A Comparison of the Efficacy of Sublingual and Oral Misoprostol 400 Microgram in the Management of Early Pregnancy Failure: A Randomized Controlled Trial

Orada Patamasingh na ayudhaya MD*,
Yongyoth Herabutya MD*, Boonsri Chanrachakul MD*,
Nathpong Israngura Na Ayuthaya MD*, Pratak O-Prasertsawat MD*

** Department of Obstetrics and Gyneacology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University*

Objective: *To compare repeated doses of sublingual with oral misoprostol in the medical management of early pregnancy failure.*
Material and Method: *One hundred and thirty eight women with a period of gestation less than 20 week calculated by her last menstrual period and less than 12 weeks by size were sequentially allocated to two groups to receive either 400 μg of misoprostol orally or sublingually every 4 hours until termination of pregnancy was completed.*
Results: *There is no difference in the mean induction to abortion interval. Fever and chill were more common in sublingual group compared with oral group. The other adverse effects were similar and included nausea, vomiting, diarrhea, abdominal pain, and headache.*
Conclusion: *Sublingual misoprostol is as effective as oral route. Most adverse effects are similar in both groups except fever was more common in sublingual group.*

Keywords: *Misoprostol, Early pregnancy failure, Management, Sublingual, Oral*

J Med Assoc Thai 2006; 89 (Suppl 4): S5-10
Full text. e-Journal: *http://www.medassocthai.org/journal*

Early pregnancy failure is a common complication affecting 10-20% of pregnant women[1]. Surgical evacuation is a standard management for termination of pregnancies of less than 12 weeks of gestation in Thailand. Although it is an effective method with a success rate of 97%, it is associated with anesthetic and surgical risks such as uterine perforation, Asherman's syndrome, cervical trauma, infection that leading to infertility, pelvic pain, and increases chance of ectopic pregnancy[2].

The alternatives to surgical treatment are either expectant management or medical treatment. Expectant management's success rate is too low to be used in routine clinical practice[2-5]. Medical treatment has been categorized as a non-invasive option as it avoids the risk of morbidity therefore, this is especially important in developing countries where surgical treatments are unsafe.

Misoprostol, a synthetic PGE1 analog, is principally used to prevent peptic ulcer induced by ingestion of non-steroidal anti-inflammatory drugs. Although misoprostol is not licensed for medical abortion, it is approved by ACOG and used in developing countries because it is inexpensive, stable at room temperature and available[6,7].

Misoprostol's adverse effects such as fever, diarrhea, vomiting, abdominal pain are still of concern. Therefore, it is very important to develop a regimen of medical abortion to optimize the doses and interval that maximize the effectiveness and minimize the complications and adverse effects.

The authors have explored the use of sublingual misoprostol in medical abortion. Misoprostol is absorbed through the vascularised buccal mucosa. It achieves the highest serum peak concentration and this was significantly higher than those in the other

Correspondence to : O- Prasertsawat P, Department of Obstetrics and Gyneacology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Rama 6 Rd, Rachavithee, Bangkok 10400, Thailand. E-mail: Rapop@mahidol.ac.th

group[6]. When comparing sublingual administration with oral administration, the sublingual avoids the first part effect through the liver. This vaginal administration method is less painful, more convenient, and more preferable for woman during abortion process[8-10].

To date, there have been no studies comparing oral and sublingual route at equal doses. The objective of this study was to compare repeated doses of sublingual with oral misoprostol in the medical management of early pregnancy failure.

Material and Method

One hundred and thirty eight women with a diagnosis of early pregnancy failure were recruited, an ultrasound examination was performed in all women to confirm the diagnosis. The ultrasound definition of this study as follow: (i) intrauterine gestational sac with a mean sac diameter of > 2 cm without fetal pole; blighted ovum. (ii) Presence of fetal pole without cardiac pulsation; dead embryo. (iii) The gestational sac < 2 cm with no interval growth or persist absence of fetal cardiac pulsation on rescanning after 7-10 days[11]. Patient who has experienced abnormal vaginal bleeding or severe abdominal pain after diagnosis of early pregnancy failure was excluded.

The study protocol was approved by Ramathibodi Hospital Ethical Committee. The Inclusion criteria were the pregnant women with a period of gestational age between 7-12 weeks and diagnosis of early pregnancy failure between November 2004 and December 2005 at antenatal care clinic in the Department of Obstetrics and Gynecology, Ramathibodi Hospital, Bangkok, Thailand. Inform consent was obtained before randomization. After hospitalization, 138 women were randomized according to computer-generated numbers into two groups. Women in controlled group received 400 μg misoprostol orally every 4 hours for the maximum of 6 doses while the woman in the study group received 400 μg misoprostol sublingually every 4 hours for maximum of 6 doses.

