A Comparison of Vaginal Misoprostol 800 μg Versus 400 μg for Anembryonic Pregnancy: A Randomized Comparative Trial

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Objective: *To compare the efficacy, side effects and patient satisfaction between 800 μg versus 400 μg intravaginal misoprostol for anembryonic pregnancy.*
Material and Method: *Women who had diagnosed as anembryonic pregnancy were treated as IPD case and randomly assigned to receive either 800 μg or 400 μg intravaginal misoprostol. The second dose was administered in the equal dose if there was no evidence of abortion in 24 hr. The treatment failure was determined by no complete abortion within 48 hr. If spontaneous abortion had not occurred, or had heavy vaginal bleeding or evidence of incomplete abortion either by clinical manifestation or sonographic finding then dilatation and curettage was performed.*
Results: *Fifty patients were enrolled into the study, 25 patients were randomized to receive 800 mg and 25 patients were received 400 mg intravaginal misoprostol. Complete abortion within 48 hr was not different between the 2 groups (72%). However complete abortion within 12 hr was significantly higher in the 800 mg group than in the 400 mg group (64% versus 20 %, respectively, p = 0.016). The median time to abortion in the 800 mg group was significantly shorter than in the 400mg group (9.0 hr versus 16.0 hr, respectively, p= 0.01). There was no significant difference in the side effects and patients' satisfaction between both groups.*
Conclusion: *Vaginal misoprostol can be used for termination of pregnancy in case of anembryonic pregnancy with high successful rate of complete abortion and no serious adverse effects. We recommend the 800 μg vaginal misoprostol regimen because within 12 hr the complete abortion rate was higher and the median time to abortion was shorter than the 400 μg regimen with no difference in side effects. This may decrease the suffering time of both physical and psychological trauma to the patient before complete abortion has occurred.*

Keywords: *Anembryonic pregnancy, Misoprostol, Pregnancy termination.*

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Missed abortion is a common complication of early pregnancy occurring in up to 15% of all clinically recognized pregnancies [1]. Over the past 50 years, suction evacuation or dilatation and curettage have been conventional method of treatment. However it may be associated with cervical injury, uterine perforation, pelvic infection and excessive bleeding, the overall complication rate varies between 4 and 10% [2,3]. Currently, medical treatment had been used for termination of early pregnancy failure with the same efficacy but less complications compared to surgical treatment [4-7].

Misoprostol (Cytotec®), a synthetic prostaglandin E1 analogue has widely been used for medical abortion, cervical ripening before surgical abortion, labor induction and used for termination of pregnancy. In the literatures; misoprostol used for induce abortion in early pregnancy failure shows wide range of regimen (200-1000 mg) and outcomes (60-93%) [8-14]. Several studies revealed different success rates even in the same dose and route [8,10]. In addition, they did not

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classify or separate the types of early pregnancy failure for analysis which might affect the outcomes. There is only one study concerned about type of pregnancy and response to the treatment. They stated less success rate in treatment of anembryonic pregnancy with placebo compared to those whom treated with intravaginal 400 mg misoprostol [8].

The purpose of this study was to compare the clinical efficacy of 2 doses of intravaginal misoprostol (800µg versus 400µg) for termination of anembryonic pregnancy and to compare the incidence of maternal side effects as well as maternal satisfactions between these 2 regimens.

Material and Method

This randomized, controlled trial was conducted at the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand between June 2004 and April 2005.

The patients participated in this study were obtained from pregnant women who came to antenatal care clinic or gynecologic outpatient department with the problem of abdominal pain or abnormal uterine bleeding.

The inclusion criteria were all pregnant women with anembryonic pregnancy as determined by transvaginal ultrasound. Early pregnancy failure was defined as 1) an irregular intrauterine gestational sac with a mean sac diameter of $\geq$ 20 mm and no embryonic pole, and 2) abnormal growth on ultrasound image over or minimum of 7 days [4].

