Efficacy of Sublingual Misoprostol With or Without Loading Vaginal Misoprostol in Second Trimester Termination of Pregnancy: A Randomized Controlled Trial

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Objective: *To compare the success rate of second trimester pregnancy termination by sublingual misoprostol with and without loading vaginal misoprostol.*

Material and Method: *The present study was a prospective, randomized controlled trial. Singleton pregnant women of 14 to 24 weeks of gestation who had indication for pregnancy termination were recruited. After the inform consent was signed, the participants were divided into two groups. The study group received misoprostol 800 µg in vagina followed by sublingual misoprostol 400 µg every three hours. The control group received only sublingual misoprostol 400 µg every three hours. Maximum doses of sublingual misoprostol in both groups were no more than five doses. If the process was not complete, another repeated course of misoprostol 400 µg sublingual every three hours was required.*

Results: *Fifty participants were recruited. The success rate of pregnancy termination at 24 hours of study and control group were 92% and 64% (p-value 0.037), respectively. The median induction-to-abortion time was 8.17 and 11.33 hours for study and control group (p-value 0.087). There was no difference in side effects and satisfaction between both groups.*

Conclusion: *Vaginal misoprostol suppository followed by sublingual administration for second trimester termination of pregnancy was more efficient than sublingual administration alone in first 24 hours.*

Keywords: *Termination of pregnancy, Medical abortion, Misoprostol, Cytotec, Abortion*

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The second trimester termination of pregnancy can be conducted via various methods, such as a surgical, medical, or expectant management. Each of these methods has both pros and cons. For instance, a surgical management has high efficiency and rapid pregnancy termination, but it involves high risks from anesthesia and the procedure itself. Serious complications are uterine perforation, uterine synechiae, uterine infection, and bleeding[1,2]. Expectant management may consume a larger amount of time than a surgical procedure. The longer time it takes, the more anxious and stressed patients will feel. Furthermore, it involves risks of incomplete abortion, retained placenta, bleeding after abortion, and uterine infection. These need an emergency intervention, which involves a higher risk of bleeding and complications. Nowadays, medical management gains more popularity because of the greatest efficiency and least complications[1-4].

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The combination of mifepristone (anti-progestin) with misoprostol (prostaglandin E_1 analogue) was proposed to be the most effective regimen for second trimester medical termination of pregnancy[5-7]. However, mifepristone is not available in Thailand.

There is a diversity of misoprostol use in terms of dosage, intervals, and routes, such as vaginal, sublingual, buccal, and oral. Each route has both advantage and inconvenience. The popular misoprostol regimen is vaginal administration. It is more efficient than the other regimens. However, it has more side effects and causes discomfort for patients due to frequent pelvic examinations[7-9]. Some studies found that sublingual administration has similar efficacy as vaginal route[10,11]. Pharmacokinetics data shows sublingual administration has superior efficiency and satisfaction. Therefore, sublingual administration should be a way of reducing patients' discomfort and should be used for terminating pregnancy[10,11]. However, one disadvantage of sublingual administration is rapid reduction in the levels of drugs in the bloodstream within three hours. In contrast for vaginal administration, drug levels gradually decrease

within six hours. Currently, there are few studies on sublingual route of administration.

The World Health Organization (WHO) and the International Federation of Gynecology and Obstetrics (FIGO) recommend the use of a vaginal or sublingual 400 µg misoprostol every three hours for second trimester termination of pregnancy[12]. Thai Society of Maternal and Fetal Medicine recommended starting with a 800 µg misoprostol vaginal suppository and then 400 µg misoprostol vaginal or sublingual administration every three hours[2]. However, there are still no studies identifying the efficiency of the regimen.

Material and Method

The present research was a randomized controlled trial, which was certified by the Office of the Committee on Ethical Review for Human Research in Prapokklao Hospital. All the 50 participants were women with singleton pregnancy and gestational age of 14 to 24 weeks, who attended the Antenatal Clinic of Prapokklao Hospital, Chanthaburi between September 2015 and June 2016. The indications for termination of pregnancy included maternal serious chronic diseases, e.g., cancer and heart diseases, fetal abnormality, fetal of major thalassemia, and intrauterine fetal demise (IUFD). Termination of pregnancy in all participants was on a voluntary basis. The exclusions consisted of the women with a history of misoprostol allergy, cesarean section or myomectomy, the present of chronic diseases that involve the risk from misoprostol use, e.g., glaucoma, liver disease, and vascular disease.

