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Preoperative Sublingual Misoprostol in Reducing Intraoperative Blood Loss During Abdominal Hysterectomy

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ABSTRACT

Objective: To study the effectiveness of a pre-operative single dose sublingual misoprostol for reducing blood loss of abdominal hysterectomy with/without salpingo-oophorectomy performed for symptomatic uterine leiomyomas.

Materials and methods: A total of 70 women undergone total abdominal hysterectomy with/without salpingo-oophorectomy for symptomatic uterine leiomyoma between June 2012 to January 2013 was double-blindly randomized into two groups to receive two tablets of misoprostol (200 microgram each) sublingual (n= 35) or two placebo tablets vitamin B6 (100 milligram each) sublingual (n=35) at 30-60 minutes before the operation. The amount of intra-operative blood loss, the change in haemoglobin level after the operation, the requirement for blood transfusion and the incidence of side effects were recorded.

Result: Our data showed no significant difference between two groups in term of intraoperative blood loss. (misoprostol, mean 549.6 ± 391.9 ml versus placebo, mean 445.0 ± 270.6 ml, p=0.20) Moreover there were no observed differences in the need for postoperative blood transfusion, the change in hemoglobin level after the operation and side effects profiles between the two groups.

Conclusion: We concluded that a single preoperative dose of sublingual misoprostol is not effective in reducing intraoperative blood loss and need for post-operative blood transfusion after total abdominal hysterectomy with/without salpingo-oophorectomy for symptomatic uterine leiomyomas.

Key words: Sublingual misoprostol, Hysterectomy, Intraoperative blood loss, Uterine leiomyomas

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Introduction

Leiomyomas are an one of the most common benign genecologic pelvic tumor that are present in the uterus of both premenopausal and postmenopausal women[1, 2]. Previous report shown the 20–50% of women with one leiomyoma or more will experience symptoms that can be directly attributed to the leiomyoma(s). There are quite variable symptom that associated with uterine leiomyomas such as abnormal uterine bleeding, pelvic pain or pressure, reduced capacity of the urinary bladder, constipation, and reproductive dysfunction[3, 4]. The treatment spectrum includes an expectant management, medical treatment[4], surgical interventions, uterine artery embolization or ablative techniques. Therefore, the expectant observation and follow-up are often recommended for these asymptomatic leiomyomas. Medical and conservative surgery such as myomectomy are options for women with symptomatic leiomyomas and consider fertility preservation[5] with recurrent rate of 15%[6]. Total abdominal hysterectomy (TAH) is the definitive treatment for large or, symptomatic leiomyoma. However TAH might be associated with significant morbidities especially the huge intraoperative blood loss which may require blood transfusion[7]. Previous studies have been reported the technique to reduce the operative blood loss during TAH for example injected the GnRH agonist for a few months before the operation to shrink the size, intraoperative uterine artery ligation, as well as giving uterotonic agents such as misoprostol and oxytoxin 1 or 2 hours before the operation[4].

Misoprostol is a prostaglandin E1 analog which is economical and stable in room temperature[8]. This medication can be administered orally, rectally or sublingually[9]. It have been showed that the pharmacokinetic in pregnancy and nonpregnancy were not difference[10, 11]. Also a recent pharmacokinetic study has shown that sublingual administration of misoprostol has maximum systemic bioavailability and achieves highest serum peak concentration as compared to either the oral or vaginal route of administration[12]. Interestingly sublingual administration avoids the first pass effect seen with oral route and inconvenience of vaginal and rectal administration. It have been demonstrated that misoprostol stimulates uterine contractions and increases in myometrial contraction which leads to increase uterine artery resistance and reduce blood flow to leiomyomas[13].

As misoprostol can stimulate uterine contraction and reduce uterine blood flow, here we hypothesized that pre-operative misoprostol may redistribute the blood from the diseased uterus back to the circulation. We conducted this study to test the effect of misoprostol can reduce operative blood loss during total abdominal hysterectomy.

Materials and Methods

This randomized controlled study was conducted at the Department of Obstetrics and Gynaecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. The study was approved by the Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects. All women requiring total abdominal hysterectomy with/without bilateral salpingo-oophorectomy for symptomatic uterine leiomyomas were invited to participate in the study and signed the informed consent forms.

