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Comparison of Sublingual and Vaginal Misoprostol for Termination of Early Pregnancy Failure: A Randomized Controlled Trial

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ABSTRACT

Objective: To compare the complete abortion rate, the induction-abortion time and the side effects of 800 µg misoprostol via vaginal and sublingual routes.

Materials and Methods: One hundred and twenty healthy pregnant women with early pregnancy failure from August 2012 to August 2013 at the Department of Obstetrics and Gynecology, Chonburi Hospital, were included. In Group 1 (n=60), 800 µg misoprostol with 2-3 drops of normal saline were placed in the posterior vaginal fornix. In Group 2 (n=60), 800 µg misoprostol was sublingually given. If the complete abortion did not occur, the repeated medication in the same route would be done every 6 hours for maximum of three doses in total.

Results: There was no difference in the complete abortion rate between two groups (60.0% vaginal; 68.3% sublingual, p=0.44). The mean induction-abortion time was shorter in the sublingual group compared to the vaginal group (21.1±10.2 hrs vaginal; 12.6±3.9 hrs sublingual p=0.03). Heavy bleeding was common in the sublingual group. Side effects of both groups were similar which included nausea, fever, headache, diarrhea and abdominal pain.

Conclusion: Sublingual misoprostol was as effective as vaginal misoprostol. Induction-abortion time was shorter in the sublingual group. Most side effects of both groups were similar except heavy bleeding was more common in the sublingual group.

Keywords: misoprostol, early pregnancy failure, sublingual, vaginal

Introduction

Approximately 15% of pregnancies result in spontaneous miscarriage[1]. Treatments usually include expectant management, medical induction of abortion or surgical evacuation[2]. Surgical abortion is currently the standard management for the termination of pregnancies occurring in the first 12 weeks gestation in many countries. The success rate of this method is more than 95%. However, the procedure is associated with major morbidity in up to 1% and minor morbidity in 10% such as pelvic infection, uterine perforation, cervical trauma and Asherman's syndrome[3,4]. Waiting for spontaneous abortion is also an option; nonetheless, the success rate is low (< 50%). Therefore, the option is inappropriate for a woman who needs immediate treatment[5].

Medical management to induce abortion has been widely used since 1970[6] and costs less than surgical treatment[7]. Mifepristone 600 mg orally followed approximately 48 hrs later by misoprostol 400 µg orally is the WHO's recommended regimen for termination of pregnancy in the first trimester[8]. Efficacy with the regimen is approximately 92% in woman with pregnancy up to 49 days[8,9]. However, mifepristone is not available in Thailand.

Misoprostol is a synthetic prostaglandin E1 analogue and is stable at room temperature. It increases uterine tone[10] and has been used for prevention of gastric ulcer, cervical priming before transvaginal procedures, induction of labor, prevention of postpartum hemorrhage and medical abortion[11]. The WHO's recommended misoprostol regimen is 800 µg vaginally or sublingually administered, and the repeated interval is not less than 3 hours and not over 12 hours for up to three doses[8]. This regimen is 75-90% effective. Oral route is not recommended due to its low efficacy. Optimal dosage and route of administration have not been definitively determined because of the different pharmacokinetic[9-11]. Earliest peak blood concentration was achieved in the sublingual group as compared to rectal, baccal and vaginal administrations[12,13]. Currently, the standard protocol for medical termination of early pregnancy in Thailand is intravaginal administration of misoprostol 200-800 µg, every 6-12 hours and maximum dosage is 3,600 µg[14]. Despite various studies, a wide variety of misoprostol regimens have been used with varying degrees of success[13,15]. Currently, there have been no previous studies comparing sublingual and intravaginal misoprostol administrations at equal doses in Thailand. We conducted this research to determine the effectiveness and side effects of vaginal and sublingual administrations of 800 µg misoprostol in case of early pregnancy failure. The primary outcome was the complete abortion rate. The secondary outcome was the mean induction to abortion interval which was defined from the first dose of misoprostol to the time when the product of conceptus passed through the cervix. Another secondary outcome was the occurrence of adverse effects.

