Thai Journal of Obstetrics and Gynaecology
October 2019, Vol. 27, No. 4, pp. 210-215

GYNECOLOGY

The Effectiveness of Sublingual Misoprostol in Reducing Operative Blood Loss during Total Abdominal Hysterectomy: A randomized controlled trial

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ABSTRACT

Objectives: To study the effectiveness and safety of preoperative sublingual misoprostol administration in reducing of operative blood loss during total abdominal hysterectomy (TAH).

Materials and Methods: Three hundred women with benign uterine diseases who were performed TAH at Khon Kaen Hospital from June 2017 to May 2018 were randomized into two groups: misoprostol group and placebo group. Intraoperative blood loss was analyzed.

Results: Baseline characteristics were similar between groups. There was no statistically significant difference in intraoperative blood loss between misoprostol and placebo group [228 ml (126-389) vs 240 ml (126-387), p = 0.943]. There was no significant difference in hemoglobin difference, blood transfusion and hospital stay between groups.

Conclusion: Misoprostol could not reduce intraoperative blood loss during total abdominal hysterectomy.

Keywords: benign uterine diseases, misoprostrol.

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Received: 28 September 2018, **Revised:** 29 October 2018, **Accepted:** 20 November 2018

ผลของยาไมโซพรอสตอลอมใต้ลิ้นในการลดปริมาณการเสียเลือดในระหว่างผ่าตัดตัดมดลูกทางหน้าท้อง: การทดลองแบบสุ่ม

ทิพย์สุคนธ์ หารินไสล, มนสิชา เมฆจรัสนภา, จรรยาภรณ์รัตนโกศล, มาลีชาติ ศรีพิพัฒนะกุล, ทุมวดี ตั้งศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลและความปลอดภัยของยาไมโซพรอสตอลอมใต้ลิ้นในการลดปริมาณการเสียเลือดในระหว่างผ่าตัดมดลูกทางหน้าท้อง*

วัสดุและวิธีการ: *ผู้ป่วยหญิงที่ได้รับการวินิจฉัยเนื้องอกมดลูกทั้งหมด 300 ราย ที่เข้ารับการผ่าตัดมดลูกที่โรงพยาบาลขอนแก่น ในช่วงเดือนมิถุนายน 2560 ถึง พฤษภาคม 2561ได้รับการสุ่ม เป็น 2 กลุ่ม คือ กลุ่มที่ได้รับยาไมโซพรอสตอลและกลุ่มที่ได้รับยาหลอก โดยดูปริมาณการเสียเลือดระหว่างผ่าตัดในกลุ่มที่ได้รับยาไมโซพรอสตอลเปรียบเทียบกับกลุ่มที่ได้รับยาหลอก*

ผลการวิจัย: *ลักษณะทางประชากรศาสตร์ไม่แตกต่างกันระหว่างสองกลุ่ม กลุ่มที่ได้รับยาไมโซพรอสตอลเสียเลือดระหว่างผ่าตัด 228 มล.(126-389) ส่วนกลุ่มที่ได้รับยาหลอกเสียเลือดระหว่างผ่าตัด 240 มล. (126-387) ซึ่งไม่มีความแตกต่างกันทางสถิติ เช่นเดียวกับความแตกต่างของความเข้มข้นของเลือดก่อนและหลังผ่าตัด การให้เลือด ระยะเวลาที่นอนโรงพยาบาล และภาวะแทรกซ้อนจากการให้ยา ที่ไม่มีความแตกต่างกันทางสถิติระหว่างสองกลุ่ม*

สรุป: *การให้ยาไมโซพรอสตอลไม่ช่วยลดปริมาณการเสียเลือดระหว่างผ่าตัดมดลูกทางหน้าท้อง*

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Introduction

Total abdominal hysterectomy (TAH) is the most common operation performed by the gynecologists. There are many indications for hysterectomy. Myoma uteri continues to be the most common indication for hysterectomy which is indicated for 40% of all abdominal hysterectomies and the second most common indication is adenomyosis (12.8%)[1].

