Misoprostol for Cervical Ripening Prior to Manual Vacuum Aspiration (MVA) in Abnormal Uterine Bleeding: Double Blinded Randomized Controlled Trial†

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Objective: *To study the effectiveness of sublingual misoprostol for cervical ripening before MVA in women aged between 35 and 55 years old.*

Material and Method: *Women aged between 35 and 55 years old who had indications for endometrial sampling were recruited. Exclusion criteria were gross pathology of cervix, pregnancy, allergy to misoprostol, and abnormal coagulopathy. Eighty women who had indication for MVA were then assigned by randomization (block of four). Participants were treated with either sublingual 200 µg of misoprostol (study group) or placebo (controlled group) for cervical priming at two hours before procedure. The largest diameter of the Hegar's dilator through internal os without any resistance before MVA was the primary collected data. Secondary data were operating time, immediate pain score, satisfactory score, complications, and side effects.*

Results: *Mean age of misoprostol and controlled group were 44.8±5.2 and 45.5±5.0 years old, respectively. One third of both groups had previously experienced uterine curettage. The initial cervical diameter before MVA of individuals receiving misoprostol and controlled group were 6.9±2.0 and 5.5±2.4 mm, respectively. The MVA time in misoprostol group was significantly shorter than controlled group (5.1±1.7 vs. 8.0±3.9 min, p<0.001). The additional analgesia was not different in both groups. Side effect before MVA were more significantly found in misoprostol group (p = 0.001). Lower post MVA pain and satisfactory score were better reported in misoprostol group than placebo's (p<0.001).*

Conclusion: *Two hundred micrograms of sublingual misoprostol administration prior to MVA gave significantly effective result of cervical priming. Satisfactory and pain scores were more favorable in misoprostol group with manageable side effects.*

Keywords: *Manual vacuum aspiration, Misoprostol, Sublingual*

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Abnormal uterine bleeding in premenopausal women aged between 35 and 55 years old were noted in Thailand. The causes are from various reasons, namely metritis dysfunctional uterine bleeding (DUB), myoma uteri,adenomyosis, and endometrial cancer[1]. These women should consult a physician to investigate the underlying cause by pathological endometrial biopsy. Data from the gynecological clinic, Thammasat University Hospital during year 2011 revealed 154 women with abnormal uterine bleeding. They were first treated by endometrial biopsy using sharp curettage (Novak's endometrial biopsy) or aspiration (Wallach Endocell). The manual vacuum aspiration (MVA) is a standard method recommended by World Health Organization (WHO) and Royal Thai College of Obstetrics and Gynaecology. MVA is now a current method of choice in endometrial sampling at Thammasat University Hospital.

MVA is an easy method that can be performed in an outpatient unit by a trained general practitioner. The flexibility of its plastic component reduces the incidence of myometrial trauma. The operating time at Thammasat University Hospital is less than five minutes. Pain from MVA procedure is less than that of

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the sharp curettage[2,3]. As a result, general anesthesia is not required during an MVA procedure. Incidence of MVA complications, i.e., cervical tear or uterine perforation, is also less than those from the use of sharp curettage. MVA is considered an ambulatory care. As a result, MVA is currently the diagnostic and therapeutic of choice in abnormal uterine bleeding patients at Thammasat University Hospital.

MVA procedure requires the use of a 50 ml syringe. One side of the syringe is connected to a 4-12 mm of Karman's cannula to provide a 60 mmHg vacuum pressure for an endometrial suction. The 3.8±1.2 mm cervical width of the nulliparous women is smaller than Karman's cannula diameter. As a result, MVA procedure cannot be used in patients with small and narrow cervix, i.e., nulliparity and menopausal women. In these cases, a cervical dilatation by Hegar's dilators is required. Complication of cervix tear or uterine perforation occurs approximately 0.76 to 10% in the application of Hegar's dilator[4]. Misoprostol has been used for cervical ripening before the operation to reduce the complications[4,5].

