Original Article

Efficacy of Sublingual Administration Misoprostol 600 mcg Versus 800 mcg for Induced Abortion in Women with Early Pregnancy Loss: A Randomized Controlled Trial

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Objective: To compare the complete abortion rate, the induction-to-abortion time, and side effects between 600 mcg and 800 mcg misoprostol sublingually.

Materials and Methods: Total, of 108 pregnant women with gestational age less than 12 weeks with early pregnancy loss from March 2020 to February 2021 at the Department of Obstetrics and Gynecology, Queen Savang Vadhana Memorial Hospital, were included. For group 1 (n=54), 600 mcg misoprostol was administrated sublingually. For group 2 (n=54), 800 mcg misoprostol was administrated sublingually. If the abortion did not occur, the repeated misoprostol in the same dose would be administrated sublingually every 6 hours for a maximum of three doses.

Results: There was no significant difference in the complete abortion rate between the two groups (55.6% in the 600 mcg misoprostol group, 64.7% in the 800 mcg misoprostol group, p=0.339, and 95% CI 0.082 to 1.862). The induction-to-abortion time was 9.5 hours (IQR 6.75 to 48.00) in the 600 mcg misoprostol group and 10 hours (IQR 6.00 to 60.00) in the 800 mcg misoprostol group. The side effects of both groups were similar, included abdominal pain, diarrhea, nausea and vomiting, fever, heavy bleeding, and headache.

Conclusion: The efficacy of the 600 mcg misoprostol was noninferior to 800 mcg misoprostol. The adverse effects were similar in both groups. Mean induction-to-abortion time was also similar in both groups.

Keywords: Early pregnancy loss; Misoprostol; Medical abortion

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Spontaneous pregnancy loss is approximately 8% to 20% of known pregnancies, and 80% of spontaneous pregnancy losses occur in the first trimester[1]. Early pregnancy loss is defined as a nonviable intrauterine pregnancy within the first 12 weeks and 6 days of gestational age[2]. Treatment options are expectant, medical, and surgical managements. Surgical management, such as evacuation or dilatation and curettage, has a success rate of more than 95%. However, the procedure is associated with morbidities, such as cervical trauma, pelvic infection, uterine perforation, and Asherman's syndrome. Therefore, surgical management is considered in pregnant women who present with hemodynamic instability, active bleeding, and signs of infection or who desire surgical management[1,2]. Medical abortion is often successful at a rate of 84% and also decreases complications from surgical management. Moreover, medical abortion with misoprostol is one of the most cost-effective managements compared with expectant and surgical managements[2,3].

Refer to World Health Organization (WHO) recommendation, 200 mcg of mifepristone was administrated orally, then followed 1 to 2 days later by 800 mcg of misoprostol administrated vaginally, sublingually, or buccally[4]. Unfortunately, mifepristone is not available in the authors' hospital, so alternative recommendation of 800 mcg of misoprostol administrated vaginally, sublingually, or buccally[4] was considered for the patients. The success rate of 800 mcg of vaginal misoprostol was reported as high as 60% to 84% without serious complications in some trials.

Misoprostol, a prostaglandin E1 analog, is commonly used for cervical priming before transvaginal procedures, induction of labor, prevention or

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treatment of postpartum hemorrhage, and medical abortion[5].

Prospective randomized controlled trials had been used to compare the efficacy between different doses of misoprostol. The first trial compared 800 mcg of misoprostol administrated vaginally with sublingually. The success rate of complete abortion was not significantly different (60% in the vaginal group and 68.3% in the sublingual group; p=0.44), and the side effects were also not significantly different[6]. The second trial compared 600 mcg of misoprostol administered between vaginally and sublingually. The success rate of complete abortion was not significantly different (26.7% in the vaginal group and 40.0% in the sublingual group; p=0.41), and the side effects were also not significantly different[7]. The other trial compared the efficacy of misoprostol between 800 mcg misoprostol administrated vaginally and 600 mcg misoprostol administrated sublingually. The success rate of complete abortion was not significantly different either (88.9% in the vaginal group and 92.9% in the sublingual group; p>0.05), and the side effects were also not significantly different[8].