Materials and Methods

A prospective randomized trial was done to one hundred and twenty healthy pregnant women with early pregnancy failure from August 2012 to August 2013, at the Department of Obstetrics and Gynecology, Chonburi Hospital, Thailand. The study received an ethical approval from the Ethical Board of Chonburi Hospital. Gestational age was calculated from last menstrual period or transvaginal ultrasonography. Early pregnancy failure is defined as 1) an intrauterine gestational sac with a mean diameter of 25 mm or greater and no visible embryonic pole; 2) an embryonic pole of 5-14 mm with no cardiac activity; and 3) abnormal growth or persistent absence of fetal cardiac activity on a second scan 7-10 days later[16]. In addition, all participants should be over 18 years old. Parental consent was required if the participant's age was less than 18 years old. Women with suspected ectopic pregnancy, heavy vaginal bleeding, and maternal history of asthma or cardiac disease, open internal cervical on speculum examination, history allergy to prostaglandins, vital sign unstable and an inability to confirm pregnancy failure or intrauterine gestational sac location were excluded from this study.

All participants gave both written and verbal informed consents and were admitted to the hospital. Complete history taking, physical examination, complete blood count and coagulation profile were performed. We used and assigned blocks of four randomizations to two groups of participants. Cards labeled with the assigned route were placed in sealed, opaque envelopes which were filled and labeled in accordance with the list of randomizations. The allocation was concealed by the use of sealed number of treatments. In Group 1 (n = 60), they were given 4 tablets of 200 µg misoprostol with 2-3 drops of normal saline placed in the posterior vaginal fornix by digital insertion. The women remained in the semiprone position for 30 min. In Group 2 (n = 60), 4 tablets of 200 µg misoprostol were sublingually given. Following misoprostol administration, vital signs, presence of uterine bleeding, conceptive products, pain intensity and side effects such as fever, abdominal pain, nausea, vomiting, diarrhea

and headache were closely observed and recorded. Complete abortion is defined as the termination of pregnancy with the complete expulsion of conceptus without the need for surgical intervention or additional misoprostol dose. If the complete abortion did not occur, the repeated induction in the same route would be done every 6 hours for maximum of three doses. The treatment was considered a failure if the pregnancy was still continuing after 48 hours from the third dose of misoprostol. Antibiotics were not routinely given. Acetaminophen was provided for pain relief[8].

Dilatation and curettage were performed when the incomplete abortion occurred. The physicians were on call based on the clinical judgment to perform emergency dilatation and curettage with being unaware of the patient's treatment before. If the pregnancy was still continuing until 48 hours after the third dose of misoprostol, elective surgical evacuation would be performed. After being discharged, women were scheduled to return in the next 2 weeks for follow up and evaluation.

The assessment of satisfaction ranged from dissatisfied, satisfied and very satisfied. The pain was assessed by visual analogue scale. Data on side effects, which included documentation of heavy bleeding, fever, chill, abdominal pain, diarrhea, nausea and vomit were collected after misoprostol administration[10,11].

In the calculation of sample size, we hypothesized that we assumed a 68.0% efficacy rate for treatment with 800 µg intravaginal misoprostol[17]. The sample size would have 80% power to detect the treatment effects with significance at 5% level (α value). The sample size formula was

$$N = \frac{[Z_{\alpha/2}\sqrt{2\bar{P}(1-\bar{P})} + Z_{\beta}\sqrt{P_1(1-P_1) + P_2(1-P_2)}]^2}{(P_1-P_2)^{2-}}$$

Sixty participants of each group were a sufficient number to give statistical significance.

