The Effectiveness of Sublingual or Oral Administration of Misoprostol for Cervical Ripening before Manual Vacuum Aspiration in First Trimester Termination of Pregnancy: Randomized Controlled Trial

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Objective: *To compare the effectiveness of misoprostol sublingual and oral routes before manual vacuum aspiration (MVA) in first trimester termination of pregnancy.*
Material and Method: *A double-blinded randomized controlled trial was conducted in first trimester termination of pregnancy cases. Eighty cases were recruited and divided into sublingual and oral groups. Both groups were randomized to receive 400 µg misoprostol two hours prior to MVA. Main outcomes were cervical dilatation, operative time, complications, side effects, pain scores, and patient satisfactions.*
Results: *Sublingual group had significantly more cervical dilatation and shorter operative time than oral group (7.3±1.5 vs. 5.9±1.4 mm, p<0.001 and 5.2±3.3 vs. 7.3±4.6 min, p = 0.02, respectively). However, there were similar side effects, pain scores, and patient satisfactions in two groups. The present study had no uterine perforation, cervical tear, hemorrhage, or re-evacuation.*
Conclusion: *Sublingual misoprostol route was more effective for cervical priming prior to MVA in first trimester therapeutic abortion than oral route.*

Keywords: *First trimester abortion, Cervical ripening, Manual vacuum aspiration, Misoprostol, Oral, Sublingual*

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Manual vacuum aspiration (MVA) has been used in surgical evacuation during the first trimester abortion for a few decades. It was a single visit routine with 99% success rate and low major complication[1,2]. It is a short procedure with only small loss of blood compared to medical abortion. MVA has been recommended by the World Health Organization (WHO) for surgical evacuation in the first trimester abortion over metallic dilation and sharp curettage. Additional benefit is a shorter hospital stay, which results in expense reduction. Patients are satisfied because they receive neuroleptic anesthesia and experience less pain[3].

The most important step of MVA is the cervical preparation. The preparation reduces overall risk of complication from abortion and the procedure difficulty[1,4-7]. Mechanical and chemical interventions are used to facilitate cervical dilatation. Misoprostol is a synthetic prostaglandin E1 analogue (15-deoxy-16-hydroxy-16-methyl prostaglandin E1). It has been used for cervical priming with greater efficacy than gameprost and PGF2α[1,6] and a shorter spending time than the used of mifepristone and laminaria[1,5]. Thus, misoprostol is suitable for cervical priming prior to day care surgical procedure[1,6].

Previous article in the year 2004[7] found no significant difference on cervical dilatation between 400 µg misoprostol sublingual and vaginal administration for cervical preparation before suction termination of first trimester pregnancy. While Aronsson et al trial in the year 2004[8] showed similar result between sublingual and oral groups. In Cochrane database of systematic review 2010, it was concluded that 400 µg misoprostol was more effective than 200 µg in the use for cervical preparation during the first trimester surgical abortion. Sublingual administration of misoprostol resulted in the most effective dilation, followed by vaginal and oral routes[6,9].

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There were only few articles reporting the use of 400 µg misoprostol in sublingual and oral administration[1,5,8,10-12]. The present investigation looked into the use of 400 µg misoprostol in sublingual and oral administrations at two hours prior to MVA (surgical evacuation) of the first trimester abortion. Cervical dilatation, operative time, blood loss, complication, side effect, pain score, and patient satisfaction were also recorded.

Material and Method

The present study was approved by the Ethics Committee, Faculty of Medicine, Thammasat University. Ninety four first trimester abortion cases with gestational age ≤12 weeks between November 2013 and March 2014 at Department of Obstetrics and Gynecology, Thammasat University Hospital were recruited. The present study was a double-blinded randomized control clinical trial (RCT). All subjects signed a written informed consent after the objective and procedures of the study were explained. The eligibility criteria was healthy women aged 18 to 45 years old. Each carried a singleton fetus gestational age ≤12 weeks with diagnosis of early pregnancy failure, blighted ovum (anembryonic gestation) and embryonic death (no cardiac activity visible on transvaginal scan (TVS) when the embryo measures 5 mm or more in length)[13]. The gestational age was verified by a reliable menstrual history and confirmed by physical or ultrasound examination. Exclusion criteria were a history of misoprostol allergy, anticoagulant usage, clinical coagulopathy, bleeding disorder, hypertension, chronic illness, active pelvic inflammatory disease, inevitable, and incomplete abortion[13].

