Effectiveness of 400 or 600 Micrograms of Vaginal Misoprostol for Terminations of Early Pregnancies

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Objectives: *To compare the effectiveness and side effects of transvaginal application of 400 or 600 ug of misoprostol for termination of pregnancy.*
Study design: *A prospective randomized single-blinded trial.*
Setting: *Department of Obstetrics&Gynecology,Bhumibol Adulyadej Hospital*
Material and Method: *One-hundred-and-twenty-five pregnant women with less than 20 weeks gestational, at Bhumibol Adulyadej Hospital from June 1,2003 to May 31,2004 were recruited. The termination of pregnancy had been suggested by the obstetrician and the decision was made by the patient and her husband. The samples were randomized into 2 groups. Group 1 had 65 patients and 400 ug of misoprostol was applied three times in a 6 hour interval. Group 2 had 60 patients and 600 ug of misoprostol was applied in the same manner. Both groups were observed and evaluated within 24 hours.*
Main outcome measures: *Rate of complete abortion and side effects of both 400 and 600 g misoprostol within 24 hours.*
Results: *No statistical significant difference was found in the general characteristics of both sample groups. Group 1 had an abortion rate of 38.3% while group 2 had an abortion rate of 56.92%. This was statistically significant ($p < 0.05$). The time interval after insertion to complete abortion was 9.15 6.09 hours in group 1 and 8.85 4.68 hours in group 2. Side effects,such as fever,lower abdominal pain,massive vaginal bleeding and diarrhea showed no statistical difference ($p > 0.05$).*
Conclusion: *Transvaginal application of 600 ug misoprostol (3 times every 6 hours) caused a higher rate of complete abortion compared with an application of 400 ug misoprostol. The side effect of both groups showed no statistical difference.*

Keywords: *Termination of pregnancy, Misoprostol*

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At Bhumibol Adulyadej Hospital, indication for termination of pregnancy occurs at an increasingly higher rate annually. For instance, blighted ovum, fetal demise in utero, severe fetal anomalies and complicated medical conditions in pregnant woman are all important indications for obstetricians' consideration for termination of pregnancy. For pregnancy of gestational age less than 14 weeks[1] dilatation and curettage is one of the standard procedures. However, it has its complications such as infection, uterine perforation and anesthetic complications. Another procedure commonly used is oxytocin intravenously but it also contains risk of uterine rupture, hypotension, oliguria and other complications from side effects of oxytocin at a higher dosage. Menstrual aspiration is also common for pregnancy with a gestational age of 5 to 7 weeks. However, termination of pregnancy by introducing intra-amniotic hyperosmotic fluid such as 20% NSS, 30% urea is no longer used because there are more fatal complications such as electrolytes imbalance, congestive heart failure, intra-abdominal infection and water intoxication Recently, the use of Prostaglan-

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dins for termination of pregnancy has become a less invasive procedure and is commonly used by many obstetricians. Prostaglandin E_2 was commonly used by many obstetricians however, as its cost was quite high, its usage declined. Synthetic Prostaglandins E_1[2,3] has been introduced with a lower cost and fewer complications. Misoprostol is a Prostaglandin E_1, or also known as Cytotec®. Initially, Cytotec® was commonly used to treat peptic ulcer. Other studies showed that it soften the cervix and induce uterine contraction. Misoprostol was first used to induced abortion in 1988 by an obstetrician in Brazil[4] Following this discovery, many studies have been done worldwide and in Thailand[5-13] to demonstrate that misoprostol can be used to terminate the pregnancy with a success rate of approximately 40%-90% thus, has become accepted among obstetricians worldwide.

However, these studies on vaginal misoprostol are still lacking evidence on dosage, success rate and frequency of application, therefore, further investigation still needs to be done. In the present study, different dosages of misoprostol via vaginal suppository were compared (400 g vs 600 g) in terms of effectiveness to induce complete abortion and the complications. Misoprostol, was introduced every 6 hours for 3 consecutive doses while the rate of complete abortion was observed and evaluated in 24 hours.