Women with symptomatic leiomyomas in out patients gynaecologic clinic indicated for total abdominal hysterectomy such as hypermenorrhea menorrhagia and pressure symptom were included in our study. All of the medical history was reviewed and clinical examinations and pelvic examination were recorded by the gynaecologists. We recruited symptomatic women planned for receiving total abdominal hysterectomy after counseling about available alternative treatments. The patient who have any contraindications to misoprostol, mitral valve stenosis, glaucoma, diastolic pressure over 100 mmHg, severe asthma or known allergy to prostaglandin, tissue pathology showed malignancy and unwilling to participate in the trial were excluded.

After recruitment all of patients were randomized by computer into two groups. Women in the study group (group 1) were received a pre-prepared sealed

opaque package containing two tablets of misoprostol, 200 microgram misoprostol (Cytotec®) tablet, which were applied sublingually 30-60 minutes before the operation. Those women in the control group (group 2) had two placebo tablets (vitamin B6, 100 milligram each) in similar package sealed opaque. The placebo tablets were similar to the misoprostol tablets in size, shape, and color. The investigators, the patients and surgeons were blinded.

We recorded the blood pressure, pulse rate and temperature and the any side effects of medication at the time of admission, and immediately before induction of anesthesia. Total abdominal hysterectomy ± bilateral salpingo-oophorectomy was performed in the usual manner by the gynecologists. Therefore the amount of intraoperative blood loss was calculated by determine the difference in weight cloths and pads used to absorb blood during operation (100 gram increase in cloth and pad weight was considered equivalent to 100 ml of blood[14]) and blood loss from collected blood in suction bottles. The duration of surgery from skin incision to skin closure was noted. Serum hemoglobin levels were determined both 20 hours before and 24 hours after the surgery. Side effects of drugs were evaluated at 6 and 12 hours after the operation such as pyrexia, nausea, vomiting and headache. Any intra-operative and post-operative transfusions were recorded. The primary outcome measure was the amount of intra-operative blood loss calculated. The secondary outcome measures included the changes in hemoglobin level after the operation, the requirement for blood transfusion and the incidence of the side effects in the two groups. Statistical analysis was performed using SPSS version 18 (IBM Company, IL, USA). Differences in continuous variables were analyzed with t-test. Differences in dichotomous variable were analyzed by chi-square test. Also for the small samples size variable was analyzed with Fisher's exact test. The sample sized was calculated to identified the difference of intraoperative blood loss of 150 milliliter with power of 0.8 and significant level of P-value 0.05.The sample size was arbitrarily defined as 70, with 35 patients in each group.

Results

A total of 70 subjects were recruited. 35 women were allocated to the misoprostol (study) group and 35 women allocated to the placebo (control) group. These were no excluded cases in both groups. The baseline demographics and clinical data and characteristics data of the two groups were similar in age, BMI, history of previous pelvic surgery, uterine weight and preoperative Hb level (Table 1).

Table 1. Demographics and characteristics of the cases

Characteristics	Misoprostol (n= 35)	Placebo (n = 35)	P
Age* (yrs)	44.8 ± 5.6	44.8 ± 4.6	0.43 [a]
BMI* (kg/m^2)	24.4 ± 4.6	25.7 ± 5.7	0.14 [a]
Previous pelvic surgery** (%)	16 (45.7)	13 (37.1)	0.47 [b]
Uterine weight* (g)	583.6 ± 270.3	566.3 ± 263.6	0.68 [a]
Preoperative Hb level* (g/dl)	12.0 ± 1.3	11.5 ± 1.2	0.78 [a]

* Data were mean ± standard deviation

** Data were number, (%)

[a] = Student's t test

[b] = Chi-square test.

The clinical indications for hysterectomy in both groups were mainly abnormal uterine bleeding, pressure symptoms and pelvic pain (Table 2). Characteristics of the intraoperative and outcomes were shown in Table 3 and Table 4. There were no significant difference between the two groups in the preoperative and postoperative haemoglobin level, and the durations of operation. Intraoperative blood loss was not different between the misoprostol group and placebo group (mean of 549.6 ± 391.9 ml versus 445.0 ± 270.6 ml) and no participant needed postoperative blood transfusion.

The incidence of the side effects after the administration of misoprostol and placebo were shown in Table 5. The side effects of pyrexia, nausea, vomiting and headache were not different in both groups whereas chill and diarrhea were not found in both groups. No major complication or morbidity found in either group.

Table 2. Indications for hysterectomy.