All selected patients who met eligible criteria were divided into two groups by computer generated random number, two hours prior to their MVA procedure. The patient received sealed envelope with label of randomization number and a pack of misoprostol and placebo. Sublingual group (SG) received a 400 µg misoprostol sublingually plus an oral placebo. Oral group (OG) received a 400 µg misoprostol orally and a sublingual placebo. The randomization was blinded to the surgeon. Demographic data, medical and obstetric histories were all recorded during the initial visit. Pre-operative pain intensity was recorded using a 10-cm visual analog score (VAS) where zero meant no pain and 10 meant the worst abdominal pain. All patients received 50 mg intravenous meperidine and 10 mg diazepam for sedation before MVA. 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. The size of largest Hegar's dilators has been recorded. In case of insufficient cervical dilatation (less than 4 mm), a dilatation was performed to achieve 4 mm opening so that a Karman's cannula could later pass through[14]. Intra-operative time was recorded from initial used of Hegar's dilator pass through cervix until finished procedure. Post-operative pain intensity was evaluated at 30 minutes after operation by a 10-cm VAS. At two hours after the end of procedure, side effect of misoprostol such as nausea, vomiting, diarrhea, fever, shivering, headache and rash were recorded. Satisfactory scores were assessed using 10 cm-scale with zero to 10. Zero meant no satisfaction and 10 was equal to the most satisfaction. Data on estimate blood loss, complications of procedure such as cervical injury, uterine perforation and intra-abdominal organ injury were also collected. All patients received antibiotics and analgesics for five days and were instructed to return to the clinic if heavy vaginal bleeding was spotted or with severe lower abdominal pain and developed fever. All patients were instructed to a follow-up within 14 days. The primary outcome was cervical dilatation measurement prior to MVA. Secondary outcome were operative time, intraoperative blood loss, intraoperative complication, needed extra cervical dilation, misoprostol side effect, pre- and post-operative pain scores and patient satisfaction.

Data were analyzed by using the SPSS 13.0 (SPSS Inc., Chicago, USA) for the statistical analysis. Continuous data between two groups were compared using mean and unpaired t-tests were applied. Fisher's exact tests and Chi-square tests were used in categorical data. Level of statistical significance was set at $p \leq 0.05$.

Results

Ninety-four patients in need of first trimester abortions had an indication for MVA during the investigation period. Fourteen patients were excluded with gestational age over 12 weeks, hypertension and no consent given to participate in this study. Participants were divided into two groups of equal numbers. Forty patients received 400 µg misoprostol sublingual administration two hours prior to MVA, the others received same dose of misoprostol in oral administration. Table 1 showed demographic and physical characteristics of the data. The two treatment

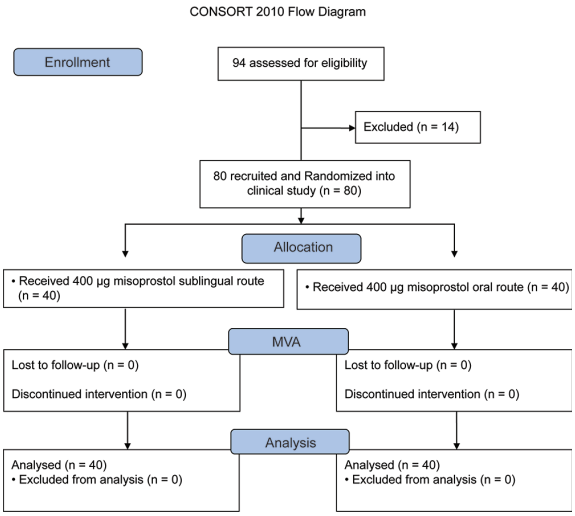

Fig. 1 Flow diagram enrollment of subjects.

groups had no statistic difference in physical characteristic and demographic profiles regarding mean age, body mass index (BMI), income, education, parity, gestational age, history of dilatation and curettage and mean time interval as shown in Table 1.