Exclusion criteria included 1) an inability to confirm pregnancy failure or intrauterine gestational sac location, 2) an inability or refusal of the patient to adhere to study follow-up requirements, 3) heavy vaginal bleeding (defined as soaking more than one heavy vaginal pad per hour for more than 2 hr or more than one heavy pad per 30 min for more than 1 hr, 4) anemia (defined as a hemoglobin concentration less than 10 mg/dl), 5) unstable vital signs, 6) maternal coagulopathy, 7) signs and symptoms of infection, 8) maternal history of asthma or cardiac disease, 9) known maternal allergy to prostaglandin or previous adverse reaction, and 10) open internal cervical os on speculum examination (as defined by allowing passage of a ring forceps).

Written informed consent was obtained in all cases. This study was approved by the ethical committee of the faculty.

Before enrollment, all patients underwent transvaginal ultrasound (5 MHz transvaginal transducer, Aloka SSD-2000, Tokyo, Japan) to confirm an anembryonic pregnancy and initial laboratory evaluation included complete blood cell count, prothrombin time and partial thromboplastin time.

The patients fulfilled our criteria were offered 3 options, the first option-expectant for complete abortion, the second option-immediate dilatation and curettage, and the third option-medical treatment by misoprostol.

Patients who chose medical treatment were admitted and subsequently randomized to receive either 800µg misoprostol (four 200-µg tablets) regimen or 400 µg misoprostol (two 200-µg tablets) regimen; opened technique, by using random number tables.

The misoprostol tablets (Cytotec®, Searle Laboratories, New South Wale, Australia, 200 mg /tab) were dampened with 2-3 drops of normal saline and placed within the posterior vaginal fornix by residents, and then the patients remained in a semiprone position for at least 1 hr. At 24 and 48 hr after initial dose, the patients were evaluated pelvic examination by residents. At 24 hr after initial dose, if complete abortion had not occurred, the second equal dose was placed. And at 48 hr after initial dose; if complete abortion had not occurred, the treatments were defined to failure.

The treatment failure was defined as no evidence of complete abortion within 48 hr. Dilatation and curettage was performed by residents when 1) spontaneous abortion had not occurred after 48 hr, 2) heavy vaginal bleeding 3) incomplete abortion, 4) endometrial thickness more than 10 mm, evaluated by transvaginal ultrasound 6 hr after the diagnosis of complete abortion, and 5) the patients' request upon dilatation and curettage. Incomplete abortion was defined as clinical findings of open cervical os with bleeding and retained conceptus or a sonographic finding of endometrial thickness more than 10 mm without midline echo. Complete abortion was defined as completely expulsion of conceptive products or pathological absence of conceptus after dilatation and curettage in patients with suspected incomplete abortion.

Vital signs were monitored every 4 hr. Pain assessment was evaluated by 10 grades visual analogue scale. Acetaminophen 1000 mg (2 tablets) were given as analgesic treatment and supplement treatment was intramuscular morphine 10 mg. Maternal side effects such as abdominal pain, fever defined as oral body temperature more than 38∫c, diarrhea, nausea, vomiting and chill were recorded. In case of emergency problems, the patients were treated by on-duty residents.

The primary outcome measure was complete abortion rate. The secondary outcome was patient's side effects and satisfaction. Patient satisfaction was assessed by asking the patients to rate their degree of agreement with the following 2 statements: 1) I would recommend the treatment to a friend or family member with early pregnancy failure. 2) I would try the treatment again if I had another early pregnancy failure. The patients indicated their degree of agreement on a five-grading scale: strongly disagree, disagree, neutral, agree, or strongly agree.

From prior pilot study: Ten patients were included and randomized divided to 2 groups (five patients for each group). In group 1 regimen (800 µg misoprostol) the outcome showed 80% of complete abortion and in group 2 regimen (400 µg misoprostol) the outcome showed 40% of complete abortion. Therefore, the sample size obtained by calculation was 25 patients in each group ($\alpha = 0.05$, $\beta = 0.02$).

$$n = \frac{2(Z_{\alpha/2}+Z_{\alpha})^2 \; P\,Q}{(P_1-P_2)^2}$$

$$= \frac{2(1.96+0.84)^2\, 0.6 \times 0.4}{(0.8-0.4)^2} = 23$$

add 10% = 25 patients/group

Statistical analysis was performed with SPSS version 11 for Window XP (SPSS, Chicago, USA). Unpaired t-test was analyzed for continuous variables, Chi-square or Fisher exact test for categorical variables. Univariate analysis was used to define the prognostic variable. The descriptive data were shown in mean ± standard deviation. A p-value of < 0.05 was considered statistically significant.