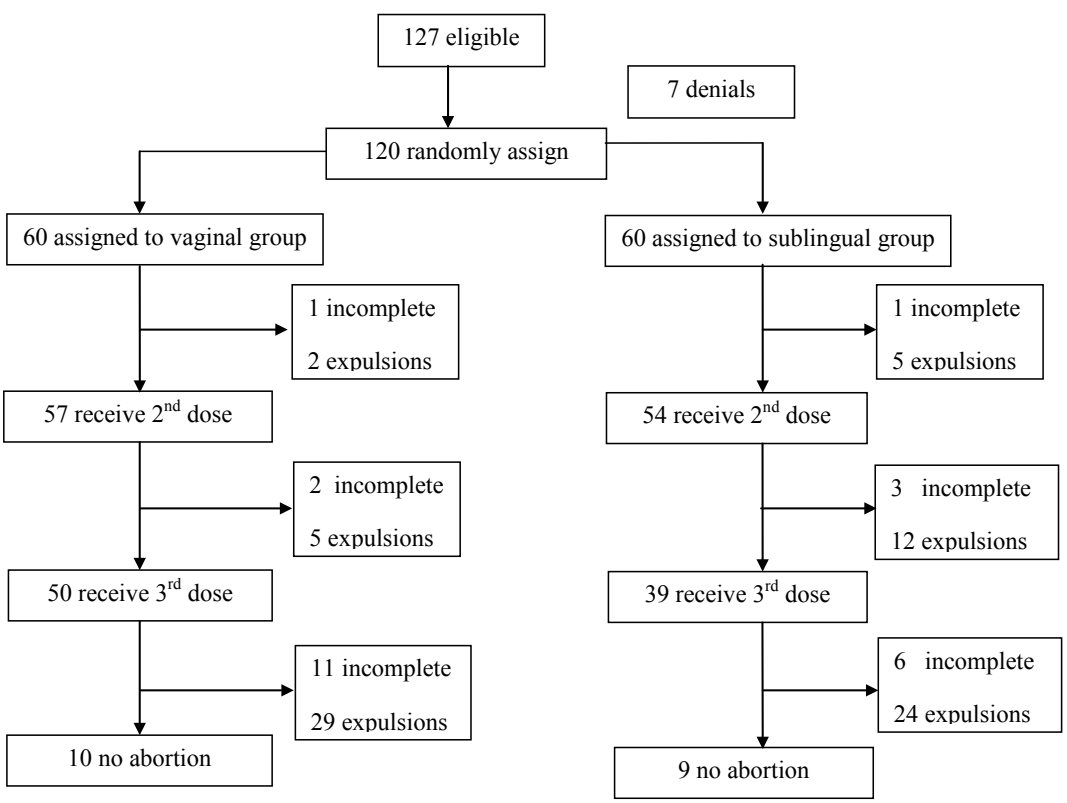

Fig. 1. Trial Profiles

Statistical Analysis

Data were analyzed with the SPSS software (version 17.0). Continuous variables were compared by Student's *t*-test if the data were normally distributed. Categorical variables were analyzed with χ^2-test and Fisher exact test. Statistical significance was considered at $p<0.05$.

Results

One hundred and twenty seven women were initially enrolled in the trial and seven women denied to join the research program. These women were randomized into either administration 800 µg of misoprostol sublingually or vaginally. Demographic characteristics of the patients are shown in Table 1. Maternal age, marital status, gestational age, parity, blood pressure, height, weight, BMI, Previous uterine scar and previous abortion history were not different between 2 groups.