The success rate of pregnancy termination at 24 hours, based on the pilot study, was used to calculate the sample size. For study group, the success rate of 24-hour pregnancy termination represented 100%, with the rate for control group accounting for 60%. The sample size required at least 48 participants, whereby the power = 90% and alpha = 0.05. The analysis used the two-tail test, and the calculation was conducted using Stata® version 12.0 (StataCorp LP, Texas, USA).

All participants provided written informed consent before enrollment. Pelvic examination underwent for Bishop score assessment. If the score was 4 points or less, the participants would undergo drug administration. If the score was greater than 4 points, they would be excluded from the study. The participants were assigned an identification number that showed their order for participating in the research, as well as an opaque sealed envelope that specified their research group using the random sequence generator program.

The study participants were administered an 800 µg vaginal misoprostol (Cytotec® 200 µg/tab), followed by a 400 µg sublingual misoprostol three hours later and then every three hours until complete abortion (maximum of five times). Whereas, the control participants were administered a 400 µg sublingual misoprostol every three hours alone until complete abortion (maximum of five doses).

Vaginal misoprostol was blended with three to five drops of normal saline before it was inserted into the participants' posterior fornix. Sublingual misoprostol was applied under tongue for 15 minutes. During this period, eating or drinking was prohibited. The vital signs were monitored every four hours. The side effects of misoprostol were recorded. Pain was assessed, using the visual rate scale (VRS), with scores ranging from 0 to 10. The level of satisfaction was evaluated by a 5-Point Scale. When they had a fever (temperature of 38.3°C or above) or VRS of 7 to 9, they received a tablet of 500-mg paracetamol, and repeated every six hours. If the pain score equaled 10, pethidine 50-mg intramuscular injection was required. However, analgesic drugs were given to them upon their request. The participants who suffered from nausea were provided with one domperidone tablet, or 10-mg of metoclopramide if they did not feel better. If they experienced diarrhea, they would receive oral rehydration salt mixed with water. After the fetus was aborted, Syntocinon® in a 1,000-ml ringer lactate solution was given via veins with a speed of 120 ml per hour until the placenta was completely expulsed. If the pregnancy was not terminated within 24 hours, the participants received 400 µg of sublingual misoprostol every three hours until complete abortion was achieved (maximum of another five doses). If the pregnancy termination was not completed within 48 hours, the procedure was considered to be a failure.

The main objective of the present study was to determine the success rate of pregnancy termination of both groups at 24 and 48 hours. The secondary objectives were to compare the median induction-to-abortion time of respective drug regimen, amount of drug use, the side effects, and the levels of the participants' satisfaction in each group.

The percentage of pregnancy termination succession at 24 and 48 hours were analyzed using the Chi-square test. The median induction to abortion time was analyzed using the log-rank test. The amount of misoprostol used was analyzed using the median

and rank-sum test. The level of satisfaction with the individual drug administration regimes and the percentage of side effects were analyzed using Chi-square test. The *p*-value of less than 0.05 was considered to indicate statistical significance. All statistical analyzes were done using Stata® version 12.0 (StataCorp LP, Texas, USA).

Results

Fifty participants were recruited to the present study and were randomly assigned to two groups equally (Fig. 1). Demographic data, e.g., age, weight, height, gestational age, hematocrit level, and parity compared between the two groups was similar (Table 1).

The success rate of pregnancy termination at 24 hours in study group was significantly higher than control group (92% vs. 64%, *p*-value 0.037). However, there was no statistical significant difference at 48 hours (96% vs. 84%, *p*-value 0.349). One participant in the study group had abortion failure but she still chose the medical method for termination. Another course of sublingual misoprostol was restarted two days later, which resumed another 24 hours. In the control group, four cases were defined as abortion failure and they chose surgical evacuation. The median induction-to-abortion time of the study group was shorter than control group (8.17 hours (IQR 4.5 to 15.7) vs. 11.33 hours (IQR 8.0 to 29.7), respectively, *p*-value 0.087) (Table 2, Fig. 2). The dosage of misoprostol in each group was similar (1,600 µg (IQR 1,200 to 2,800) vs. 1,600 µg (IQR 1,200 to 3,600), *p*-value 0.709) (Table 2).