Misoprostol is a synthesized prostaglandin and PGE1 analogue. It has been used as an oral tablet in the treatment of peptic ulcer in patients with prolonged non-steroidal anti-inflammatory usage[6]. The misoprostol tablet is very soluble and can be dissolved in 20 minutes when it is put under the tongue. A pharmacokinetic study compared the absorption kinetics of oral, vaginal, and sublingual routes of administration of misoprostol. It was found that sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration, and the greatest bioavailability when compared to other routes[6]. The peak concentration is achieved about 30 minutes after sublingual application. Misoprostol is also used in inducing labor, termination of pregnancy, and preventing a postpartum hemorrhage[7].

This investigation was to study the use of 200 µg of sublingual misoprostol for cervical ripening prior to manual vacuum aspiration in abnormal uterine bleeding of premenopausal women.

Material and Method

This prospective study was approved by the Faculty of Medicine, Thammasat University ethics review committee. The investigation was conducted prospectively between June 2012 and May 2013 at the outpatient Gynecologic Clinic of Thammasat University Hospital, Thailand. Sublingual misoprostol and placebo groups were recruited for a double-blinded randomized controlled clinical trial (RCT). Eighty pre-menopausal women aged between 35 and 55 years old with abnormal uterine bleeding, and who had indication of endometrial pathological sampling, were recruited. Any woman with a gross pathology of the cervix, or with abnormal vaginal bleeding caused by complications of pregnancy, misoprostol allergy, coagulopathy, pelvic inflammatory disease, or anyone who did not want to participate in the present study were excluded.

A sample size was calculated by pilot study data that resulted from thirty participants. Random block of four was the method for dividing the participants in two groups (control and study groups). The mean cervical dilation was measured by gentle Hegar's dilator insertion. The sample size was calculated to measure the cervical dilation effect with a (two-sided) & β errors (one-sided) at 0.05 and 0.1, respectively. The sample size formula was shown in Fig. 1. Forty participants of each groups were a sufficient number to give a statistical significance.

Information about the present study was given to participating patients. They all gave informed consents prior to the start. After randomization in blocks of four, each patient received either a 200 µg of misoprostol or a lactose filler placebo (Sahapadvejakum, Bangkok, Thailand) given in an envelope. The pill was sub-lingually taken two hours prior to the procedure start time under a supervision of a registered nurse. Both physicians and patients were unaware as to which medication was allocated to which patients.

The patient's position and the direction of cervix compared with the uterus cavity were initially evaluated by the physician. Vital signs were also recorded. The cervical width was measured using Hegar's dilators. The measurement started from the smallest size dilator to the largest size until they could not be passed through the internal os without resistance. When the width of the cervix was less than 4 mm, dilation was performed to achieve 4 mm opening so that a Karman's cannula could later pass through.

$$N = \frac{2(Z_{\alpha/2}+Z_{\beta})^2\,\sigma^2}{(\mu_c-\mu_t)^2}$$

M_c = mean cervical dilation after sublingual misoprostol
M_t = mean cervical dilation after sublingual placebo
σ = variance of outcome for single individual
$Z_{\alpha/2} = 1.96$ $Z_{\beta} = 1.28$

Fig. 1 Sample size calculation.

The Karmann's cannula, the same size as the largest Hegar's dilator, was then chosen for the MVA. Patients who had pain score of more than 5, received parenteral analgesia.

The degrees of pain was assessed using a 10-cm VAS (visual analogue scale), with zero signifying no pain and 10 signifying the worst pain. Satisfactory score was assessed using 10-cm scale with zero signifying no satisfaction and 10 signifying the most satisfaction. Pain and satisfactory scores were immediately evaluated after MVA completion.

Operating time, side effects, complications, pain and satisfactory scores were considered during cervical dilation. SPSS 13.0 (SPSS Inc., Chicago, USA) was used for the statistical analysis. Mean or median of continuous variables were compared between two groups using t-test or Mann-Whitney U test where appropriate. Chi-square test or Fisher's exact test was applied for discrete variables. The p-value of less than 0.05 was considered significant.

