs. 35.4±5.6 min respectively). 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). There was a significant (p<0.01) rise of body temperature in group B (38.5±0.7 vs. 37.18±0.84 °C). There were no differences between the two groups regarding hemoglobin levels, post-operative febrile morbidity or hospital stay (Table 2).

### Discussion

There are different procedures to minimize blood loss during myomectomy for uterine fibroids. Three categories of interventions can be identified (a) interventions on uterine arteries such as laparoscopic uterine artery ligation, uterine artery embolization, pericervical mechanical tourniquet for uterine arteries and hormonal tourniquets such as vasopressin; (b) uterotonics such as ergometrine, oxytocin, misoprostol and sulprostone and (c) myoma dissection techniques which include the use of laser, electrosurgery and chemical dissectors such as sodium-2-mercaptoethanesulfonate (Mesna) (5-10). Kongnyuy et al. (2008) identified 8 well designed randomized trials that have assessed the effect of each intervention on blood loss. The largest effect on blood loss during myomectomy was recorded by the study that combined the occlusion of the uterine arteries and ovarian arteries using tourniquets prior to myoma enucleation (11).

Medical agents are always an attractive option. Significant reduction of intra-operative blood loss

was noted when vasopressin was injected into the uterine muscles overlying the myomas. Vasopressin is costly and can cause temporary increase in blood pressure, pulmonary edema, myocardial infarction and life-threatening hypotension, all can limit its routine use (12, 13). The injection of bupivacaine plus epinephrine into the myometrium overlying the myoma was also evaluated in one study and the result showed evidence of reduction in blood loss (14). Some trials on oxytocin showed no evidence of its effect on blood loss during myomectomy and this is consistent with other evidence that the myometrial concentration of oxytocin receptors is very low in non-pregnant uteri (15). GnRH analogues have been used prior to myomectomy and there is clear evidence that their use reduces uterine volume and fibroid size and reduces blood loss and operating time during myomectomy (16, 17).

Misoprostol acts by one of two mechanisms to reduce blood loss in the uterus. First, it increases myometrial contractions (18) and affects the vascular structures which stem from both uterine artery and utero-ovarian anastomosis and blood flow is reduced. The second mechanism may be the direct vasoconstrictive impact on uterine arteries (19). Misoprostol seems to have many advantages in this respect. Misoprostol, both in single or double doses, is not expensive which is a crucial factor in low resource settings for the choice of medicines. In this study, it was demonstrated that two pre-operative doses of misoprostol, 400 microgram each, resulted in a statistically significant reduction in operative time and intra-operative blood loss and consequently no need for post-operative blood transfusion when

compared to a single dose use. These results were consistent with the one found by Husnu and Ekrem but they used a single dose "400 microgram", one hour before operation while in this study single or double dose regimen was used (20).

Misoprostol works rapidly. Therefore it can be administered an hour before the operation and significantly reduces intra-operative blood loss. This in fact is due to absorption kinetics studies which indicate that 400  $\mu\text{g}$  microgram of vaginal misoprostol reaches its peak concentration in the plasma approximately 60 *min* after it is administered and remains at levels close to this peak concentration for at least 60 *min* (21). In this study, we have used 2 doses pre-operatively, versus a single dose to reduce blood loss in myomectomies where uterine congestion is excessive and abrupt bleeding is threatening the operation.

It was reported that the most common side effects after administration of 400  $\mu\text{g}$  of vaginal or oral misoprostol were chills, nausea and vomiting, headache and vertigo, abdominal pain and diarrhea (22). In this study, however, despite the elevated body temperature above normal in double versus single dose (mean body temperature:  $38.5 \pm 0.7$  and  $37.18 \pm 0.8$  respectively and  $p < 0.005$ ), this rising did not increase during few hours and was not associated with serious systemic side effects.

### Conclusion

Despite the small number of patients included in this study, it clearly showed that the use of intra-vaginal prostaglandin  $\text{E}_2$  "misoprostol" was easy and it was an inexpensive method to reduce blood loss during abdominal myomectomy. Doubling the dose rendered more reduction of intra operative blood loss and made the procedure less time consuming.

### Conflict of Interest

The authors state that there is no conflict of interest.

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