The sublingual route of misoprostol is more convenient than the vaginal route for patients to provide by themselves and there were no previous studies that compared 600 mcg and 800 mcg of misoprostol in the same sublingual route. The success rate of 600 mcg misoprostol sublingually in prior studies was so variable (40.0%[7], 65.5%[9], 88.8%[10], and 92.9%[8]). However, the authors assumed from the general knowledge that the side effects are proportionally related to the dose of the drugs. The authors assumed that 600 mcg of sublingual misoprostol had fewer side effects, such as abdominal pain, nausea and vomiting, diarrhea, and headache, than that of 800 mcg. So, the authors conducted the present study to analyze the effectiveness between 600 mcg and 800 mcg of sublingual misoprostol in early pregnancy loss in the present study population with the least side effects.

Materials and Methods

Study design and participants

A prospective, single-blind, randomized controlled trial was conducted at Queen Savang Vadhana Memorial Hospital, Chonburi, Thailand, between March 2020 and February 2021, after the approval of the Institutional Review Board of Queen Savang Vadhana Memorial Hospital (IRB No. 007/2563), and registered in the Thai Clinical Trials Registry (TCTR20210303009).

Over 18-year-old pregnant women who were below 12 weeks of gestational age and diagnosed with an early pregnancy loss were informed and enrolled in the present study. Around 49 participants in each group would provide 80% power based on Kelsey and Fleiss continuity correction at 5% significance to detect the difference[6]. A 28% difference between the two groups was expected. Totally, 54 pregnant women were included in each group while accounting a 10% dropout rate.

Gestation age was calculated from the last menstrual period or transvaginal ultrasonography. Diagnosis of early pregnancy loss was made by obstetrician-gynecologists. According to ACOG, the early pregnancy loss is defined as: 1) an intrauterine gestation sac with mean sac diameter of 25 mm or greater and no embryo, 2) crown-rump length of 7 mm or greater and no cardiac activity, 3) absence of embryo with the cardiac activity of 2 weeks or more after a scan that showed a gestational sac without the yolk sac, and 4) absence of embryo with the cardiac activity of 11 days or more after a scan that showed a gestational sac with the yolk sac[1,2]. The transvaginal ultrasonography was repeated for 7 days after random assignment. Women with stable vital signs, closed internal cervical os, no contraindication for misoprostol, no active bleeding, and no abnormal pregnancy (ectopic pregnancy or molar pregnancy) were included. Women who were not able to follow up were excluded from the present study (Figure 1)[11].

Procedure

Research assistants approached the participants and checked eligibility for the study. They informed all participants, and written consents were obtained before starting the study process. The authors used computer-generated randomization; cards labeled with the assigned dose were placed in sealed; and opaque envelopes were filled and labeled in accordance with the list of randomizations. The allocation was concealed by the use of a sealed number of the treatment. In group 1 (n=54), the participants were sublingually given 600 mcg misoprostol every 6 hours. In group 2 (n=54), participants were sublingually given 800 mcg misoprostol every 6 hours. The maximum was three doses in both groups. Participants were informed of the side effects of misoprostol. All of the participants were appointed to evaluate whether abortion was complete on the 7th day after receiving medication. They were advised to come to the hospital earlier in case of heavy bleeding, allergies to medication, or expulsion. Asking about

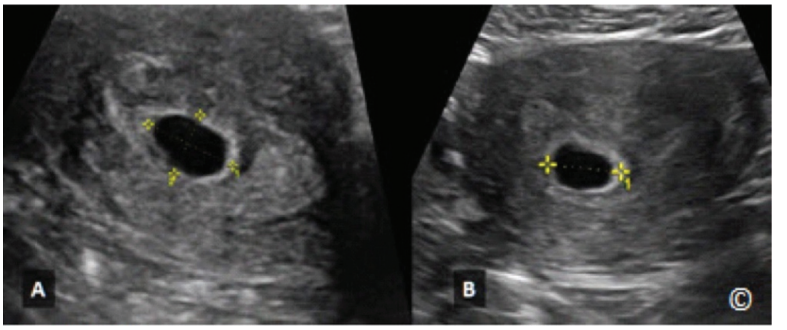

Figure 1. Measurement of mean sac diameter (MSD)[11].

the time of expulsion, tracking the side effects (such as abdominal pain, diarrhea, nausea and vomiting, fever, heavy bleeding, headache, or allergy), physical examination, and transvaginal ultrasonography were performed at the follow-up.