Results

Eighty pre-menopausal women aged between 35 and 55 years old who had an indication for endometrial sampling were enrolled in the present study and underwent MVA. Forty women received misoprostol and placebo respectively. There were no statistical differences between two groups regarding mean age, BMI, gravida, parity and experience of uterine curettage as shown in Table 1.

The mean initial cervical diameters before MVA of misoprostol and placebo group were 6.9 and 5.5 mm, respectively. Consequently, the placebo group needed wider cervical dilation than the misoprostol group. The mean duration of MVA of the misoprostol and placebo group were 5.1 and 8.0 min, respectively. One (2.5%) and seven (17.5%) subjects in needed additional cervical dilatation in misoprostol and placebo group respectively. The side effects before MVA, only occurred in the misoprostol group (40.0%), and mostly involved abdominal pain (Table 2).

One subject in the placebo group had a cervical tear during the MVA. There was no uterine perforation in the present study. The mean pain score after MVA of the misoprostol and placebo groups were 5.0 and 6.5, respectively, whereas the mean satisfactory score of the misoprostol and placebo groups were 9.4 and 8.2, respectively (Table 3).

Discussion

Misoprostol has been used for cervical ripening before pregnancy termination and diagnostic hysteroscopy[5,8-11]. Sublingual route had more effectiveness than oral route for pre-abortion cervical ripening[12,13].

The present study demonstrated the effectiveness of 200 μg of misoprostol administered sublingually for cervical ripening prior to MVA in premenopausal women who had abnormal uterine bleeding. To the best of our knowledge, it was the first trial of misoprostol in MVA procedure in premenopausal women.

Cervical dilation, dilation needed and duration of MVA of the misoprostol treated group were better than the placebo group. Manageable side effects were found in only the misoprostol group. The pain score of the misoprostol group was lower than the placebo group. Satisfactory score of the misoprostol group was also higher than placebo group. There was no serious complication in the present study.

The use of 400 μg misoprostol for cervical priming in the first trimester pregnancy termination was

Table 1. Demographics data

	Misoprostol (n = 40)	Placebo (n = 40)	p-value
Age* (years)	44.8±5.2	45.5±5.0	0.53
BMI* (kg/m^2)	26.2±5.4	25.6±5.1	0.60
Gravida*	2.0±1.3	2.1±1.4	0.81
Parity			
Nulliparous (%)	20 (50.0)	17 (42.5)	0.50
Multiparous (%)	20 (50.0)	23 (57.5)	
Experience of uterine curettage			
Yes (%)	14 (35.0)	13 (32.5)	0.81
No (%)	26 (65.0)	27 (67.5)	

* Mean ± SD; p-value <0.05, significant
BMI = body mass index

Table 2. Cervical dilatation, further dilation need and side effects

	Misoprostol (n = 40)	Placebo (n = 40)	p-value
Dilatation* (mm)	6.9±2.0	5.5±2.4	0.005
Cervical dilatation need			
Yes (%)	1 (2.5)	7 (17.5)	0.02
No (%)	39 (97.5)	33 (82.5)	
Duration of MVA* (min)	5.1±1.7	8.0±3.9	<0.001
Side effect (%)			
Nausea	2	0	<0.001
Vomiting	0	0	
Fever	0	0	
Diarrhea	1	0	
Abdominal pain	13	0	
Headache	0	0	

* Mean ± SD; p-value <0.05, significant
MVA = manual vacuum aspiration

Table 3. Complications, pain and satisfactory score

	Misoprostol (n = 40)	Placebo (n = 40)	p-value
Complications			
Cervical tear (%)	0	1 (2.5)	0.31
Uterine perforation (%)	0	0	
No complications (%)	40 (100)	39 (97.5)	
Pain score*	5.0±1.6	6.5±2.0	0.001
Satisfactory score*	9.4±1.0	8.2±1.4	<0.001