The women in the sublingual group were administered two misoprostol tablets under the tongue by a nurse. They were not allowed to eat any food for the next 20 minutes to complete dissolution of the tablets. A nurse was also responsible for oral administration of the misoprostol tablets to the patients. Patients were allowed drinking 30 ml of water then misoprostol was given in the same route every 4 hours until product of conceptus was detected. The blood pressure, pulse rate, body temperature were recorded every 4 hours. Adverse effects including abdominal pain, diarrhea, nausea, vomiting, chill, and headache were recorded. Two oral tablets of 500 mg paracetamol were given if patients complain of severe abdominal pain. Parenteral pethidine would be given if the pain persisted. If the body temperature was > 38^{O}C, two tablets of paracetamol were also provided every 4 hours.

Whenever patients passed the product of conceptus or have bleeding per vagina, they have to inform the nurses who then notify the attending doctors. The doctors then determine whether the abortion is complete by performing a vaginal examination. The results depend on the following: Was the women still active bleeding? Was the cervical os opened ? The ultrasound was done to measure the endometrial thickness.

If the patients have no active bleeding, cervical os is closed and endometrial thickness is < 1 cm, they were classified as complete abortion[12,13]. If the patients have active vaginal bleeding or opened cervical os and endometrial thickness > 1 cm they were then classified as incomplete abortion and undergone emergency surgical evacuation under local anesthesia (20 cc of 1% xylocaine paracervical block).

The patients who received misoprostol 6 doses and did not pass product of conception were classified as medical failure. Surgical evacuation would be performed the next morning under general anesthesia. The product of conception was sent for histological diagnosis. All women had post abortion check-up two weeks after discharge.

Primary outcome was mean induction to abortion interval and was defined as the time from first doses of misoprostol to the time when the product of conceptus passed through the cervix. A secondary outcome was the incidence of adverse effects.

Based on the mean induction to abortion interval of our pilot study sixty four women in each group were needed to have 95% confidence interval and alpha error of 0.05 (two sides). Continuous variables were analyzed with unpaired t test and the Mann-Whitney U–test. Categorical variables were analysed with χ^2-test. Statistical significance was considered at $p < 0.05$.

Results

One hundred and thirty eight women were recruited. Two women in oral group were excluded because of incomplete medical record. The demographic characteristics of the women who underwent medical management of early pregnancy failure are shown in Table 1. There were no significant differences between

Table 1. Demographic data

	Oral misoprostol (n = 68)	Sublingual misoprostol (n = 70)
Age (years)[a]	32.00 (5.8)	33.44 (6.2)
Gestational age (weeks)[a]	10.65 (1.5)	10.95 (1.4)
Total doses (μg)[a]	1706 (90.1)	1640 (83.0)
Nulliparous (cases)	31 (45.6%)	27 (38.6%)

[a] Data are presented as mean (SD)
No significant difference was detected between the two groups

Table 2. Clinical outcomes of medical management of early pregnancy failure

	Oral misoprostol (n = 68)	Sublingual misoprostol (n = 70)
Induction to abortion interval (h) mean (SD)	10.7 (6.6)	8.7 (5.4)
Clinical outcomes		
Complete abortion	17 (25.8%)	15 (21.4%)
Incomplete abortion	23 (34.8%)	27 (38.6%)
Medical failure	26 (39.4%)	28 (40.0%)

No statistical significance was detected between the two groups

Table 3. Side effects of treatment

	Oral misoprostol (n = 68)	Sublingual misoprostol (n = 70)	p-value
Abdominal pain	40 (58.8%)	47 (67.1%)	0.31
Diarrhea	7 (10.3%)	6 (8.6%)	0.73
Nausea vomiting	3 (4.4%)	2 (2.9%)	0.68
Fever	2 (2.9%)	15 (21.4%)	0.001
Chill	0	4 (5.7%)	0.045

the two groups with respect to age, gestational age, and parity. There were no significant differences in the required mean overall doses of misoprostol.

Table 2 shows abortion rate within 24 hours after misoprostol administration. There was no significant different in complete abortion, incomplete abortion and medical failure between two groups.