The cervical outcomes, satisfactory scores and side effects were shown in Table 2. The sublingual group had statistically significant larger mean cervical dilatation than the oral group (7.3±1.5 vs. 5.9±1.4 mm, $p<0.001$). The results were the same both nulliparous and multiparous subgroups (7.1±1.1 vs. 5.7±1.5 mm, $p<0.001$ and 7.7±2.1 vs. 6.2±1.2 mm, $p = 0.02$, respectively). Mean operative time of the sublingual administration was shorter statistical difference than the oral group (5.2±3.3 and 7.3±4.6 min, $p = 0.02$ respectively). One and two patients needed extra cervical dilatation in sublingual and oral administration group respectively. Mean operative blood loss in sublingual and oral were 17.4 and 17.9 ml, respectively (range 5 to 40 ml).

The most common post-operative side effect was abdominal pain. It affected both sublingual and oral group in 45.0 and 52.5 percent of patients respectively. No incidence of cervical injury, uterine perforation, hemorrhage, and re-evacuation were found during the study. The sublingual and oral mean pre-operative pain score were 3.3 and 3.6, while post-operative pain score were 3.4 and 3.7, respectively. The mean patient satisfactory score was equal in both groups. Eight patients had history of previous dilatation and curettage (D&C). They were more satisfied with MVA compared to their previous D&C experiences.

Table 1. Demographic and physical characteristics data

	Sublingual (n = 40)	Oral (n = 40)	*p*-value
Age (years)	30.6±6.0	32.1±6.3	0.31
BMI (kg/m^2)	23.1±4.0	24.5±4.5	0.15
Income (baht/month)			0.48
<10,000	6 (15.0)	3 (7.5)	
>10,000	34 (85.0)	37 (92.5)	
Education			0.12
No	3 (7.5)	5 (12.5)	
Primary school	5 (12.5)	10 (25.0)	
High school	16 (40.0)	11 (27.5)	
Bachelor or higher	16 (40.0)	14 (35.0)	
Obstetric history			
Parity			0.82
Nulliparous	25 (62.5)	23 (57.5)	
Multiparous	15 (37.5)	17 (42.5)	
Gestational age (weeks)	10.1±1.4	9.8±1.4	0.38
History of D&C			1.00
Yes	4 (10.0)	4 (10.0)	
No	36 (90.0)	36 (90.0)	
Time interval (min)	145.1±20.7	140.1±21.1	0.29

Values are presented as mean ± SD or n (%)
BMI = body mass index; D&C = dilatation & curettage
Time interval: mean time interval between taking misoprostol until starting manual vacuum aspiration (MVA)

Table 2. Cervical outcome, satisfactory score and side effect

	Sublingual (n = 40)	Oral (n = 40)	*p*-value
Cervical diameter (mm)			
Nulliparous	7.1±1.1	5.7±1.5	<0.001
Multiparous	7.7±2.1	6.2±1.2	0.02
Cervical dilatation need			1.00
Yes	1 (2.5)	2 (5.0)	
No	39 (97.5)	38 (95.0)	
Operative time (min)	5.2±3.3	7.3±4.6	0.02
Blood loss (ml)	17.4±7.4	17.9±8.6	0.78
Side effect			
Abdominal pain	18 (45.0)	21 (52.5)	0.65
Nausea & vomiting	0 (0)	2 (5.0)	0.49
Fever (≥38°C)	1 (2.5)	0 (0)	1.00
Shivering	1 (2.5)	0 (0)	1.00
Headache	1 (2.5)	2 (5.0)	1.00
Rash	1 (2.5)	0 (0)	1.00
Pain score			
Pre-operative	3.3±3.3	3.6±2.6	0.56
Post-operative	3.4±2.6	3.7±3.2	0.67
Satisfactory score	9.2±1.2	9.2±1.2	0.92

Values are presented as mean ± SD or n (%)
Operative time: mean time between initiate Hegar's dilator until finish MVA

Discussion

WHO recommended cervical preparation prior to surgical evacuation for all women with pregnancy of any gestational age. Any one of these methods, namely oral 200 mg mifepristone, intracervical laminaria, 400 µg sublingual, or vaginal misoprostol was recommended as golden standards[1,5,6].