* Mean ± SD; p-value <0.05, significant

evaluated in the study of Tang et al[9]. Sublingual and vaginal misoprostol were assigned for randomized preoperative cervical priming. The result showed that both sublingual and vaginal misoprostol was equally efficacious. There was a different outcome than Saxena report in 2008, which showed that a sublingual misoprostol administration yielded a better result than an oral or vaginal route in cervical priming of first trimester pregnancy termination[13]. Later in 2010, Lee et al studied the use of 400 µg misoprostol for cervical priming before hysteroscopy in premenopausal and non-pregnant women[11]. Oral, vaginal, and sublingual administrations were utilized. All administrative routes were equally effective in cervical width and operating time.

The effectiveness of 200 µg of misoprostol showed a good result by the vaginal route in Preutthipan et al[4]. The subjects in this study were premonopausal women who received hysteroscopy. In the year 2008, Batukan et al report the effectiveness of 400 µg oral and vaginal misoprostol for pre-operative cervical ripening in premenopausal women before hysteroscopic surgery. The mean cervical widths in the vaginal and oral misoprostol groups after treatment were 7.3 and 6.0 mm, respectively. Vaginal misoprostol administration gave shorter time of operation and more cervical dilation effect than the oral route[14]. The present study led to a subsequent study to reduce the dosage of vaginal misoprostol[15]. El-Mazny and his group reported the efficacy and safety of 200 µg vaginal misoprostol for cervical priming before diagnostic hysteroscopy. The results in the present study show that vaginal misoprostol had an attractive outcome for cervical priming as per the present study of Batukan[15]. Side effects and complications were infrequent[15].

A report by da Costa et al studied efficacy of 200 µg misoprostol for cervical priming in postmenopausal women before hysteroscopy via a different route. The pre-operative misoprostol reduced posthysteroscopic pain[10]. Mulayim et al later studied the use of 200 µg sublingual misoprostol for cervical ripening before diagnostic hysteroscopy in premenopausal women. Although the additional cervical dilatation needed was lower in the misoprostol group, there was no statistical difference[5]. It is

difficult to compare these two studies due to the amount of cases involved in each study.

Although all studies above showed an unclear indication of the misoprostol efficacy for cervical ripening, these studies considered various conditions such as pregnancy, menopause, dosage of misoprostol and route of administration.

The present study was conducted in non-pregnant patients who required endometrial aspiration (MVA). The results were similar to the study of El-Mazny in 2011 but using different administrative route. Sublingual and vaginal route gave the peak misoprostol blood level at 30 and 70 to 80 seconds, respectively[9]. This could be explained by the absorption hypothesis[6]. Sublingual administration was chosen for the current study for it gives peak blood level in a shorter duration. The result is satisfactory with all involved.

In summary, 200 µg sublingual misoprostol was used successfully for cervical ripening. It gave the excellent satisfactory and pain scores. The application of these results (cervical diameters) was suitable for a minor operation. The sublingual route is a convenient route of administration for subjects. The present study suggested that 200 µg of sublingual misoprostol was suitable for pre MVA in premenopausal women who had abnormal uterine bleeding.

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Potential conflicts of interest

None.

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การเตรียมปากมดลูกด้วยการให้ยาไมโซพรอสทอลอมใต้ลิ้นก่อนการทำหัตถการดูดเนื้อเยื่อบุโพรงมดลูกด้วยเครื่องมือสุญญากาศชนิดมือถือในสตรีที่มีเลือดออกผิดปกติจากโพรงมดลูก โดยวิธีการศึกษาแบบสุ่มและมีกลุ่มควบคุม