Results

Fifty patients were enrolled this study. Twenty five patients were randomized to the group 1 regimen (800 µg misoprostol) and 25 patients were randomized to the group 2 regimen (400 µg misoprostol). The patient characteristics were similar between the 2 groups (Table 1).

Table 2 shows the outcomes of patients. Complete abortion rate (72% in both groups), incomplete abortion rate (16% in group 1 versus 8% in group 2, p = 0.55), and rate of dilatation and curettage (32% in group 1 versus 28% in group 2, p = 1.00) were not statistically significant difference between the 2 groups. However, median time to abortion in the 800 µg group was significantly shorter than in the 400µg group (9.0 hr versus 16.0 hr, respectively, p = 0.01). Eight patients (3 patients in the 800 µg group and 5 patients in the 400 µg group) failed to achieve complete abortion and underwent dilatation and curettage without complications.

Univariate analysis of variance was used to evaluate the prognostic factors of the outcomes; such as maternal age, parity, previous cesarean section, previous abortion, previous dilatation and curettage, gestational age, and body mass index. There was no statistically significant variables demonstrated to influence the outcomes.

Table 3 shows the maternal side effects which were found to have no statistically significant difference between the 2 groups.

All patients completed the post treatment questionnaires for assessment of satisfactions. Overall, patients' satisfactions with the treatment appeared to be high and there was no statistically significant difference between the 2 groups (Table 2). 42 of 50 (84%) patients were satisfied or strongly satisfied. No one disagreed with the treatment.

Discussion

In recent years misoprostol, a synthetic analogue of prostaglandin E 1, has attracted attention as an effective and cost- efficient agent for medical interruption of the first trimester pregnancy with minimal side effects and no serious complication [8-14]. Vaginal misoprostol is found to be more effective than oral misoprostol for uterine evacuation of early pregnancy

Table 1. Patient demographic characteristics

	Misoprostol 800 µg (No.=25)	Misoprostol 400 µg (No.= 25)
Age, mean±S.D.,years	29.2±6.0	33.3±5.9
Nulliparous, No. (%)	14 (56%)	12 (48%)
Previous abortion, No. (%)	11 (44%)	6 (24%)
Previous dilatation and curettage, No. (%)	6 (24%)	4 (16%)
Gestational age, mean±S.D., weeks	14.3±3.8	14.1±3.6
Hematrocrit, mean±S.D., volume percent	36.9±3.0	35.4±2.7

Table 2. Patients' outcomes

	Misoprostol 800 µg (No. =25)	Misoprostol 400 µg (No. =25)	p value
Hospitalization, mean±S.D., days	2.84±0.98	2.76±0.83	0.75
Complete abortion, No. (%)			
In 12 hours	14 (64%)	5 (20%)	0.016
In 24 hours	17 (68%)	13 (52%)	0.55
In 48 hours	18 (72%)	18 (72%)	1.00
Incomplete abortion, No. (%)	4 (16%)	2 (8%)	0.558
No abortion, No. (%)	3 (12%)	5 (20%)	
Dilatation and curettage, No. (%)	7 (28%)	7 (28%)	1.00
Median time to abortion,(range), h	9.0 (3.0-30.0)	16.0 (4.3-44.2)	0.01
Total dose, mean±S.D., µg	1024±360	576±200	0.24
Satisfaction, No. (%)			
Neutral	5 (20%)	3 (12%)	0.74
Agree	11 (44%)	12 (48%)	
Strong agree	9 (36%)	10 (40%)	

Table 3. Side effects

	Misoprostol 800µg (No. =25)	Misoprostol 400µg (No. =25)	p value
Pain scale, mean±S.D., scores	4.80±2.84	3.72±3.11	0.20
Pain scales ≥ 5 scores, No., (%)	12 (48%)	8 (32%)	0.24
Analgesic used, No. (%)	11 (44%)	14 (56%)	0.67
Acetaminophen, No. (%)	12 (48%)	9 (36%)	
Morphine, No. (%)	2 (8%)	2 (8%)	
Diarrhea, No. (%)	6 (24%)	6 (24%)	1.00
Nausea and vomiting, No. (%)	0 (0%)	4 (16%)	0.12
Chill, No. (%)	6 (24%)	4 (16%)	0.72
Fever, No. (%)	6 (24%)	1 (4%)	0.09
Heavy vaginal bleeding, No. (%)	1 (4%)	0	1.00
Infection needed intravenous antibiotic, No. (%)	0	0	1.00