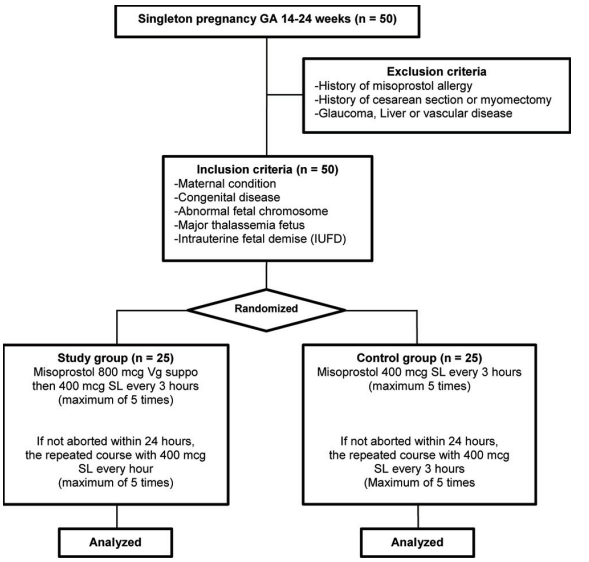

Fig. 1 Study flow of participants.

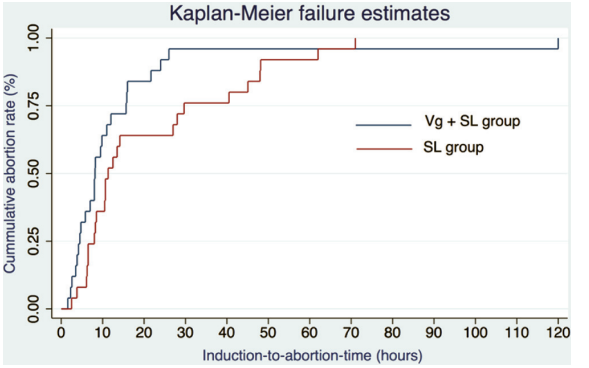

Fig. 2 Cumulative abortion rate for the sublingual misoprostol with or without loading vaginal misoprostol pretreatment in second trimester medical termination of pregnancy.

Table 1. Demographic data

Parameters	Study group (n = 25)	Control group (n = 25)	*p*-value
Age (years)	27.52±8.1	27.00±7.8	0.819
Weight (kg)	58.27±11.7	63.18±16.7	0.236
Height (cm)	159.28±5.1	158.36±5.4	0.538
Gestational age (weeks)	18.38±3.7	18.87±3.4	0.622
Hematocrit level (gm/dl)	36.01±2.9	35.09±4.8	0.412
Parity, n (%)			0.776
Primigravida	12 (48)	10 (40)	
Multigravida	13 (52)	15 (60)	

Result are expressed as mean ± standard deviation or number (%)

Table 2. Treatment outcome

Characteristics	Study group	Control group	*p*-value
Success rate of pregnancy termination at 24 hours	23 (92)	16 (64)	0.037
Success rate of pregnancy termination at 48 hours	24 (96)	21 (84)	0.349
Failure	1 (4)	4 (16)	0.349
Median induction-to-abortion-time in hours (IQR)	8.17 (4.5 to 15.7)	11.33 (8.0 to 29.7)	0.087*
Median amount of misoprostol used in microgram (IQR)	1,600 (1,200 to 2,800)	1,600 (1,200 to 3,600)	0.709**

IQR = interquartile range, * Log rank test, ** Rank-sum test
Result are expressed as number (%)

Three cases in the study group and two cases in the control group needed manual vacuum aspiration (MVA) due to the retained pieces of placenta. However, the difference between both groups had no statistical significance. As for blood components used, there was no statistically significant difference between the two groups (8% vs. 4%, *p*-value 1.00).