The definition of early pregnancy failure was included the patient who was diagnosed dead embryo or blighted ovum. In this study, dead embryo was diagnosed in 50% of cases while blighted ovum was diagnosed in 50% too. We found that in the dead embryo group had shorter induction to abortion interval than blighted ovum group (8.4 h vs 11.4 h, $p = 0.027$).

Adverse effects are shown in Table 3. No major complication occurred in either of the two groups. Lower abdominal pain was most common side effect in both groups. In oral group, 17.5% need parenteral analgesia while 21.3% in sublingual group. However, this is not statistically significant. The incidence of fever and chill were higher in sublingual group ($p < 0.05$). All the adverse effects occurred after 2 doses of misoprostol.

Discussion

Since 1995, our team from Ramathibodi hospital had been investigating the role of misoprostol for term labor induction, termination of pregnancy in first and second trimester abortion[14-19]. The authors tried to find the optimum regimen for the use of misoprostol. The authors' previous studies focused on vaginal administration and found that 600 μg of misoprostol is more effective than 200 and 400 μg. Until now, we have not investigated for the proper regimen by another route.

There have been a few randomized trials that compared different route, doses and dosing interval of misoprostol in the medical abortion[20, 21]. Some studies used the single dose of misoprostol and waiting until passing of the product of conceptus, some manage as self-administered out patient. However, in Thailand, abortion except for medical indication is illegal and misoprostol is government controlled. The women have to be admitted. We designed the study as one-day regimen to minimize the hospital stay.

The objective of this study was to compare the repeated doses of sublingual and oral misoprostol in medical management of early pregnancy failure. This is the first randomized trial comparing the clinical use of sublingual versus oral misoprostol in the aspect of termination of early pregnancy failure. The clinical efficacy of sublingual is the same as oral misoprostol. The induction to abortion interval was slightly shorter in sublingual group but not statistically significant.

Some previous studies have evaluated the use of sublingual misoprostol as termination of pregnancy in the first trimester and have shown that it is a promising method that may be used as an alternative for women who do not want surgical evacuation[22,23].

In a study by Tang OS, et al on the pharmacokinetics of oral, sublingual, vaginal and vaginal moistened tablets of misoprostol 400 μg in 40 women undergoing a first-trimester abortion, they found that sublingual misoprostol achieved a significantly higher maximum plasma concentration compared with the other groups. The time to maximum plasma concentration was similar in both the sublingual and oral groups (20-27 minutes). They also found that the area under the curve at 360 minutes in the sublingual group was significantly greater than those in the oral group. They concluded that the sublingual route of administration of misoprostol demonstrated great potential[6].

In the subgroup analysis, the authors found that the induction to abortion interval in dead embryo group was shorter than blighted ovum group. This may be because the prostaglandin releases from dead embryo and provide uterine contraction and the ripening of the cervix.

Clinical outcome percentage as complete abortion aspect was lower than previous studies[2-5,22]. The authors analyzed this result and found that the surgical evacuation was done very early, whenever the women had vaginal bleeding although some was inactive bleeding. When after six doses of misoprostol and women did not pass the conceptive tissue, we classified the event as medical failure. The authors did not have a waiting period as in some other studies.

However, Tang OS, et al found that an additional one-week course of sublingual misoprostol did not improve the success rate or shorten the duration of vaginal bleeding. Instead, it increased the incidence of diarrhea[24]. Further studies need to investigate the proper time from last dose of misoprostol to the time doing surgical evacuation as well as doses and dosing interval.

The definition of success of treatment varies among different studies in the literature. Most studies used ultrasonographical evidence of empty uterus as definition of treatment[12,25,26]. The authors used the ultrasound as one of the criteria to diagnosed complete abortion. The women with incomplete abortion diagnosed by ultrasound examination may not have required surgical evacuation. It was suggested that the need for surgical evacuation after abortion should be indicated by clinical rather than ultrasonographical criteria.

The adverse effects of various misoprostol regimens are another important factor for determining their usefulness and acceptability. Previous pilot studies suggest that sublingual misoprostol is associated with a higher incidence of adverse effects especially diarrhea, fever and chill[10,22,24,27]. This was supported by present study in respect to fever and chill, as they were significantly higher in the sublingual group. This may be explains by higher bioavailability.

There are some theoretical advantages in favor of oral and sublingual administration including similarly high absorption and possible greater patient acceptance. A previous study found that sublingual misoprostol resulted in higher bioavailability compared with oral misoprostol. Sublingual administration in an 800 μg dose was also associated with more symptoms and less acceptability compared with oral misoprostol[28-30]. Oral route of administration is needed to be further studied in the aspect of termination of pregnancy.