Among the above choices, misoprostol had the shortest lead-time to action of two to three hours. Thus, it is suitable for cervical priming prior to day-care surgical procedure[1,4,6,7,15].

Misoprostol has difference route administration by sublingual, oral, vaginal, buccal, and rectal routes. Each route has a different pharmacokinetics character[16,17]. Time to peak concentration (TPC) reports revealed that oral and sublingual administration had rapid TPC at about 30 minutes. This is superior to 70-80 minutes of vaginal administration. Level of misoprostol in oral administration rapidly declines by 120 minutes because of first-pass metabolism (de-esterification). However, in vaginal administration, the level was gradually reduced and could still be detected after six hours. The sublingual route achieved the highest peak concentration than oral and vaginal administration (574.8, 287.7 and 125.2 pg/ml, respectively)[16,17]. This is due to the fact that sublingual absorption allowed avoidance of misoprostol's first pass via liver. A lot of blood supply under the tongue and neutral pH in oral cavity were also contributing factors[17]. Misoprostol increased tonus of uterine contractility in eight and 11 minutes for oral and sublingual administration, respectively, compared to 20 minutes for vaginal administration[17].

Previous studies compared misoprostol sublingual and vaginal administration for cervical ripening prior to surgical abortion. They found no significant in cervical dilatation[7,18,19]. The vaginal route showed similar cervical dilation result compared to the oral group[20]. Cervical dilatation and cumulative dilation force of the cervical canal were similar in both oral and sublingual misoprostol administration in Aronsson et al in 2004 trial[8]. Other found that the sublingual route was better than the oral and vaginal routes for cervical priming resulted in more cervical dilation and less side effect than oral administration[10-12].

The current investigation compared the effectiveness of sublingual misoprostol in cervical priming to oral administration. In Thailand, vaginal route was psychologically uneasy for patients and was difficult to be self-administered. Four hundred microgram of misoprostol sublingually administered two hours prior to MVA yielded more cervical

dilatation than oral administration. The difference can be accredited to the absorption kinetic, more systemic bioavailability to cause highest peak concentration level. The mean operative time was less in the sublingual group probably because more cervix dilatation allowed more ease of operation. This was a similar result as those found by Saxenagroup[10,11] and Parveen et al[12].

The limitation of the study was the method for measuring the cervical os by pass through initial Hegar's dilator without resistance. It therefore lacked a tonometer to record pressure when Hegar's was passed through the cervix. All cervical diameters were recorded by surgeons using the relative ease of pass though the initial Hegar's dilator.

Conclusion

The 400 µg misoprostol sublingual administration was more effective than oral administration for cervical preparation prior to MVA in first trimester termination of pregnancy. Both routes of administration had no statistical difference in complication, side effect, blood loss and patients satisfy. No complication was found in the present study. Among Thai population sublingual misoprostol was preferable for cervical priming before MVA.

What is already known on this topic?

Manual vacuum aspiration (MVA) is the better method in surgical abortion more than dilational and curettage. The most important step of MVA is the cervical preparation. Misoprostol has been used for cervical priming that has a shorter spending time than the used of mifepristone and laminaria. Thus, misoprostol is suitable for cervical priming prior to day care surgical procedure. Sublingual administration of misoprostol resulted in the most effective dilation, followed by vaginal and oral routes. However, there are only a few articles reporting comparison the use of 400 µg misoprostol in sublingual and oral administration.

What this study adds?

This investigation looked into the effectiveness of 400 µg misoprostol in sublingual compare to oral administrations at two hours prior to MVA of the first trimester abortion among Thai population.

Ethical approval

The study was approved by Ethics Committee, Faculty of Medicine, Thammasat University, study protocol numbers MTU-EC-OB-1-058/56.

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Potential conflicts of interest

None.

