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Comparison of Sublingual and Vaginal Misoprostol for Cervical Ripening before Curettage: A Randomized Controlled Trial

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ABSTRACT

Objective: To compare the effectiveness and side effects of misoprostol as a cervical ripening agent through two different routes of administration before curettage.

Materials and Methods: The study employed a hospital based prospective randomized controlled trial. A total of 70 patients were simple random divided in two groups for 400 micrograms sublingual and vaginal administration. The drug was administered 6 hours before dilatation and curettage or fractional curettage. Efficacy was assessed on cervical dilatation achieved, pain score and vaginal blood loss. The tolerable limit was noted based on side effects.

Results: The sublingual group had significantly more cervical dilatation than the vaginal group (median cervical dilatation 7 mm vs. 5 mm, $P < 0.001$). Significantly less pain scores (VAS) in sublingual group than vaginal group (3.3 vs. 4.8, $P < 0.001$). Postoperative vaginal blood loss in the sublingual group was significantly greater than the vaginal group (20 ml vs. 10 ml, $P < 0.001$). Other side effects such as fever, chill, nausea, vomiting and diarrhea did not differ in both groups.

Conclusion: Sublingual misoprostol could be more effective for cervical dilatation, but presents greater postoperative vaginal blood loss than vaginal route.

Keywords: Misoprostol, cervical dilatation, local anesthesia

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Introduction

Cervical ripening is necessary for gynecological procedures such as fractional curettage, dilatation and curettage to prevent complications such as cervical injury. Pharmacological cervical ripening is preferable to reduce cervical trauma and make procedures easier[1-3].

Misoprostol is a synthetic prostaglandin E_1 analogue. It has been found to be a useful drug for obstetrics and gynecology because it has the advantages of ease to access, ease to administer, lower cost, stability at room temperature, availability in

different dosage forms and few systemic side effects[1, 4].

Misoprostol is rapidly absorbed and converted to misoprostol acid (active metabolite). Plasma concentration of misoprostol acid reaches its peak in about 30 minutes and declines rapidly. It is primarily metabolized in the liver. The most common side effects after oral administration are nausea, vomiting, diarrhea, abdominal cramps, fever and shivering and are dose dependent[1 ,5, 6]. Vaginal administration has been found to be more effective than oral because of a slower but more constant absorption through vaginal mucosa, but most women try to avoid the vaginal route due to inconvenience and lack of privacy[1]. Sublingual administration has been proven to be more effective than oral because it avoids the first pass effect through the liver and is the most vascular area of the buccal cavity that patients accept due to self-administration and convenience[1, 7].

Studies have shown that 400 micrograms of sublingual misoprostol was very effective for cervical ripening before first trimester abortion[7]. The objective of this study was to assess efficacy of 400 micrograms misoprostol between sublingual and vaginal administration for cervical ripening before curettage.