In conclusion, the overall efficacy and acceptability of medical abortion of early pregnancy failure were good. Both sublingual and oral misoprostol result in the same clinical outcomes. The adverse effects were similar in both groups except that fever was more common in sublingual group. The induction to abortion interval might be shorter in sublingual group but not significantly.

References

1. AlbermaE, Grudzinskas G, Chardt G. Spontaneous abortion: diagnosis and treatment. London: Springer-Verlag; 1992: 9-20.

2. Graziosi GMC, Mol BW, Ankun WM, Bruinse HW. Management of early pregnancy loss. Int J Gynaecol Obstet 2004; 86: 337-46.
3. Jurcovic C, Rose JA, Nicolaides KH. Expectant management of missed abortion. Br J Obstet Gynaecol 1998; 105: 670-1.
4. Nielsen S, Hahlin M. Expectant management of first trimester spontaneous abortion. Lancet 1995; 345: 84-6.
5. Ngai SW, Chan YM, Tang OS, Ho PC. Vaginal misoprostol as medical treatment of first trimester miscarriage. Human Reprod 2001; 16: 1493-6.
6. Tang OS, Soohweer H, Seyberth HW, Lee SW, Ho PG. Pharmacokinetics of different route of administration of misoprostol. Hum Reprod 2002; 17: 322-6.
7. Chong YS, Su LL, Arulkumaran S. Misoprostol: a quarter century of use, abuse and creative misuse. Obstet Gynecol Surv 2004; 59: 128-40.
8. Ho PC, Ngai SW, Lui KL, Won GCY, Lee SWH. Vaginal misoprostol compared with oral management in second trimester pregnancy. Obstet Gynecol Surv 1997; 90: 735-8.
9. Tang OS, Lau WN, Chan CW, Ho PC. A prospective randomized comparison of sublingual and vaginal misoprostol in second trimester termination of pregnancy. Br J Obstet Gynaecol 2002; 111: 1001-5.
10. Tang OS, Miao BY, Lee SWH, Ho PC. Pilot study on the use of repeated doses of sublingual misoprostol in the termination of pregnancy up to 12 weeks of gestation. Hum Reprod 2002; 17: 1738-40.
11. Bernard KG, Cooperberg PL. Sonographic differentiation between blighted ovum and early viable pregnancy. Am J Roentgenol 1985; 144: 597-602.
12. Rulin MC, Bornstein SC, Campbell JD. The reliability of ultrasonography in the management of spontaneous abortion, clinically thought to be complete: a prospective study. Am J Obstet Gynecol 1993; 168: 12-5.
13. Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC III, Hankins GDV, et al. Williams obstetrics. 20th ed. Connecticut: Appleton & Lange; 2005: 579-605.
14. Herabutya Y, O-Prasertsawat P, Pokpirom J. A comparison of intravaginal misoprostol and intracervical prostagandin E2 gel for ripening of unfavorable cervix and labor induction. J Obstet Gynaecol Res 1997; 3: 369-74.
15. Herabutya Y, O-Prasertsawat P. Misoprostol in the management of missed abortion. Int J Gynaecol Obstet 1997; 56: 263-6.
16. Herabutya Y, O-Prasertsawat P. Second trimester abortion using intravaginal misoprostol. Int J Gynaecol Obstet 1998; 60: 161-5.
17. Herabutya Y, Chanrachakul B, Punyavachira P. Vaginal misoprostol in termination of second trimester pregnancy. J Obstet Gynaecol Res 2000; 26: 121-5.
18. Herabutya Y, Chanrachakul B, Punyavachira P. Second trimester pregnancy termination: a comparison of 600 and 800 micrograms of intravaginal misoprostol. J Obstet Gynaecol Res 2001; 27: 125-8.
19. Herabutya Y, Chanrachakul B, Punyavachira P. Induction of labor with vaginal misoprostol for second trimester termination of pregnancy in the scarred uterus. Int J Gynaecol Obstet 2003; 83: 293-7.
20. Mitchell DC, Robert M, Richard G. Misoprostol for medical evacuation of early pregnancy failure. Obstet Gynecol Surv 1997; 89: 768-72.
21. Tang OS, Lau WNT, Yu H, Lee SW, Ho PC. A prospective randomized study to compare the use of repeated doses of vaginal with sublingual misoprostol in the management of first trimester silent miscarriage. Hum Reprod 2002: 20: 176-81.
22. Cheung W, Tang OS, Lee SW, Ho PC. Pilot study on the use of sublingual misoprostol in terminaton of pregnancy up to 7 weeks gestation. Contraception 2003; 68: 97-9.
23. Wagaarachchi P, Ashok P, Smith N, Templeton A. Medical management of early fetal demise using sublingual misoprostol. BJOG 2002; 109: 462-5.
24. Tang OS, Ong CY, Tse XY, Ng EH, Lee SW. A randomized trial to compare the use of sublingual misoprostol with or without additional 1 week course for management of first trimester silent miscarriage. Hum Reprod 2006; 21: 189-92.
25. Alcazar JL, Baldonado C, Larpatec C. The reliability of transvaginal ultrasonography to detect retained tissue after spontaneous first-trimester abortion, clinically thought to be complete. Ultrasound Obstet Gynaecol 1995; 6: 126-9.
26. Chung TK, Cheung L. Misoprostol in the management of spontaneous abortion. BJOG 1995; 102: 832-5.
27. Vimala N, Mittal S, Kumar S, Dadhwal V, Sharma Y. A randomized comparison of sublingual and vaginal misoprostol for cervical ripening before suction termination of first trimester pregnancy. Contraception 2004; 70: 117-20.