Table 1. Demographic characteristics

	Vaginal	Sublingual	P
Mean ± SD of maternal age at delivery	28.02 ± 7.23	33.25 ± 6.19	< 0.05
Mean ± SD of pre-pregnancy BMI (kg/m^2)	22.85 ± 9.30	28.34 ± 5.25	< 0.05
Mean ± SD of total weight gain (kg)	12.28 ± 5.94	9.23 ± 4.52	< 0.05
Primigravida	357 (34.90%)	64 (18.82%)	< 0.05
Age (years)	29.4 (7.3)	29.5 (6.2)	0.22
Weight (kg)	54.8 (14.1)	55.2 (11.4)	0.59
Height (cm)	155.9 (6.3)	155.1 (6.3)	0.77
BMI (kg/m^2)	22.5 (4.4)	22.9 (4.0)	0.51
Hemoglobin (g/dl)	11.7 (1.1)	11.8 (1.4)	0.26
Preabortion systolic blood pressure (mmHg)	112.9 (12.9)	111.4 (11.2)	0.43
Preabortion diastolic blood pressure (mmHg)	70.8 (11.1)	69.3 (9.1)	0.56
Preabortion pulse rate counts/min	78.8 (8.3)	76.9 (10.1)	0.43
Nulliparity	24 (40.0%)	24 (40.0)	1.00
Married	31 (51.7%)	38 (63.3%)	0.26
Previous uterine scar	3 (5.0%)	6 (10.0%)	0.30
Previous abortion	7 (11.6%)	5 (8.3%)	0.26
Gestational age (day)	69.0 (15.4)	67.9 (13.7)	0.36
Type			
Embryonic death	29 (48.3%)	24 (40.0%)	0.46
Anembryonic pregnancy	31 (51.6%)	36 (60.0%)	

Data are presented as numbers of SD or percent.
No significant difference was detected between two groups

Outcomes stratified by medical abortion regimen are presented in Table 2. The rate of success was 60.0% and 68.3% in Groups 1 and 2, respectively.

Table 2. Outcomes of medical abortion stratified by two different regimens

	Vaginal (n = 60)	**Sublingual (n = 60)**	**P**
Abortion with single dose	3 (5.0%)	6 (10.0%)	0.49
- Complete abortion	2 (3.3%)	5 (8.3%)	0.44
- Incomplete abortion	1 (1.7%)	1 (1.7%)	1.00
Received second dose	57 (93.3%)	54 (90.0%)	0.49
Abortion with two doses	7 (11.7%)	15 (25.0%)	0.09
- Complete abortion after second dose	5 (8.3%)	12 (20.0%)	0.11
- Incomplete abortion after second dose	2 (3.3%)	3 (5.0%)	1.00
Received third dose	50 (83.3%)	39 (65.0%)	0.06
Abortion with three doses	40 (66.7%)	30 (50.0%)	0.09
- Complete abortion after third dose	29 (48.3%)	24 (45.3%)	0.46
- Incomplete abortion after third dose	11 (18.3%)	6 (10.0%)	0.29
Overall abortion	50 (83.3%)	51 (85.0%)	1.00
Overall complete abortion	36 (60.0%)	41 (68.3%)	0.44
Overall incomplete abortion	14 (23.3%)	10 (16.7%)	0.49
No abortion	10 (16.7%)	9 (15.0%)	0.22
Overall curettage	24 (40.0%)	16 (26.7%)	0.35

Data are presented as numbers of percent.
No significant difference was detected between two groups.

The abortion rate was not different between sublingual and vaginal groups and there was no statistical significance of the complete abortion in the sublingual group (68.3%) compared with those who received 800 µg intravaginal misoprostol (60.0%). The induction-abortion time was significantly shorter in the sublingual group compared to the vaginal group (Table 3).

Table 3. Induction-abortion time stratified by two different regimens

	Vaginal n = 50	**Sublingual n = 51**	**P**
Induction-abortion time (hr)	21.1(10.2)	12.6(3.9)	0.03*
Min-max (hr)	4.0-45.0	4.0-22.0	

Data are presented as mean (SD)

There was no difference in the abdominal pain between two groups (31.7% vaginal; 45.0% sublingual). Similarly, there was no difference in the report of headache (13.3% vaginal; 6.7%sublingual), nausea (11.7% vaginal; 10.0% sublingual) and diarrhea (5.0% vaginal; 6.7% sublingual). However, there was significantly higher rate of heavy bleeding in the sublingual group compared to the vaginal group (5.0% vaginal; 20.0% sublingual, p = 0.01). Mean pain score was not different between two groups. Women from both groups were equally satisfied with the treatments that they have received; none of the participants was dissatisfied.