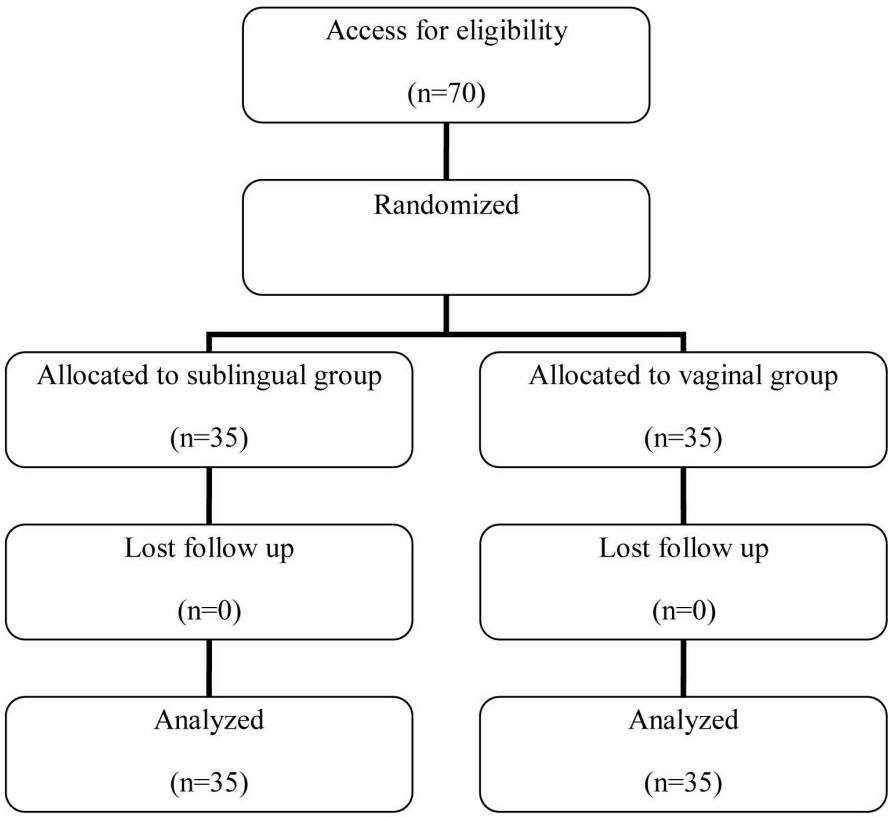
Material and Methods

A simple randomized controlled trial was conducted among 70 patients scheduled for fractional curettage for indication: perimenopausal bleeding or postmenopausal bleeding, dilatation and curettage for first trimester abortion: blighted ovum or fetal demise from May 2014 to December 2014, at the Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Thailand. The study protocol received ethics approval from the Institutional Review Board, Royal Thai Army Medical Department Phramongkutklao Hospital. Patients were recruited after signing a written informed consent. All patients received detailed verbal and written information regarding what to expect after sublingual and vaginal misoprostol administration.

Seventy patients were simple randomized by table of random number in sublingual or vaginal groups of 35 each. All patients were admitted on the day before operation and underwent detailed history-taking and physical examination. The patients in the study group (sublingual route) self-administered 400 micrograms misoprostol (two 200 micrograms misoprostol tablets) in the sublingual area 20 minutes then swallowed 6 hours before operative procedures. Patients in the control group (vaginal route) received 400 micrograms misoprostol (two 200 micrograms misoprostol tablets) soaked in saline and placed in the posterior fornix of the vagina 6 hours before operative procedures performed by resident doctors on duty. After misoprostol administration, vital signs and pain scores were observed and recorded 6 hours after administering the drug, then recorded at intraoperative, 6 and 12 hours postoperative by nurse on duty. The pain scoring used a visual analogue score (VAS), recordings were made on a 0-10 numerical scale; scores between 0 to 3 were considered to be mild, 4 to 6, moderate and 7 to 10 as severe pain[8]. The operative procedures were started using local anesthesia (1% xylocaine without adrenaline 10 ml by paracervical block).

Primary outcomes included cervical dilatation measured with maximum size of Hegar's dilator (sizes 1 to 12) passing through the cervical area without resistance at the beginning of the surgical procedures. Secondary outcomes assessed pain during dilatation, surgical procedures and postoperative side effects such as nausea, vomiting, fever, shivering, diarrhea and vaginal bleeding (4 × 4-inch gauze, 1 piece, 2.5 ml)[9] at 6 and 12 hours after surgery.

The data were analyzed using STATA/MP 12 statistical software. Continuous variables were compared by student's t-test when data were normally distributed or Mann-Whitney U test when data were not normally distributed. Categorical variables were analyzed with Chi-square test or Fisher's exact test to compare the outcomes between the study and the control groups. A p-value less than 0.05 was considered statistically significant.