Intraoperative blood loss requiring blood transfusion is one of the most frequently complications of this procedure, occurring in 2-12% of cases[2]. Several methods for reducing blood loss during TAH such as injection of gonadotropin-releasing hormone (GnRH) agonist, uterine artery ligation, uterotonic agents such as misoprostol, oxytocin before operation were studied. However, there are many studies showed that GnRH agonist may effective in reducing blood loss during TAH but may cause significant side effects, high cost and can use only short period of time[3].

Misoprostol, a synthetic analog of prostaglandin E1 is economical and stable in room temperature. It can be administered orally, rectally or sublingually and has no serious side effect[4]. It can lessen blood loss during TAH by decreasing in uterine artery blood flow due to direct vasoconstriction in uterine arteries. Strong myometrial contractions lead to increase contraction of the vessels supplying blood to the myoma and may also contribute to a reduction in bleeding[5].

In this study, we used sublingual route because a pharmacokinetic study found that sublingual misoprostol has shortest time to peak concentration, the highest peak concentration and the greatest bioavailability when compared to other routes, it can avoid the first-pass metabolism via the liver that found in oral route, it is more convenient than using via vaginal or rectal administration, and no need to repeat dose because the uterine contraction is sustained and will decrease activity after 3 hours of drug administration. Patient undergoing TAH require preoperative cleaning of vagina so administration via vaginal route may be interfered[4].

According to the previous studies, Biswas et al, showed that a single dose of misoprostol administered before TAH resulted in a significant reduction of intraoperative blood loss[5]. By contrast, a similarly designed study by Panichpongpan, et al and Chai, et al, showed no significant effectiveness in reducing intraoperative blood loss during TAH by misoprostol administration before an operation[6, 7]. Therefore, we conducted this study because the previous studies have shown varying results and its effectiveness is still unproven.

Materials and Methods

Women with diagnosed of myoma uteri or adenomyosis who were scheduled to perform TAH between June 2017 and May 2018 at Khon Kaen Hospital were recruited, Written informed consent was obtained from each eligible participant. The study was approved by Khon Kaen Hospital Institute Review Board in Human Research and the randomization was generated by computer using block of four.

The participants were randomly allocated into two groups, study and control group. Study group received two tablets of 200 microgram misoprostol (Cytotec®), sublingually 30 minutes before the operation. Control group received two placebo tablets with identical in appearance to misoprostol. The drug was administered by unaware nurse at gynecologic ward. The randomization list was kept in a sealed opaque envelope.

Contraindications of misoprostol administration including mitral stenosis, glaucoma, sickle cell anemia, diastolic blood pressure over 100 mmHg, severe asthma, known allergy to prostaglandin, known case of coagulopathy, previous pelvic surgery, women who had pre-operative mifepristone or GnRH treatment, preoperative diagnosis of gynecologic cancer, emergency procedure and mental impairment or incompetent in giving consent were excluded.

We recorded blood pressure, pulse rate and body temperature at the time of admission and during 24 hours after administration of the drug. TAH with or without adnexal surgery was performed in the usual manner by the gynecological staff and residents.

Intraoperative blood loss was measured by adding blood volume in suction bottles to the difference in weight between the dry and wet swabs and gauzes before and after operation (1 gm is equivalent to 1 ml)[6] that measured by standard scales. The operative time from skin incision to close was recorded. Side effects of drug such as fever, chill, nausea/vomiting, diarrhea and headache were evaluated at 6 hours after the operation. Any intraoperative and postoperative transfusion were recorded. Hemoglobin level was determined by preoperative evaluation and 24 hours after the surgery. Postoperative diagnosis was confirmed by pathological report.

The sample size calculation was based on the data from Biswas, et al with 90% power at the 5% level of significance. The sample size in each group was 145 cases.