Outcomes

The primary outcome was the success rate of the treatment that was defined as complete abortion, diagnosed by endometrial thickness less than or equal to 10 mm on transvaginal ultrasonography after expulsion or 7 days from receiving medication. If there was incomplete abortion or no abortion, the dilatation and curettage were performed under general anesthesia. The secondary outcomes were the induction-to-abortion time and side effects, such as abdominal pain, diarrhea, nausea and vomiting, fever, heavy bleeding, headache, or allergy.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed using mean and standard deviation, which were compared with the unpaired t-test. Categorical variables were presented as numbers and percentages then compared with the chi-square test. A comparison of results and side effects of misoprostol between the intervention group and controlled group was carried out using a z-test for proportion difference. The authors performed a per-protocol analysis. Statistical significance was considered at the p-value of less than 0.05.

Results

Total of 108 pregnant women were initially enrolled in the trial. They were randomly assigned to receive either 600 mcg (54 women) or 800 mcg (54 women) of sublingual administrated misoprostol.

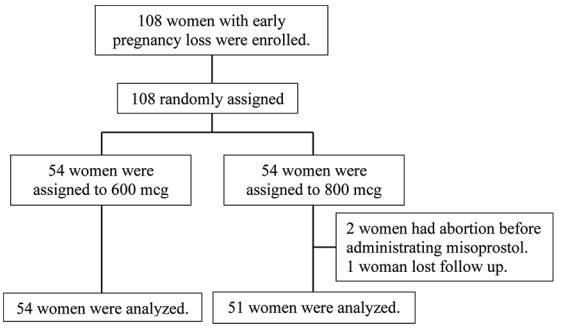

Figure 2. Study flowchart.

Out of 108 women, 105 (97.2%) had available data for the primary outcome. Two women of the 800 mcg misoprostol group had an abortion before administering the misoprostol, and one woman lost the follow-up. One hundred and five pregnant women were analyzed, 54 women in the 600 mcg misoprostol group and 51 women in the 800 mcg misoprostol group (Figure 2). Demographic characteristics were similar between the two trial groups showed in Table 1.

The success rate was 30 of the 54 women (55.6%) in the 600 mcg misoprostol group and 33 of the 51 women (64.7%) in the 800 mcg misoprostol group, which was not a statistically significant difference between the two groups, (p=0.339; 95% CI 0.082 to 1.862) (Table 2). The 8 of the 54 women (14.8%) in the 600 mcg misoprostol group had a complete abortion with a single dose compared with 11 of the 51 women (21.6%) in another group (p=0.364; 95% CI 0.404 to 1.296) (Table 2). The induction-to-abortion time was 9.5 hours (IQR 6.75 to 48.00) in the 600 mcg misoprostol group and 10 hours (IQR 6.00 to 60.00) in the 800 mcg misoprostol group (Table 4). The failure rate was 44.4% in the 600 mcg misoprostol group and 35.3% in the 800 mcg misoprostol group; the incomplete abortion in the 600 mcg misoprostol

Table 1. Demographic characteristics

	600 mcg misoprostol (n=54); n (%)	800 mcg misoprostol (n=51); n (%)	p-value
Maternal age (years); mean±SD	30.6±6.0	31.5±5.7	0.463
Age <35 years	37 (68.5)	34 (66.7)	0.839
Age 35 years	17 (31.5)	17 (33.3)	0.839
Pre-pregnancy BMI (kg/m^2); mean±SD	23.1±3.9	22.7±5.4	0.655
Gestational age (days); mean±SD	69.4±12.3	70.3±12.7	0.688
Nulliparity	20 (37.0)	20 (39.2)	0.993
Type			
Anembryonic pregnancy	15 (27.8)	17 (33.3)	0.537
• MSD (cm)	1.1 (1.3)	1.4 (1.5)	0.285
Embryonic death	39 (72.2)	34 (66.7)	0.537
• CRL (cm)	1.1 (1.9)	0.7 (1.1)	0.239
Presenting symptoms			
No	24 (44.4)	22 (43.1)	0.350
Yes	30 (55.6)	29 (56.9)	0.350
• Vaginal bleeding	29 (96.7)	25 (86.2)	0.631
• Pelvic pain	1 (3.3)	4 (13.8)	0.150