Results

Patients' demographic characteristics of both the study (sublingual route) and control groups (vaginal route) were compared as shown in Table 1. Age, parity and height did not differ between the 2 groups but patients in the sublingual group had significantly more body weight than those in the vaginal group (59.1 kg vs. 51.8 kg, P 0.003). Underlying disease such as hypertension, diabetic mellitus, asthma, thyroid and thalassemia were similar: 40% in the sublingual group and 31.5% in the vaginal group, indicating curettage did not differ between the two groups.

All patients received local anesthesia (paracervical block). Surgical procedure was classified as fractional curettage, 45.7% in the sublingual group and 42.9% in the vaginal group, dilatation and curettage, 54.3% in the sublingual group and 57.1% in the vaginal group. Surgery and anesthetic times for both groups were similar, approximately 20 minutes. Primary outcomes for cervical dilatation and parameter of operative procedures undertaken in both groups were also compared as shown in Table 2.

Median cervical dilatation was more significant in the sublingual group than in the vaginal group (7 mm vs. 5 mm, $P < 0.001$). Patients in the sublingual group had significantly less pain scores (VAS) than in the vaginal group (3.3 vs.4.8, $P < 0.001$. Of a total of 35 patients in the vaginal group, for 5 (14%) patients, the tablet was only partially absorbed, while in the sublingual group, the drug was absorbed completely in 20 minutes by all patients. All patients reported no complications such as cervical laceration and uterine perforation during surgery.

Vaginal bleeding occurred more in the sublingual group than in the vaginal group concerning 6 hours postoperative side effects (20 ml vs.10 ml, $P < 0.001$). Other side effects at 6 and 12 hours postoperative did not significantly differ between groups. Secondary outcomes to assess postoperative side effects are presented in Table 3.

Table 1. Patient characteristics.

	Sublingual N (%)	Vaginal N (%)	P
Age* (years) (mean ± SD)	39.1 ± 11.8	40.8 ± 15.8	0.621
Weight** (kg) (mean ± SD)	59.1 ± 11.6	51.8 ± 7.4	0.003[t]
Height** (cm) (mean ± SD)	157.3 ± 5.1	158.3 ± 6.2	0.441
Parity (N, %)			0.089
Nulliparous	24 (68.6)	17 (48.6)	
Multiparous	11 (31.4)	18 (51.4)	
Procedure			0.810
Fractional curettage	16 (45.7)	15 (42.9)	
Dilatation and curette	19 (54.3)	20 (57.1)	
Indication			0.201
Blighted ovum	12 (34.3)	10 (28.6)	
Fetal demise	7 (20)	10 (28.6)	
Perimenopausal bleeding	12 (34.3)	6 (17.1)	
Postmenopausal bleeding	4 (11.4)	9 (25.7)	

* Data were median(min-max)

** Data were mean ± SD

[t] $p < 0.05$ was statistically significant

Table 2. Intra-operative parameters.

	Sublingual N (%)	Vaginal N (%)	P
Surgeon			0.925
3rd year resident	2 (5.7)	2 (5.7)	
2nd year resident	17 (48.6)	15 (42.9)	
1st year resident	16 (45.7)	18 (51.4)	
Pain, VAS (mean ± SD)	3.3 ± 1.2	4.8 ± 1.5	< 0.001*
	Median (min-max)	**Median (min-max)**	
Cervical dilatation (mm)	7 (5-12)	5 (3-10)	< 0.001*
Temperature pre-operative (°C)	36.8 (35.5-37.2)	36.9 (36-37)	0.103
Temperature post-operative (°C)	37 (36.5-37.8)	37.2 (36.3-37.7)	0.381

*$p < 0.05$ was statistically significant

Table 3. Side effects.