The comparison of side effects for misoprostol showed no difference. No serious complication was found in either groups (Table 3).

The participants' satisfaction and pain score of both groups were evaluated (Table 4) and no difference was identified.

Discussion

Second trimester medical termination of pregnancy, combination of vaginal misoprostol administration with sublingual misoprostol was more efficient than sublingual misoprostol administration alone in the first 24 hours. However, it was not statistically significant different for the 48-hour period.

Table 3. Side effects

Side effects	Study group	Control group	*p*-value
Fever (≥38.3°C)	16 (64)	15 (60)	1.000
Nausea	5 (20)	8 (25)	0.520
Vomiting	4 (16)	5 (20)	1.000
Chill	6 (24)	12 (48)	0.140
Diarrhea	9 (36)	10 (40)	1.000
Rash	5 (20)	7 (28)	0.742
Headache	1 (4)	2 (8)	1.000
Breast tenderness	1 (4)	0 (0)	1.000
Need for analgesia			
Paracetamol	15 (60)	16 (64)	1.000
Pethidine	3 (12)	7 (28)	0.289
Retained placenta	3 (12)	3 (12)	1.000
Blood transfusion	2 (8)	1 (4)	1.000

Result are expressed as number (%)

Table 4. Satisfaction on routes of administration and pain scores

	Study group (n = 25)	Control group (n = 25)	*p*-value
Satisfaction			0.44
Extremely dissatisfied	-	-	
Dissatisfied	-	-	
Neither satisfied nor dissatisfied	4 (16)	7 (28)	
Satisfied	10 (40)	11 (44)	
Extremely satisfied	11 (44)	7 (28)	
Pain score	5.68±2.90	6.82±2.64	0.146

Result are expressed as number (%) or mean ± standard deviation

In a previous study comparing between vaginal misoprostol alone and sublingual alone for termination of 13 to 20-week gestation, the success rates of complete abortion at 24 hours of vaginal misoprostol was comparable to sublingual. It also was the same when compared at 48 hours[9,15]. Although the side effects of the drugs between the two groups were similar, the participants preferred sublingual to vaginal route because of less frequent pelvic examination.

However, the present study is consistent with Tang's study that reported the success rate of pregnancy termination at 24 hours as higher in vaginal than sublingual route[8]. The success rate at 48 hours was not different. Misoprostol used via vagina seems to be more effective than sublingual administration but the participants' satisfaction was not the same. In our study, the benefit from vaginal misoprostol administration was that there was only one pelvic examination. It also took a shorter time to abort as most of them aborted in 24 hours. However, there were some difference in the population enrolled, which made it impossible to compare directly.

A major part of the present research is that it can serve as a guideline for choosing medical pregnancy termination regimen for women with 14 to 24 weeks of pregnancy. Not only that this study showed a high success rate of pregnancy termination within 24 hours, it did it in a shorter time and with less misoprostol. The side effects of the regimen are not different from other methods, and do not cause serious complications. The satisfactions of the participants between both administration routes were not different.

The limitation of the present research was that it involved a new administration regimen, so it did not have previous RCT for a comparison. The present study was not a double-blinded RCT because the participants knew the route of administration. For further study, well designed for investigation should be considered.

Conclusion

Second trimester medical termination of pregnancy by combination of vaginal misoprostol administration with sublingual misoprostol was more efficient than sublingual misoprostol administration alone in the first 24 hours. However, it was no statistically significant difference after 48 hours.

What is already known on this topic?

Termination of pregnancy in second trimester has many methods, such as surgical and medical technique. The medication termination has the least

complications, making it the most satisfactory. Currently, there is a diversity of misoprostol use in terms of dosage, intervals, and routes, such as vaginal, sublingual, buccal, and oral. Each route has both advantage and inconvenience. However, there are some controversy in dosage use and no studies identifying the efficiency of the regimen.

What this study adds?

Vaginal misoprostol 800 µg suppositories followed by sublingual misoprostol 400 µg every three hours for second trimester termination of pregnancy was more efficient and took shorter time than the original 400 µg sublingual administration alone. There is no difference in side effects and satisfaction between both groups.

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Potential conflicts of interest

None.