BMI=body mass index; MSD=mean sac diameter; CRL=crown rump length; SD=standard deviation

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

	600 mcg misoprostol (n=54); n (%)	800 mcg misoprostol (n=51); n (%)	p-value
Success rate	30 (55.6)	33 (64.7)	0.339
Single dose	8 (14.8)	11 (21.6)	0.364
Two doses	9 (16.7)	7 (13.7)	0.494
Three doses	13 (24.1)	15 (29.4)	0.179
Failure rate	24 (44.4)	18 (35.3)	0.339
Incomplete abortion	16 (29.6)	11 (21.6)	0.345
• Single dose	1 (1.9)	4 (7.8)	0.048
• Two doses	3 (5.6)	1 (2)	0.488
• Three doses	12 (22.1)	6 (11.8)	0.268
No abortion	8 (14.8)	7 (13.7)	0.873
Induction-to-abortion time (hours); median (IQR)	9.50 (6.75 to 48.00)	10.00 (6.00 to 60.00)	

IQR=interquartile range

group was higher than another group (29.6% in the 600 mcg misoprostol group and 21.6% in the 800 mcg misoprostol group); and also no abortion rate was higher in the 600 mcg misoprostol group (14.8% in the 600 mcg misoprostol group and 13.7% in the 800 mcg misoprostol group).

There was no statistically significant difference in maternal age, pre-pregnancy body mass index (BMI), gestational age, parity, type of early pregnancy loss, and presenting symptoms, which were suspected to be the factors affecting successful medical treatment between the success group and the failure group (Table 3).

There was no significant difference in the abdominal pain (37% in group 600 mcg and 41.2% in group 800 mcg), diarrhea (24% in group 600 mcg and 19.6% in group 800 mcg), nausea and vomiting (7.4% in group 600 mcg and 5.9% in group 800 mcg), fever (1.9% in group 600 mcg and 7.8% in group 800 mcg), heavy bleeding (7.4% in group 600 mcg and 2.0% in group 800 mcg), and headache (1.9% in group 600 mcg and 2.0% in group 800 mcg), and no

Table 3. Characteristics between the success group and the failure group

	Success; n (%)	Failure; n (%)	p-value
Maternal age (years); mean±SD	30.3±5.9	32.2±5.6	0.100
Age <35 years	45 (71.4)	26 (61.9)	0.307
Age 35 years	18 (21.6)	16 (38.1)	0.307
Pre-pregnancy BMI (kg/m^2); mean±SD	22.5±4.8	23.4±4.3	0.325
Gestational age (days); mean±SD	69.6±14.0	70.2±9.8	0.796
Nulliparity	28 (44.4)	12 (28.6)	0.101
Type			
Anembryonic pregnancy	17 (27.0)	15 (35.7)	0.341
• MSD (cm)	1.3 (1.5)	1.3 (1.3)	0.809
Embryonic death	46 (73.0)	27 (64.3)	0.341
• CRL (cm)	1.0 (1.9)	0.7 (1.0)	0.388
Presenting symptoms			
No	21 (33.3)	25 (59.5)	0.012
Yes	42 (66.7)	17 (40.5)	0.012
• Vaginal bleeding	37 (58.7)	17 (40.5)	0.032
• Pelvic pain	5 (8.0)	0 (0.0)	0.053

BMI=body mass index; MSD=mean sac diameter; CRL=crown rump length; SD=standard deviation

Table 4. Side effects

Side effects	600 mcg misoprostol (n=54); n (%)	800 mcg misoprostol (n=51); n (%)	p-value
Abdominal pain	20 (37.0)	21 (41.2)	0.644
Diarrhea	13 (24.0)	10 (19.6)	0.580
Nausea and vomiting	4 (7.4)	3 (5.9)	0.754
Fever	1 (1.9)	4 (7.8)	0.150
Heavy bleeding	4 (7.4)	1 (2.0)	0.190
Headache	1 (1.9)	1 (2.0)	0.967

participants had allergies (Table 4).