Differences in continuous variables were analyzed with student t-test or non-parametric test due to characteristics of data distribution and were presented as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were analyzed by chi-square or fisher's exact test and were presented as number and percentage.

Results

There were 370 women who had been diagnosed of symptomatic myoma uteri or adenomyosis and underwent TAH with or without adnexal surgery. Sixty one women did not meet the criteria and nine rejected to participate in the study. Therefore, 300 women were recruited into the study, 150 in each group. Intraoperative finding found that there were three women who were diagnosed as ovarian tumor, 1 pelvic mass, 2 uterine cancer, 1 colon cancer, 1 endometrial polyp and 2 myomectomy, and five in each group. These women were withdrawn from the study (Fig. 1).

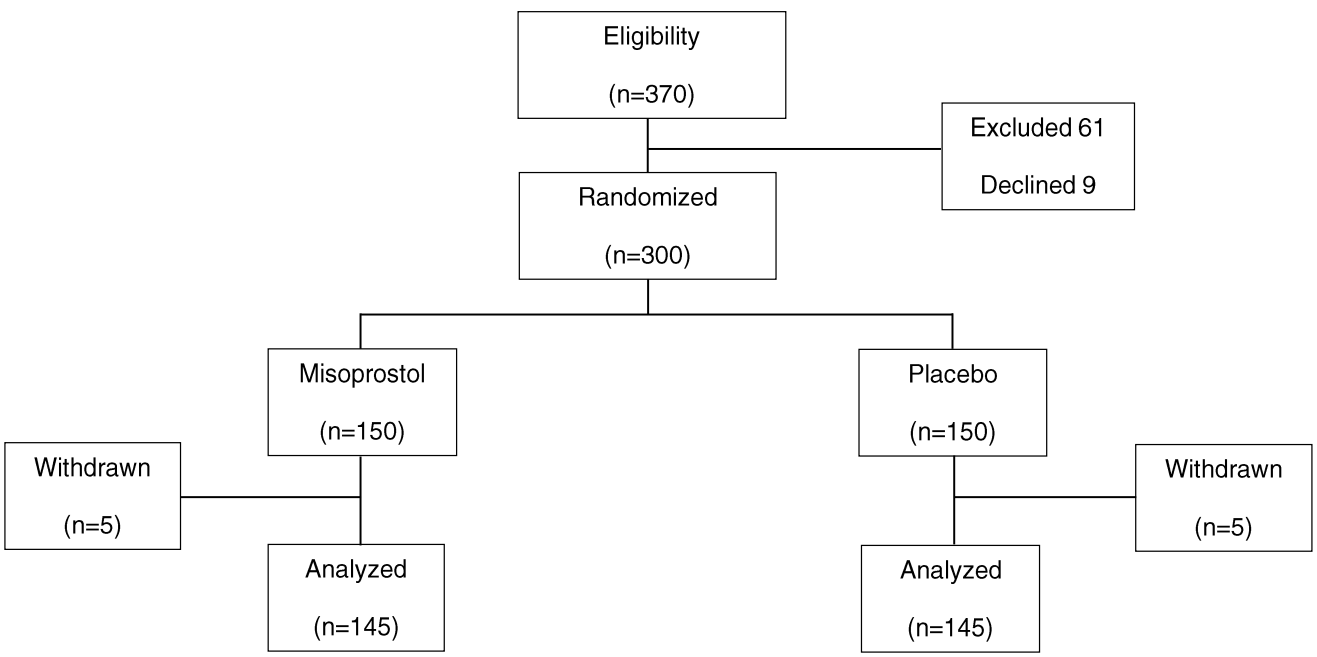

Fig. 1. Study flow.

Both groups had similar baseline characteristics such as age, body mass index (BMI), uterine weight, pre-operative hemoglobin (Hb), operation time, diagnosis and surgeon (Table 1). There was no significant difference of intraoperative blood loss between misoprostol and placebo group

[228 ml (126-389) versus 240 ml (126-387)]. Similarity, the median of Hb difference, blood transfusion and length of hospital stay in both groups had no significant difference and serious adverse effects were not found in both groups (Table 2).