failure [1,10]. There have been several clinical trials that have evaluated the efficacy of vaginal misoprostol for the evacuation of the first trimester uterus [1,8-14]. Many studies have reported and recommended that vaginal dose of 400 to 1000 µg of misoprostol alone are effective in producing complete abortion in cases of early pregnancy failure up to 12 weeks of gestation in approximately 60 to 88%.[8-14] However, they did not classify or separate the types of early pregnancy failure for analysis which might affect the outcomes. In addition variation in regimen, doses and route of administration may also affect the success rate. The recent studies support that moistened vaginal misoprostol is effective method[17-19].

Wood and Brain [1] performed a randomized trial which compared the efficacy of 800 µg of intravaginal misoprostol every 24 hr up to a maximum of 2 doses versus a placebo for termination of missed abortion. They found that the success rate of complete abortion in the misoprostol group was 80% which was significantly higher than in the placebo group (16%). However, they did not mention much about the side effects of the study group. Carbonell et al [12] reported the safety and efficacy of 1000 µg misoprostol vaginally self-administered into the vagina every 24 hr up to a maximum of 3 doses for early abortion. They found that complete abortion occurred in 93.0% of patients with the mean expulsion time of 8.1 hr. However, the frequencies of nausea and diarrhea were high. Prasartsakulchai and Tannirandorn [9] have recently reported that two vaginal doses of 400 µg of misoprostol were as effective as two vaginal doses of 800 mg of misoprostol in producing complete abortion (76% versus 72%, respectively) with similar rate of the

need for dilatation and curettage (28%) in both embryonic death and anembryonic pregnancy. The median time to abortion in the 800 mg group was significantly shorter than in the 400 μg group (9.0 hr versus 15.3 hr, respectively). Fever was the only side effect which was found to be significantly increased in the 800 mg group (28%). Kovavisarach and Sathapanachai [8] investigated the effectiveness and side effects of intravaginal misoprostol 400 μg compared with a placebo for facilitating complete abortion in cases of anembryonic pregnancy with gestational age of up to 12 weeks. They found that complete abortion rate was significantly higher in the women receiving misoprostol (63%) compared with those receiving the placebo (18.5%). However, lower abdominal pain (74.1%) and fever (14.8%) were significantly higher in the misoprostol group than in the placebo group (22% and 0%, respectively). However, they used only single dose and evaluated at 24 hours after drug administration. Our study, which specifies only anembryonic pregnancy, found that within 12 hours the successful rate in the 800 μg misoprostol group was significantly higher than the 400 μg misoprostol group (64% versus 20 %, respectively, $p < 0.01$). But in 12-24 hr (with the single dose of 400 or 800 μg misoprostol), the success rate were not significant difference (68% vs 52%, p=0.55) that stated the initial high dose (800 μg) gave more rapid action than the lower dose (400 μg). Then, in 12-48 hr, the effectiveness of the 400 and 800 mg were equal. Even the increasing of dose; as much as two times of 800 μg, the success rates were not much increase. It was meant there were some of the population did not response to the medication that needs further studies for the response- association factors in this group. Median time to abortion in the 800 μg misoprostol group was significantly shorter than in the 400 μg misoprostol group (9 hr versus 16 hr, respectively, p=0.01). The side effects were not statistically different between both groups. The common side effects were lower abdominal pain, diarrhea and fever with chill. However, all women considered the side effects were tolerable and transient. No serious maternal complications were demonstrated.

In our study, we also assessed patient satisfaction as an outcome measure and we found that patient satisfaction (agree or strongly agree) in both groups was high (80% in the 800 μg misoprostol group and 88% in the 400 μg misoprostol group) with no statistically significant difference between both groups which is consistent with the study of Prasartsakulchai and Tannirandorn [9]. Cabezas [15] found a significantly greater percentage of women in the misoprostol group than in the surgical group who appeared to be highly satisfied with the procedure (68.5% versus 54.4%, respectively). Lee et al [16] also found that significantly more participants who experienced successful evacuation of the uterus with the misoprostol would choose the same method of treatment.