Indications *	**Misoprostol (n = 35)**	**Placebo (n = 35)**	**P**
Abnormal uterine bleeding (%)	24 (68.6)	26 (74.3)	0.40 [b]
Pressure symptoms (%)	28 (80)	16 (45.7)	0.01 [a]
Pelvic pain (%)	4 (11.4)	6 (17.1)	0.37 [b]
Others (%)	1 (2.9)	2 (5.7)	0.51 [b]

* Some cases had more than one indication for surgery

[a] = Chi-square test.

[b] = Fischer's exact test

Others = anemia, rapid growth leiomyoma

Table 3. Surgical procedure characteristics.

Characteristics	**Misoprostol (n = 35)**	**Placebo (n = 35)**	**P**
Surgeon level			0.64 [a]
- Staff (%)	2 (5.7)	3 (8.6)	
- Resident (%)	33 (94.3)	32 (91.4)	
Pfannensteil incision(%)	15 (42.9)	16 (45.7)	0.81 [b]
Adhesion			0.22 [b]
- None (%)	12 (34.3)	20 (57.1)	
- Filmy (%)	11 (31.4)	9 (25.7)	
- Moderate (%)	8 (22.9)	5 (14.3)	
- Severe (%)	4 (11.4)	1 (2.9)	

[a] = Chi-square test.

[b] = Fischer's exact test

Table 4. Outcomes.

Outcomes	Misoprostol (n = 35)	Placebo (n = 35)	P [a]
Intra-operative blood loss*(ml)	549.6	445.0	0.20
(95% CI)	(415.0 - 684.2)	(352.0 - 538.0)	
Hemoglobin (g/dl)			
- Pre-operation	12.09 ± 1.3	11.53 ± 1.2	0.78
- Post-operation	10.31 ± 1.3	9.84 ± 1.4	0.54
- Hemoglobin differences	1.67 ± 0.9	1.66 ± 1.1	0.91
Duration of surgery (min)	111.9 ± 33.3	110.9 ± 27.3	0.20

* Data were presented in mean and 95% confidential interval (95%CI)

[a] = Student's t test

Table 5. Side effects of misoprostol and placebo treatments.

Side effects (hr)		Misoprostol (n=35)	Placebo (n=35)	P [a]
Pyrexia (%)	6 hr	3 (8.6)	2 (5.7)	0.50
	12 hr	4 (11.4)	1 (2.9)	0.18
Nausea (%)	6 hr	8 (22.9)	9 (25.7)	0.50
	12 hr	4 (11.4)	3 (8.6)	0.50
Vomiting (%)	6 hr	2 (5.7)	1 (2.9)	0.50
	12 hr	1 (2.9)	2 (5.7)	0.50
Headache	6 hr	0	0	NA
	12 hr	1 (2.9)	1 (2.9)	0.75

NA = Not evaluate

[a] = Fischer's exact test

Discussion

Total abdominal hysterectomy is the standard treatment of the large symptomatic leiomyomas for women who have completed child bearing. The major significant morbidities in total abdominal hysterectomy is intra-operative blood loss that possible required blood transfusion. Reducing blood loss during surgery decreases the need for blood transfusion and decreases post-operative morbidity. Our study is study to prove the effectiveness of pre-operative sublingual misoprostol on decreasing hemorrhage during total abdominal hysterectomy for large leiomyoma. Previous study reported that the misoprostol 400 microgram had benefit to reducing the blood loss intra-operative for myomectomy[15]. Also we designed to use the misoprostol sublingually 60 minutes before the operation. Due to a recent pharmacokinetic study has revealed that sublingual administration of misoprostol has maximum systemic bioavailability between 30-60 minutes and achieves highest serum peak concentration in compare to either the oral or vaginal route of administration[12]. Its effect on uterine contractility lasted for about 3 hours and the bioavailability of misoprostol after the administration also higher than those after vaginal or oral administrations[16]. Over 50% of women studied who had symptomatic uterine myomas complained of abnormal uterine bleeding. Furthermore, it was common to present with complex symptoms including pressure symptom which increased surgical risk.

This study was insufficient to detect a reduction of blood loss in the misoprostol group. Therefore our data were minimal increased of the intraoperative blood loss in the misoprostol group but it was not statistical significant. On the other hand, previous studies reported the benefit of misoprostol used for reducing the intraoperative blood loss in myomectomy and laparoscopy-assisted vaginal hysterectomy[15, 17]. Our result may be explained by the sample size is too small to detect the less distinct differences in the blood loss. Additionally, our study did not control all of the parameter that might be effect to the results for example the techniques of the surgery. One of the major techniques in total abdominal hysterectomy is to firstly ligate the major blood vessels which minimizes the blood loss by itself. This is the one of weak point in our study and also might be a one of confounding factor.