วงศ์ษา มณีศร, อธิตา จันทเสนานนท์, กรณ์กาญจน์ ภมรประวัติธนะ, คมสันติ์ สุวรรณฤกษ์

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของยาไมโซพรอสทอลโดยวิธีอมใต้ลิ้นเพื่อเตรียมปากมดลูกก่อนการทำ MVA ในสตรีก่อนวัยหมดระดูที่มีอายุระหว่าง 35-55 ปี*

วัสดุและวิธีการ: ศึกษาในสตรีก่อนวัยหมดระดูอายุระหว่าง 35-55 ปี ที่มาด้วยภาวะเลือดออกผิดปกติจากโพรงมดลูกที่จำเป็นต้องได้รับการส่งตรวจเยื่อบุโพรงมดลูกทางพยาธิวิทยา จำนวน 80 ราย โดยมีเกณฑ์การคัดออกจากการศึกษา คือมีพยาธิสภาพของโรคที่เกิดบริเวณปากมดลูกที่เห็นได้อย่างชัดเจน มีเลือดออกผิดปกติทางช่องคลอดที่เกิดจากภาวะแทรกซ้อนของการตั้งครรภ์ แพ้ยาไมโซพรอสทอลหรือมีภาวะเลือดแข็งตัวผิดปกติ ผู้ป่วยที่เข้าร่วมการศึกษานี้ถูกสุ่มเลือกเป็นสองกลุ่มโดยวิธี block of four คือกลุ่มที่ได้ยาไมโซพรอสทอล 200 ไมโครกรัม และยาหลอกหลังจากอมใต้ลิ้น 2 ชั่วโมง เพื่อเตรียมปากมดลูกก่อนการทำ MVA ผู้ป่วยจะได้รับการประเมินขนาดของปากมดลูก เวลาของการทำหัตถการ ระดับความเจ็บปวด ความพึงพอใจในการรักษา ผลแทรกซ้อนระหว่างการทำหัตถการ ตลอดจนผลข้างเคียงของยาที่ได้รับ

ผลการศึกษา: *ค่าเฉลี่ยอายุผู้ที่ได้รับยาไมโซพรอสทอลและยาหลอกคือ 44.8±5.2 ปี และ 45.5±5.0 ปี ตามลำดับ ซึ่งไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ 1 ใน 3 ของผู้เข้าร่วมการศึกษาเคยผ่านการขูดมดลูก เมื่อเปรียบเทียบเส้นผ่านศูนย์กลางของปากมดลูกหลังจากได้รับยาไมโซพรอสทอลและยาหลอก พบว่ามีขนาด 6.9±2.0 มิลลิเมตร และ 5.5±2.4 มิลลิเมตร ตามลำดับ ซึ่งมีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p<0.001$) อีกทั้งระยะเวลาในการทำหัตถการในกลุ่มที่ใช้ยาไมโซพรอสทอลใช้เวลาสั้นกว่ายาหลอกอย่างมีนัยสำคัญทางสถิติ (5.1±1.7 นาที และ 8.0±3.9 นาที ที่ $p<0.001$) และมีคะแนนความเจ็บปวดน้อยกว่าในกลุ่มที่ใช้ยาหลอกอย่างมีนัยสำคัญทางสถิติ โดยคะแนนความพึงพอใจในกลุ่มที่ใช้ยาไมโซพรอสทอลยังสูงกว่าในกลุ่มยาหลอก อย่างไรก็ตามผลข้างเคียงของยาพบเฉพาะในกลุ่มที่ใช้ยาไมโซพรอสทอล*

สรุป: *การใช้ยาไมโซพรอสทอลขนาด 200 ไมโครกรัม อมใต้ลิ้นเพื่อเตรียมปากมดลูกก่อนการทำ MVA ได้ผลเป็นที่น่าพอใจทั้งในด้านความพึงพอใจของผู้รับบริการ และความเจ็บปวดที่น้อยกว่า และถึงแม้จะมีผลข้างเคียงจากยาบ้างแต่เป็นผลข้างเคียงที่ไม่รุนแรง และสามารถแก้ไขได้*