Limitation in our study is the difference of success rate between pilot study and study's outcome of 400 μg (40% vs 72%). There may because few samples (five patients) in the pilot study that result in overestimate of percentage for sample size calculation. In summary, vaginal misoprostol of both regimens can be used for termination of pregnancy in case of anembryonic pregnancy with high successful rate of complete abortion and no serious adverse effects. We recommend the 800 μg vaginal misoprostol regimen because within 12 hr the completed abortion rate was three times of the 400 μg regimen and the median time to abortion was significant shorter than the 400 μg regimen with no difference in side effects. This may decrease the suffering time of both physical and psychological trauma to the patient before complete abortion has occurred.

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การศึกษาเปรียบเทียบการใช้ยามิโสพรอสตอลขนาด 800 และ 400 ไมโครกรัม เหน็บทางช่องคลอดในการตั้งครรภ์ที่ไม่มีตัวอ่อน

นาฏนภา ศรีขาว, เยื้อน ตันตินิรันดร

วัตถุประสงค์ : *เพื่อศึกษาเปรียบเทียบประสิทธิผล ผลข้างเคียง และความพึงพอใจ ในการใช้ยา มิโสพรอสตอลขนาด 800และ 400 ไมโครกรัมเหน็บทางช่องคลอดในการตั้งครรภ์ที่ไม่มีตัวอ่อน*

วัสดุและวิธีการ : *ผู้ป่วยที่ได้รับการวินิจฉัยเป็นการตั้งครรภ์ที่ไม่มีตัวอ่อน จะถูกรับไว้ในโรงพยาบาลและสุ่มแบ่งเป็น 2กลุ่ม กลุ่มแรกใช้ยามิโสพรอสตอลขนาด 800 ไมโครกรัมเหน็บทางช่องคลอด และ กลุ่มที่สองใช้ยามิโสพรอสตอลขนาด 400 ไมโครกรัมเหน็บทางช่องคลอด ยาจะถูกเหน็บซ้ำในขนาดเดิมถ้าไม่มีการแท้งเกิดขึ้นหลังเหน็บยา 24 ชั่วโมง และถ้าไม่มีการแท้งอย่างสมบูรณ์เกิดขึ้นใน 48 ชั่วโมง ถือว่าผลจากการเหน็บยาล้มเหลว ผู้ป่วยจะได้รับการขูดมดลูกถ้าไม่มีการแท้งเกิดขึ้น มีเลือดออกจากช่องคลอดมากหรือแท้งไม่ครบ*

ผลการศึกษา : *ผู้ป่วยที่นำมาศึกษาทั้งหมดมี 50 คน แบ่งเป็น 2 กลุ่ม กลุ่มละ 25 คน พบว่าไม่มีความแตกต่างในอัตราการแท้งอย่างสมบูรณ์ (ร้อยละ 72ในทั้ง 2 กลุ่ม) แต่พบว่าในกลุ่มที่ใช้ยามิโสพรอสตอลขนาด 800 ไมโครกรัมจะใช้เวลาเฉลี่ยในการแท้งน้อยกว่าอย่างมีนัยสำคัญทางสถิติ (9 ชั่วโมงต่อ 16 ชั่วโมง) โดยที่ไม่พบว่ามีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในเรื่องภาวะแทรกซ้อนจากการเหน็บยาและความพึงพอใจของผู้ป่วย*

สรุป : *ยามิโสพรอสตอลเหน็บทางช่องคลอดสามารถนำมาใช้ให้เกิดการแท้งในผู้ป่วยตั้งครรภ์ที่ไม่มีตัวอ่อนได้โดยมีอัตราการแท้งครบที่สูงและไม่มีภาวะแทรกซ้อนที่รุนแรง โดยภายในเวลา 12 ชั่วโมง ขนาดยา 800 ไมโครกรัมให้อัตราการแท้งครบมากกว่าขนาดยา 400ไมโครกรัม และระยะเวลาเฉลี่ยในการแท้งน้อยกว่าในกลุ่ม 400 ไมโครกรัม ซึ่งช่วยลดระยะเวลาที่ผู้ป่วยต้องทนทรมานในการรอแท้ง*