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การเปรียบเทียบประสิทธิภาพของการใช้ยาไมโสพรอสตอล ในรูปแบบการเหน็บทางช่องคลอดก่อนการให้ยาอมใต้ลิ้นเทียบกับการอมใต้ลิ้นเพียงอย่างเดียวในการยุติการตั้งครรภ์ในช่วงไตรมาสที่สอง

เกียรติศักดิ์ พรหมวังขวา, บุณยาพร พันธิตพงษ์, วัชรินทร์ เฉิดฉิ้ม, ปัญญา สนั่นพานิชกุล

วัตถุประสงค์: *เพื่อเปรียบเทียบอัตราความสำเร็จของการยุติการตั้งครรภ์โดยการใช้ยาไมโสพรอสตอล ระหว่างรูปแบบการเหน็บทางช่องคลอดก่อนการให้ยาอมใต้ลิ้นเทียบกับการอมใต้ลิ้นเพียงอย่างเดียวที่ 24 และ 48 ชั่วโมง*

วัสดุและวิธีการ: *การศึกษาโดยการทดลองและศึกษาไปข้างหน้า กลุ่มประชากรที่ศึกษาเป็นสตรีตั้งครรภ์เดี่ยว อายุครรภ์ 14-24 สัปดาห์ ที่มีข้อบ่งชี้และสมัครใจในการยุติการตั้งครรภ์ที่มารับบริการ ณ คลินิกฝากครรภ์ โรงพยาบาลพระปกเกล้า จันทบุรี โดยแบ่งที่ผู้ร่วมการศึกษาเป็น 2 กลุ่ม กลุ่มศึกษาได้รับการบริหารยาโดยการเหน็บยาไมโสพรอสตอลทางช่องคลอด ขนาด 800 ไมโครกรัม ตามด้วยการอมยาใต้ลิ้น ขนาด 400 ไมโครกรัม ใน 3 ชั่วโมงถัดมา และอีกทุก 3 ชั่วโมง จนกระทั่งสิ้นสุดการตั้งครรภ์ใน 24 ชั่วโมง กลุ่มควบคุมได้รับการบริหารยาไมโสพรอสตอลขนาด 400 ไมโครกรัม โดยการอมยาใต้ลิ้นทุก 3 ชั่วโมง จนกระทั่งสิ้นสุดการตั้งครรภ์ใน 24 ชั่วโมง (จำนวนครั้งการอมใต้ลิ้นของทั้งสองกลุ่มไม่เกิน 5 ครั้ง) หากไม่สำเร็จให้เริ่มการบริหารยาไมโสพรอสตอลขนาด 400 ไมโครกรัม ด้วยการอมใต้ลิ้นทุก 3 ชั่วโมง อีกรอบ และไม่เกิน 5 ครั้ง ถ้าไม่สามารถสิ้นสุดการตั้งครรภ์ในเวลา 24 ชั่วโมง ให้ถือเป็นความล้มเหลวของรูปแบบการบริหารยานั้น*

ผลการศึกษา: *กลุ่มประชากรที่ศึกษาจำนวน 50 คน อัตราความสำเร็จของการยุติการตั้งครรภ์ที่ 24 ชั่วโมง ระหว่างกลุ่มศึกษาและกลุ่มควบคุม คิดเป็น 92% และ 64% (p-value 0.037) ระยะเวลาของการยุติการตั้งครรภ์ระหว่างกลุ่มคิดเป็น 8.17 และ 11.33 ชั่วโมง ตามลำดับ (p-value 0.087) ไม่มีความแตกต่างกันอย่างมีนัยสำคัญของผลข้างเคียงจากการใช้ยาไมโสพรอสตอล ผู้เข้าร่วมการศึกษามีความพึงพอใจต่อการบริหารยาทั้งสองรูปแบบอย่างเท่าเทียมกัน*

สรุป: *การยุติการตั้งครรภ์ในช่วงไตรมาสที่สองด้วยการใช้ยาไมโสพรอสตอลเหน็บทางช่องคลอดก่อนการให้ยาอมใต้ลิ้น มีประสิทธิภาพที่เหนือกว่าการอมยาใต้ลิ้นเพียงอย่างเดียวที่ 24 ชั่วโมง*