Discussion

The present study was a randomized controlled trial illustrated the success rate between 600 mcg and 800 mcg of misoprostol administered sublingually every 6 hours up to 3 doses for complete abortion was not significantly different (55.6% and 64.7%, respectively). The success rate in the present study result was similar to the previous trials in a range of 60% to 80%[6,12].

Many randomized trials found that the misoprostol alone is effective for termination of pregnancy in the early pregnancy loss women with a range of 60% to 80%[6,12].

The success rate in the present study is similar to a previous study that compared between sublingual route and vaginal route of 800 mcg of misoprostol every 6 hours, found that the complete abortion rate was not different (intravaginal group 60%, sublingual group 68.3%, p=0.44)[6], and also has higher success rate than the previous study which compared success rate between sublingual and vaginal routes of 600 mcg misoprostol. They found that rate of complete abortion (intravaginal route 26.67%, sublingual route 40.0%, p=0.406)[7].

The American College of Obstetricians and Gynecologists suggest using misoprostol for early pregnancy loss. Many previous researches studied the randomized controlled trial and case-controlled study in the USA showed that 71% was completely aborted in 3 days after 800 mcg vaginal misoprostol. The proportion was rise to 84% after the second dose[1], which is higher than the present study because of the shorter interval of repeated doses.

Moreover, the presented study reported that there was no significant difference (p>0.05) in the duration of induction to abortion time between 600 mcg and 800 mcg sublingually, approximated 9.5 hours and 10 hours, respectively. In addition, the side effects of 600 and 800 mcg sublingual misoprostol were also not statistically different. The present study result is identical to the previous reports. From the present trial, the authors concluded that 600 mcg of misoprostol has a statistically equal effect as 800 mcg of misoprostol without contrast in side effects.

Uterine curettage is an effective procedure and has a success rate of more than 95%. However, there are many complications, such as vaginitis, metritis, uterus perforation, cervical injury, and also as severe as pelvic adhesion. The cost of the procedure is usually around 8,000 Baht and could be as expensive as 12,000 Baht per case. On the other hand, medical abortion has fewer complications. The misoprostol side effects are gastrointestinal symptom, fever, heavy bleeding, headache, and also allergic reactions. The drug cost is only 500 to 1,000 Baht. Additionally, the use of 600 mg of misoprostol can reduce cost compared with 800 mcg of misoprostol with the same success rate and side effects.

The strength of the present study was the use of a randomized controlled trial. However, there were some limitations in the time of repeated doses. Participants may not exactly administrate the repeated doses every 6 hours as in the hospital. Further study should calculate the success rate after complete 3 doses of misoprostol, the success rate may increase.

Conclusion

In addition to surgical intervention, medical abortion with misoprostol is an alternative treatment for termination of pregnancy in early pregnancy failure. Apart from its equal effectiveness, it is more convenient than surgical choice. Patients with early pregnancy loss can administer the pill on their own. The present study demonstrated that the efficacy of the 600 mcg misoprostol is statistically noninferior to 800 mcg misoprostol. The failure rate of medical abortion was acceptable, and the adverse effects were similar in both groups. The mean duration of induction-to-abortion time was also similar in both groups.

What is already known on this topic?

Misoprostol has already known as the alternative drugs to induce abortion in early pregnancy loss which the recommended dose is 800 mcg sublingual, buccal or vaginal administration without the recommended interval of repeated doses(4). There are no serious side effects. However, there are uncomfortable effects from misoprostol such as vaginal bleeding, pelvic pain, diarrhea, nausea and vomiting, or fever.

What this study adds?

The effectiveness between 600 mcg and 800 mcg are not different for medical abortion in early pregnancy loss and also the side effects are similar.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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