	Sublingual	Vaginal	P
Side effects 6 hr. post-operative*	32 (91.4)	40.8 ± 15.8	
Total side effects**	49	25	
Nausea and vomiting	10 (20.4)	7 (28.0)	0.403
Diarrhea	4 (8.2)	5 (20.0)	1.000
Shivering	10 (20.4)	4 (16.0)	0.073
Fever	5 (10.2)	1 (4.0)	0.198
Vaginal bleeding	20 (40.8)	8 (32.0)	0.003[t]
blood loss (ml)***	20 (15-25)	10 (5-15)	< 0.001[t]
Side effects 12 hr. post-operative*	8 (22.8)	9 (25.7)	
Total side effects**	8	9	
Nausea and vomiting	1 (12.5)	1 (11.1)	1.000
Diarrhea	1 (12.5)	-	1.000
Shivering	-	-	-
Fever	-	-	-
Vaginal bleeding	6 (75.0)	8 (88.9)	0.550
blood loss (ml)***	5 (5-7.5)	5 (5-7.5)	0.680

Data are presented as numerals (%)

*Data are presented as total number equal to 35 each group

**Data indicated one or more side effects each person

***Data used median (min-max)

[t] $p < 0.05$ was statistically significant

Discussion

Different gynecological problems including abnormal uterine bleeding, perimenopausal bleeding, postmenopausal bleeding and first trimester abortion need to be diagnosed and treated by gynecologic procedures: fractional curettage, dilatation and curettage or operative hysteroscopy. Cervical dilatation is the most critical surgical procedure as most cervical injuries and uterine perforation are due to forceful dilatation of the cervix. Adequate cervical dilatation decreases pain and facilitates an uncomplicated operation. Previously, an osmotic dilator (laminaria) has been used for cervical ripening. These days, misoprostol, a synthetic prostaglandin E^1 analog is widely prescribed to prevent and treat gastric ulcer resulting from long term use of nonsteroidal anti-inflammatory drugs. Currently, misoprostol is used for cervical ripening in labor induction and termination of pregnancy in the first trimester. The primary advantages of misoprostol are low cost, ease to access, ease to administer, stability at room temperature, few systemic side effects and availability in different dosage forms. It can be given by oral, sublingual, vagina or rectal routes.

The present study assessed that cervical dilatation achieved with misoprostol was more favorable with the sublingual group compared with the vaginal group. The vaginal route has been claimed to be more beneficial than the oral route. The study by Zieman et al[10], regarding pharmacokinetics of misoprostol reported that systemic bioavailability after vaginal administration was three times higher than after oral administration. This finding was probably due to prolonged contact with vaginal mucosa that being vary vascular, leads to a long lasting and progressively increasing plasma level. However, drug absorption through the vaginal mucosa is inconsistent with large

individual variations. Another way misoprostol is rapidly absorbed is through the vascular buccal mucosa completely within 10-15 minutes. The study of Tang et al compared the pharmacokinetics of misoprostol by sublingual, oral and vaginal route with the addition of water and found that sublingual misoprostol had shortest time to peak concentration, achieved significantly higher peak serum concentrations and demonstrated the greatest bioavailability of all other routes[11,12]. The present study enrolled patients including pregnant women from the first trimester abortion and nonpregnant women from perimenopausal or postmenopausal bleeding, and all patients used a simple randomized sampling to compare the effectiveness of sublingual and vaginal misoprostol for cervical ripening. The surgeon was blinded to the route of administration of misoprostol before dilatation and curettage or fractional curettage.

In our study, the sublingual misoprostol group could dilate the cervix more than the vaginal misoprostol group (7 mm vs. 5 mm) with similar results found by Saxena et al[1]. Parveen et al[13], and Vimala et al[14]. This result can be attributed to the different absorption and pharmacokinetics described as above. Regarding intraoperative pain scores, the sublingual misoprostol group had lower moderate pain scores compared with the vaginal group (51.4% vs. 74.3%) according to the study by Saxena et al[1]. Our study found vaginal blood loss occurred more in the sublingual group (20 ml vs. 10 ml) as similarly reported by Parveen et al[13], and Kaur et al[15], that could be explained based on the greater cervical ripening and dilatation achieved in this group. A slight blood loss occurred in the vaginal group similar to that found by Preutthipan S et al[16]. This was confirmed by a pharmacokinetic finding that sublingual misoprostol was more effective than the vaginal route leading to better ripening cervix and greater dilatation of vascular tissue supplied at the cervical area. Other side effects 6 hours after curettage included nausea and vomiting (20.4% vs. 28%, P = 0.403), diarrhea (8.2% vs. 20%, P = 1.000), shivering (20.4% vs. 16%, P = 0.073) and fever (10.2% vs. 4%, P = 0.198), respectively. These were observed more frequently in the sublingual group, probably due to the higher bioavailability of sublingual misoprostol, but the side effects in both groups did not differ significantly.