28. Chaff EA, Dicenzo RLS. Comparison of misoprostal plasma concentration following buccal and sublingual administration. Contraception 2005; 71: 22-5.
29. Todd C, Soler M, Castleman L, Roger M, Bluementhal P. Buccal misoprostol as cervical preparation for second trimester pregnancy termination. Contraception 2002; 65: 415-8.
30. Carlan S, Blust D, O'Brien W. Buccal versus intravaginal misoprostol administration for cervical ripening. Am J Obstet Gynecol 2002; 186: 229-33.

การเปรียบเทียบประสิทธิภาพของยา misoprostol ขนาด 400 ไมโครกรัม โดยวิธีอมใต้ลิ้นและวิธีรับประทานในการรักษาภาวะการสิ้นสุดการตั้งครรภ์ในอายุครรภ์น้อย

อรดา ปัทมสิงห์ ณ อยุธยา, ยงยุทธ เหราบัตย์, บุญศรี จันทร์รัชชกูล, ณัฐพงศ์ อิศรางกูร ณ อยุธยา, ประทักษ์ โอประเสริฐสวัสดิ์

วัตถุประสงค์ในการทำวิจัย เพื่อศึกษาเปรียบเทียบประสิทธิภาพและผลข้างเคียงของการใช้ยา misoprostol โดยวิธีอมใต้ลิ้นและวิธีรับประทาน เพื่อรักษาภาวะการสิ้นสุดการตั้งครรภ์ในอายุครรภ์น้อย โดยทำการศึกษาในกลุ่ม สตรีตั้งครรภ์ที่มีอายุครรภ์ไม่เกิน 20 สัปดาห์ซึ่งได้รับการตรวจพบว่ามีขนาดมดลูกเล็กกว่าอายุครรภ์ ได้รับการตรวจ ด้วยเครื่องเสียงความถี่สูง และให้การวินิจฉัยว่ามีภาวะการสิ้นสุดการตั้งครรภ์ในอายุครรภ์น้อย จำนวน 138 คน จะถูก แบ่งด้วยวิธีสุ่มให้ได้รับยา misoprostol 400 ไมโครกรัมโดยวิธีอมยาใต้ลิ้นและวิธีรับประทานทุก 4 ชั่วโมง จนกระทั่งเกิด การสิ้นสุดการตั้งครรภ์โดยสมบูรณ์

ผลการศึกษาพบว่าระยะเวลานับตั้งแต่ผู้ป่วยได้รับยาครั้งแรกจนถึงตรวจพบถุงการตั้งครรภ์ หรือชิ้นส่วนของถุงการตั้งครรภ์หลุดออกมาจากโพรงมดลูกทั้งสองกลุ่มไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ในกลุ่มที่ได้รับยาโดยวิธีอมใต้ลิ้นพบว่าเกิดไข้และหนาวสั่น ได้มากกว่ากลุ่มที่ได้รับยาโดยวิธีรับประทานสรุปได้ว่าการใช้ยา misoprostol โดยวิธีอมใต้ลิ้นและวิธีรับประทานมีประสิทธิภาพในการรักษาไม่แตกต่างกัน