Table 1. Demographic characteristics.

Characteristics	Misoprostol (n=145)	Placebo (n=145)	p value
Age (years)	46.2±5.2	45.5±5.2	0.203
BMI (kg/m^2)	25.3±4.3	24.9±4.3	0.338
Uterine weight (gm)	609±417.9	564.5±380.3	0.515
Preoperative Hb level (gm/dl)	11.5±1.7	11.3±1.6	0.579
Operative time (min)	90±25	91.8±29.2	0.607
Diagnosis			0.479
Myoma uteri	82 (56.55)	76 (52.41)	
Adenomyosis	63 (43.45)	69 (47.59)	
Surgeon			1.000
Staff	136 (93.79)	136 (93.79)	
Resident	9 (6.21)	9 (6.21)	

Data are presented as mean ± SD or n (%)
BMI: body mass index, Hb: hemoglobin

Table 2. Outcome measures.

Characteristics	Misoprostol (n=145)	Placebo (n=145)	p value
Intraoperative blood loss (ml)	228 (126-389)	240 (126-387)	0.943
Difference Hb (gm/dl)	1.1 (0.5-1.8)	1.2 (0.6-1.8)	0.203
Blood transfusion (unit)	5 (3.45)	5 (3.45)	1.000
Length of hospital stay (day)	4	4	0.391
Side effect			
Fever	52 (35.86)	43 (29.66)	0.260
Chill	10 (6.90)	7 (4.83)	0.309
Nausia and vomiting	49 (33.79)	47 (32.41)	0.803
Headace	6 (4.41)	6 (4.41)	1.000

Data are presented as median (IQR) or n (%)
Hb: hemoglobin

Discussion

This randomized controlled trial investigated the effect of effectiveness of preoperative sublingual misoprostol administration in reducing operative blood loss during total abdominal hysterectomy and safety. We found that misoprostol could not reduce intraoperative

blood loss when compared to placebo.

The present study confirmed the similar results of Panichpongpan, et al and Chai, et al revealed that using misoprostol 400 microgram did not reduce intraoperative blood loss. But with larger sample size, intraoperative blood loss was not significant different from those who received placebo. The possible reasons might be the different in degree of pelvic adhesion such as endometriosis was accidentally found during operation which was not excluded. Women with pelvic adhesion took risk of adjacent organs injury e.g. bowel, colon, ureter, bladder, etc. The variety of operative techniques of the surgeons were also one of all causes. Misoprostol induced uterine contraction resulting to reduce uterine blood flow only. But after the uterus was removed, the bleeding from other sources such as vaginal stump, the pedicles of cardinal ligaments could also cause additional bleeding.

By contrast, Biswas, et al reported that using misoprostol 400 microgram could significantly decrease evidence of intraoperative blood loss in myoma uteri patients who received TAH with or without BSO. However, intraoperative blood loss in misoprostol group was borderline lower than placebo group ($p = 0.049$).

There was no significant difference in serious side effects between misoprostal and placebo group. However, one of each group had fever which might be a reactionary fever after the operation (35.86% and 29.66% in misoprostol and placebo group, respectively). Other complications were nausea and vomiting from opioid effect (33.79% and 32.41% in misoprostol and placebo group, respectively).

The strengths of this study were a randomized double blinded, placebo controlled trial and measurement blood loss.

Limitations of this study were we studied only in elective cases as well as only in benign uterine diseases. Therefore, for further research, the study in difference population such as in gynecologic cancer patient or in case of emergency surgery should be considered.

Conclusion

Sublingual misoprostol 400 microgram before performing TAH with or without BSO in symptomatic myoma uteri or adenomyosis patients could not reduce intraoperative blood loss when compared to placebo.

Potential conflicts of interest

The authors declare no conflict of interest.

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