The sublingual route can be self-administered, avoids pain from vaginal administration and decreases hospital stay and costs. The limitation of this study was the number of patients enrolled was too small to make a definitive conclusion. A larger sample size and assessing the acceptability by patients should be considered for future research.

Conclusion

The sublingual misoprostol route might be more effective than the vaginal route for cervical dilatation before curettage. However, greater postoperative blood loss was observed while other side effects did not differ.

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การศึกษาเปรียบเทียบวิธีบริหารยาไมโซพรอสทอล โดยการอมใต้ลิ้นกับเหน็บยาทางช่องคลอด เพื่อเตรียมความพร้อมของปากมดลูกสำหรับการขูดมดลูก

สุกัญญา ชำนาญ, สุทธิดา อินทรบุหรั่น

วัตถุประสงค์*: เพื่อศึกษาประสิทธิภาพและผลข้างเคียงของการให้ยาไมโซพรอสทอล ระหว่างอมใต้ลิ้นเปรียบเทียบกับเหน็บช่องคลอด ในการเตรียมความพร้อมของปากมดลูกสำหรับการทำหัตถการทางนรีเวช*

วัสดุและวิธีการ*: ผู้ป่วยที่ได้รับการนัดหมายมาทำหัตถการขูดมดลูกจำนวน 70 คน จะถูกสุ่มแบ่งเป็น 2 กลุ่ม โดยทั้งสองกลุ่มจะได้รับยาไมโซพรอสทอล 400 ไมโครกรัม ก่อนทำหัตถการ 6 ชั่วโมง กลุ่มแรกจะบริหารยาโดยการอมใต้ลิ้น และกลุ่มที่สองจะเหน็บยาทางช่องคลอด ประสิทธิภาพจะประเมินจากการขยายของปากมดลูก อาการปวด ภาวะเลือดออกจากช่องคลอด*

ผลการศึกษา*: กลุ่มที่บริหารยาโดยการอมใต้ลิ้นสามารถขยายปากมดลูกได้มากกว่ากลุ่มที่เหน็บทางช่องคลอดอย่างมีนัยสำคัญ (7 มิลลิเมตร และ 5 มิลลิเมตร ตามลำดับ P < 0.001) อาการปวดขณะทำหัตถการในกลุ่มอมใต้ลิ้นพบน้อยกว่ากลุ่มที่เหน็บทางช่องคลอดอย่างมีนัยสำคัญ (3.3 คะแนน และ 4.8 คะแนน ตามลำดับ P < 0.001) ภาวะเลือดออกทางช่องคลอดพบในกลุ่มอมใต้ลิ้นมากกว่ากลุ่มที่เหน็บทางช่องคลอดอย่างมีนัยสำคัญ (20 มิลลิลิตร และ 10 มิลลิลิตร ตามลำดับ P < 0.001) ส่วนผลข้างเคียงอื่นๆ ได้แก่ ไข้หนาวสั่น คลื่นไส้ อาเจียน ถ่ายเหลว พบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญ*

สรุป*: ยาไมโซพรอสทอล 400 ไมโครกรัม ใช้วิธีบริหารโดยการอมใต้ลิ้น พบว่า มีประสิทธิภาพในการขยายปากมดลูกได้ดีกว่า แต่มีผลทำให้เลือดออกทางช่องคลอดมากกว่าวิธีเหน็บทางช่องคลอด สำหรับผลข้างเคียงอื่นไม่แตกต่างกัน*