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ประสิทธิภาพของวิธีบริหารยาไมโซพรอสทอลโดยการอมใต้ลิ้นหรือการกินสำหรับการเตรียมปากมดลูกก่อนการทำการขูดมดลูกด้วยเครื่องมือหลอดดูดสุญญากาศชนิดมือถือในการยุติการตั้งครรภ์ไตรมาสแรกโดยวิธีการแบบสุ่มและมีการควบคุม

อวัสดา บุณยัษเฐียร, เด่นศักดิ์ พงศ์โรจน์เผ่า, คมสันติ์ สุวรรณฤกษ์, กรณ์กาญจน์ ภมรประวัติธนะ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิผลของยา misoprostol โดยบริหารยาด้วยการอมใต้ลิ้นเทียบกับการบริหารยาด้วยการกินยาในการขยายปากมดลูกก่อนการทำ MVA ในการยุติการตั้งครรภ์ไตรมาสแรก*

วัสดุและวิธีการ: *สตรีตั้งครรภ์ไตรมาสแรกที่มีภาวะแท้งบุตรและจำเป็นต้องได้รับการขูดมดลูกจำนวน 80 ราย โดยสุ่มแบ่งผู้ป่วยเป็นสองกลุ่ม คือกลุ่มที่ได้รับยาไมโซพรอสทอล 400 ไมโครกรัม อมใต้ลิ้น และกลุ่มที่ได้รับยาไมโซพรอสทอล 400 ไมโครกรัม กินเพื่อเตรียมปากมดลูกก่อนการทำ MVA 2 ชั่วโมง โดยผู้ป่วยจะได้รับการประเมินขนาดของปากมดลูกก่อนการทำ MVA, เวลาที่ใช้ทำหัตถการ, ภาวะแทรกซ้อน, ผลข้างเคียง, ระดับความเจ็บปวด ตลอดจนระดับความพึงพอใจของผู้ป่วยในการขูดมดลูก*

ผลการศึกษา: *ลักษณะของผู้ป่วยทั้งสองกลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติทั้งสองกลุ่ม (อายุเฉลี่ย, ค่าดัชนีมวลกาย, รายได้, ระดับการศึกษา, จำนวนผู้ป่วยที่เคยและไม่เคยคลอดบุตรทางช่องคลอด, อายุครรภ์) เมื่อเปรียบเทียบขนาดของเส้นผ่านศูนย์กลางของปากมดลูกในผู้ป่วยที่อมยาไมโซพรอสทอลใต้ลิ้นกว้างมากกว่ากลุ่มที่กินยาไมโซพรอสทอลอย่างมีนัยสำคัญทางสถิติ (7.3±1.5 และ 5.9±1.4 มิลลิเมตร ตามลำดับ, $p<0.001$) กลุ่มที่อมยาใต้ลิ้นใช้เวลาทำหัตถการ MVA สั้นกว่ากลุ่มกินยาอย่างมีนัยสำคัญทางสถิติ (5.2±3.3 และ 7.3±4.6 นาที ตามลำดับ, $p = 0.02$) ทั้งนี้ผลข้างเคียง ระดับความเจ็บปวด และระดับความพึงพอใจของผู้ป่วยไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติทั้งสองกลุ่ม และไม่พบผู้ป่วยที่มีภาวะแทรกซ้อน เช่น มดลูกทะลุ, ปากมดลูกฉีกขาด, แท้งไม่ครบ และตกเลือดในการศึกษานี้*

สรุป: *การได้รับยาไมโซพรอสทอล 400 ไมโครกรัม 2 ชั่วโมง ก่อนทำหัตถการโดยวิธีการอมใต้ลิ้นมีประสิทธิผลมากกว่าการบริหารยาโดยการกินยาไมโซพรอสทอล ในการเตรียมปากมดลูกก่อนการขูดมดลูกโดยวิธี MVA ในสตรีแท้งบุตรไตรมาสแรก โดยที่ผลข้างเคียง ภาวะแทรกซ้อน ระดับความเจ็บปวด และระดับความพึงพอใจของผู้ป่วยไม่แตกต่างกันทั้งสองกลุ่มอย่างมีนัยสำคัญทางสถิติ*