Table 4. Adverse effects that occur within 48 hours after last dose

Side effects	Vaginal	Sublingual	P
Diarrhea	3 (5.0%)	4 (6.7%)	0.60
Abdominal pain	19 (31.7%)	27 (45%)	0.23
Nausea	7 (11.7%)	6 (10.0%)	0.58
Fever	4 (6.7%)	7 (11.7%)	0.34
Heavy bleeding	3 (5.0%)	12 (20.0%)	0.01*
Headache	8 (13.3%)	4 (6.7%)	0.44

Data are presented as mean (%)

Discussion

There are many randomized trials that compare different routes, doses and dosing intervals of misoprostol used in the medical abortion[13, 19-23]. Some studies investigate outpatient services. However, in Thailand, an abortion without medical or legal indication is illegal and the misoprostol used is under control of the government. For this reason, all women were admitted. Several studies found that the misoprostol alone is effective for termination in pregnancy with a range of 60-80%[8, 9, 24].

Our primary outcome was efficacy rate of complete abortion in 48 hours after last dose of misoprostol. There was no difference in complete abortion rate between 800 µg misoprotol sublingually applied every 6 hours and 800 µg misoprostol vaginally applied every 6 hours. The findings are very similar to previous studies[15, 22, 23]. However, the success rate of sublingual protocol is higher than previous study of sublingual misoprostol in Thailand (68.3% compared 32.1%)[19] because of different doses among two studies.

Previous study found that an additional 1 week course of sublingual misoprostol did not improve the success rate or shorten the duration of vaginal bleeding[15]. Further studies need to investigate the proper doses and dosing intervals as well as the time from last dose of misoprostol to the time of surgical evacuation.

Tang OS, et al. studied[12] the pharmacokinetics of oral, rectal, buccal, sublingual, vaginal and vaginal moistened tablets of misoprostol 400 µg in 40 women undergoing the first trimester abortion. They found that the sublingual misoprostol had shortest time to peak concentration, highest peak concentration and greatest bioavailability when compared to other routes. The vaginal misoprostol has sustained its activity for longer period than after sublingual treatment, with decreased activity occurring only after 4 hours. At the end of 6 hours, the serum of misoprostol acid after vaginal ministration is higher than those of sublingual and oral route. In contrast to study from Zieman, et al[25], the bioavailability after vaginal and sublingual administrations is similar. In addition, regular uterine contractions are sustained for longer period of time (> 4 hours) after vaginal administration than after sublingual route (2-3 hours) which may lead to stronger contractility during the treatment period in vaginal

administration[13,15]. Furthermore, a direct transport of prostaglandins seems to occur from vagina to the uterus which can also contribute to the better efficacy after vaginal administration[25].

Creinin et al.[26] showed that there was no obvious relationship between the ultrasound finding and the need for surgical intervention in women treated with misoprostol for early pregnancy failure. They suggested that a thickened endometrial lining is a normal finding after miscarriage. Therefore, decisions regarding treatment should be based on clinical signs and symptoms rather than endometrial thickness alone. In this study, incomplete abortion was diagnosed based on bleeding and abdominal pain persisted or increased after passing conceptus and the vaginal ultrasonographic scan showed a hyperechoic or a mixed hyper/hypoechoic region of any diameter in the uterine cavity. If the incomplete abortion or no abortion occurred, dilatation and curettage was performed instead of MVA because MVA is more costly than dilatation and curettage and MVA is not available in our hospital.

Mean time to fetal expulsion was 21.1 hours after vaginal administration and 12.6 hours in sublingual administration. There is the statistical significance in difference of induction-abortion time between two groups ($p = 0.03$). This finding may be explained by that the sublingual route is shortest to peak of concentration and greatest bioavailability in some researches[12,13].