No major complication was associated with use of the medication. Neither group in this study had major side effects. These were not difference in the side effects between both groups. The most incidence of side effects in this study: 22.9% nausea in misoprostol groups and 25.7% in placebo group, were possible the side effects of opioid administration for pain control.

The strength of this study was that the data obtained from the randomized patient and also double blind study which showed the similar cases in both groups. Furthermore, we evaluated the primary and secondary outcomes in all of cases. Since this study was done in total abdominal hysterectomy patient with single dose of misoprostol, the result could not be extrapolated to the other operation, the different dose of misoprostol and also the different route of administration of misoprostol. Our data do not allow for estimation of an optimal duration of abstinence for fertility purposes. Further study is needed to confirm this result.

Conclusion

We concluded that the additional a single sublingual misoprostol dose prior to the total abdominal hysterectomy with/without salpingo-oophorectomy for symptomatic uterine leiomyoma could not significantly improve the reducing intraoperative blood loss and the number of post-operative blood transfusion.

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การใช้ Misoprostol อมใต้ลิ้นเพื่อลดภาวะเสียเลือดระหว่างการผ่าตัดมดลูกทางหน้าท้อง

อัจฉรา พานิชพงษ์พันธุ์, ชลธิชา สถิระพจน์, ภุชงค์ ลิขิตธนสมบัติ, ณัฐพงศ์ อิศรางกูร ณ อยุธยา

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของยา Misoprostol โดยการบริหารยาด้วยวิธีอมใต้ลิ้นก่อนการผ่าตัด เพื่อลดภาวะการณ์เสียเลือดในระหว่างการผ่าตัดมดลูกทางหน้าท้องและ/หรือร่วมกับตัดท่อนำไข่และรังไข่ ในผู้ป่วยเนื้องอกกล้ามเนื้อมดลูกชนิดไม่ร้ายแรงที่มีอาการ*

วัสดุและวิธีการ: *ผู้ป่วย 70 รายที่ได้รับการวินิจฉัยว่าเป็นเนื้องอกกล้ามเนื้อมดลูกชนิดไม่ร้ายแรงที่มีอาการโดยสูตินรีแพทย์ และเข้ารับการรักษาโดยการผ่าตัดมดลูก และ/หรือผ่าตัดมดลูกปีกมดลูกและรังไข่ ทางหน้าท้องที่โรงพยาบาลรามาธิบดี ระหว่างเดือนมิถุนายน 2555 ถึง มกราคม 2556 แบ่งอาสาสมัครเป็นสองกลุ่มโดยใช้วิธีการสุ่มแบบปกปิด กลุ่มแรก 35 ราย ได้รับ Misoprostol 2 เม็ด (200 ไมโครกรัม/เม็ด) กลุ่มที่สอง 35 ราย ได้รับยาเทียม คือ Vitamin B6 (100 มก./เม็ด) 2 เม็ดเป็นยาเทียม อมใต้ลิ้นเป็นเวลา 30-60 นาที ก่อนเข้ารับการผ่าตัด จากนั้นมีการจดบันทึกการประเมินปริมาณเลือดที่ออกระหว่างผ่าตัด การเปลี่ยนแปลงของระดับฮีโมโกลบินหลังการผ่าตัด การได้รับเลือดและปริมาณเลือดที่ได้รับหลังการผ่าตัด และการประเมินผลข้างเคียงของยา*

ผลการวิจัย: *จากข้อมูลการศึกษาพบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในทั้ง 2 กลุ่ม ในการเสียเลือดระหว่างการผ่าตัดมดลูก (misoprostol, mean 549.6 ± 391.9 มล. versus ยาเทียม, mean 445.0 ± 270.6 มล, p=0.2) และทั้ง 2 กลุ่ม ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในการที่ต้องได้รับเลือดหลังการผ่าตัด รวมถึงการเปลี่ยนแปลงของระดับฮีโมโกลบิน และผลข้างเคียงของยาที่เกิดขึ้น*

สรุป: *การใช้ Misoprostol โดยวิธีการบริหารยาอมใต้ลิ้น ไม่มีประสิทธิภาพในการช่วยลดการเสียเลือดระหว่างการผ่าตัด และการต้องการรับเลือดหลังการผ่าตัดมดลูกทางหน้าท้องในผู้ป่วยเนื้องอกกล้ามเนื้อมดลูกชนิดไม่ร้ายแรงที่มีอาการ*