When comparing between two routes, our study found that most of side effect profiles were similar for both routes with no statistically significant difference. However, heavy bleeding was more prevalence in sublingual group ($p = 0.01$). Nonetheless, recording heavy bleeding was performed by history inquiry which defined poor definition use over 3 pads per day or falling hematocrit in selective cases that have anemic symptom .We do not serial hematocrit in all cases.

Conclusion

In addition to surgical evacuation, misoprostol offers a treatment for termination in early pregnancy failure as an alternative because it is effective, easily tolerated by women and can be provided by practitioners who are without surgical skills. Our data demonstrate that overall efficacy and acceptability of medical abortion of early pregnancy failure are good. Both sublingual and vaginal misoprostols resulted in same clinical outcomes. The adverse effects were similar in both groups except bleeding was more common in sublingual group. Mean induction-abortion time was significantly shorter in sublingual group.

Advantages

Our results showed that there is no statistical significance in the efficacy rate from termination in early pregnancy failure. The intravaginal misoprostol can sometimes be uncomfortable and invasive in patients, especially in women with a history of sexual violence and post traumatic stress disorder[27]. Additionally, the sublingual administration did not need the practitioners to provide drugs.

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Conflict of interest

The authors do not have any conflict of interest.

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การศึกษาเปรียบเทียบการใช้ยามิโซพรอสตอลเหน็บทางช่องคลอดและอมใต้ลิ้นในการยุติครรภ์ล้มเหลวระยะแรก

อารีรัตน์ สอนเสนาะ, ธีรภัทร จุลละพราหมณ์

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบอัตราความสำเร็จในการยุติการตั้งครรภ์อย่างสมบูรณ์ ระยะเวลาที่ใช้ และผลข้างเคียง ในการใช้ยามิโซพรอสตอลเหน็บทางช่องคลอดและอมใต้ลิ้นในการยุติครรภ์ล้มเหลวระยะแรก*

วัสดุและวิธีการ: *ผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นการตั้งครรภ์ล้มเหลวในระยะแรกจะถูกสุ่มแบ่ง ได้กลุ่มละ 25 คน กลุ่มแรกได้ขนาด 800 ไมโครกรัม เหน็บทางช่องคลอด และกลุ่มที่สองได้ขนาด 800 ไมโครกรัม อมใต้ลิ้น ถ้าไม่พบการแท้งอย่างสมบูรณ์เกิดขึ้น ให้ยาซ้ำในช่องทางเดิมได้ทุก 6 ชั่วโมง เต็มที่ 3 ครั้ง*

ผลการศึกษา: *ไม่พบความแตกต่างในจำนวนผู้ป่วยที่เกิดการแท้งอย่างสมบูรณ์ (60% และ 68.3% ตามลำดับ p = 0.44) ค่าเฉลี่ยเวลาที่ใช้ในการแท้งน้อยกว่าในกลุ่มที่สองอย่างมีนัยสำคัญ (21.1±10.2 ชั่วโมง เหน็บช่องคลอด; 12.6±3.9 ชั่วโมง อมใต้ลิ้น p = 0.03) ภาวะเลือดออกมากพบได้บ่อยกว่าในกลุ่มที่สอง ผลข้างเคียงอื่นเช่นการปวดท้อง ปวดศีรษะ อาเจียน ไข้ และถ่ายเหลว พบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญ*

สรุป: *ไม่พบความแตกต่างในประสิทธิผลของยามิโซพรอสตอลขนาด 800 ไมโครกรัม เหน็บทางช่องคลอดและอมใต้ลิ้นในการเกิดการแท้งอย่างสมบูรณ์ เวลาในการแท้งน้อยกว่าในกลุ่มอมใต้ลิ้น ผลข้างเคียงไม่แตกต่างกันยกเว้นเรื่องเลือดออกมากพบได้บ่อยในกลุ่มอมใต้ลิ้น*