Material and Method

The present study recruited 125 pregnant women with a gestational age of less than 20 weeks with indication to terminate pregnancy; e.g. blighted ovum, fetal demise in utero, severe fetal anomalies or complicated medical conditions in pregnant woman, between June 1,2003 and May 31, 2004. This study was done with the approval of the Bhumibol Adulyadej Hospital Board of ethical committee and informed consent from the patients to use their medical record in the present study. Pregnant women with a history of prostaglandins allergy, asthma, hypertension, heart diseases, renal insufficiency, hepatic dysfunction and previous uterine surgery were excluded from the present study. Gestational age was calculated and confirmed by LMP, height of fundus and ultrasonogram. Data such as clinical backgrounds and features were gathered and examined from the medical records of the patients. Laboratory parameters, including CBC, PT, and PTT were evaluated. The patients were divided into two groups by simple randomization technique: Group 1 (n = 60), patients received misoprostol 400 g, and group 2 (n = 65), patients received misoprostol 600 g. After applying vaginal misoprostol, the patients were restricted to bed rest for at least 30 minutes and their clinical signs and complication were observed closely for 24 hours. Meanwhile, the patients were restricted to Nothing Per Oral (NPO) and intravenous fluid was administered. The clinical condition of patients with complete abortion was closely observed for 24 hours after the abortion. In cases of incomplete abortion with or without excessive vaginal bleeding or for patients without signs and symptoms of abortion within 24 hours, dilatation and curettage was performed to terminate the pregnancy. Patients were asked to report for follow-up 1 week after discharge to observe for any complication. The patients who had excessive bleeding and Hct $\leq$ 30% were considered for blood transfusion. Patients with fever $\geq 38^0$ c received paracetamol (500 mg) 2 tabs oral prn q 4-6 hr. Patients who suffered from severe abdominal pain received pethidine 50 mg intramuscularly and phenergan 25 mg intramuscularly to prevent nausea and vomiting. The initiated abortion was observed by an obstetrician from the time misoprostol was applied to the posterior fornix of the vagina until the time of completed expulsion of the conceptus. The side effects of misoprostol observed and recorded included lower abdominal pain, bleeding per vagina, diarrhea and fever. The data were analyzed using chi-squared test, Students' t-test, and arithmetic mean, standard deviation, and range. The level of statistical significant was set at $p < 0.05$. All data were collected and analyzed using the computer software programs SPSS.

Results

One hundred and twenty-five women were initially enrolled in the trial; 60 cases in the 400 g misoprostol group and 65 cases in the 600 g misopostol group. Patient's demographic data and BMI are presented in Table 1. There are no statistically significant differences between the two groups. Table 2 shows the indication for termination of pregnancy between the two groups. There was a significantly higher complete abortion rate in the women receiving 600 g misoprostol (56.99%) compared with those receiving 400 g misoprostol (38.3%). The total abortion rate (complete and incomplete abortion) was higher in the 600 g misoprostol group than those in the 400 g misoprostol group, 81.5% and 71.7%, respectively (Table 3). Time interval after insertion to complete abortion was not statistically significantly different between the two groups as shown in Table 4. Side effects within 24 hours after drug administration are demonstrated in Table 5.

Table 1. Patient characteristics

Patient characteristics	Misoprostol (g)		p-value
	400 (n = 60)	600 (n = 65)	
1. Age (years) Mean ± SD	30.81±6.38	29.61±5.81	0.15
2. Parity (No) Range	0 (0-3)	0 (0-3)	0.27
3. BMI (Kg/m^2) Mean ± SD	22.52±1.73	22.50±1.67	0.84
4. Prior abortion (No) Range	0 (0-3)	0 (0-3)	0.37
5. Gestational Age (wks) Mean ± SD	10.00±2.98	10.13±3.04	0.53

Table 2. Indication for terminations of pregnancy

Indications	Misoprostol (g)		p-value
	400 (n = 60)	600 (n = 65)	
Fetal demise in utero	42	41	0.539
Blighted ovum	16	21	
Others	2 -multiple defect 1 -anencephaly 1	3 -trisomy18 1 -acranium 1 -maternal RPGN*, SLE** 1	

* Rapidly progressive glomerulonephritis
** Systemic lupus erythrematosus

Table 3. Abortion rate within 24 hours

Type of abortion	Misoprostol (g)		p-value
	400 (n = 60)	600 (n = 65)	
Complete abortion	23 (38.3%)	37 (56.9%)	0.04
Incomplete abortion	20 (33.3%)	16 (24.6%)	0.72
Total abortion	43 (71.7%)	53 (81.5%)	0.65

Table 4. Induction to abortion time

	Misoprostol (g)		p-value
	400 (n = 60)	600 (n = 65)	
Mean of induction interval (hours)	9.15±6.09	8.85±4.68	0.165

Table 5. Side effects within 24 hours after drug administration

Side effects	Misoprostol (g)		p-value
	400 (n = 60)	600 (n = 65)	
Lower abdominal pain	24 (40%)	28 (43%)	0.373
Excessive bleeding	10 (16%)	12 (18%)	
Fever	3 (5%)	4 (6%)	
Diarrhea	2 (3%)	2 (3%)	

Discussion

Recently, misoprostol has been used by many obstetricians worldwide and has been considered as an alternative treatment for termination of pregnancy. Serious consideration should be made to use this alternative treatment instead of a standard termination of pregnancy such as dilatation & curettage. This is because the standard termination has a higher rate of infection, uterine perforation, ectopic pregnancy, anesthetic complications, and a much higher cost compared to vaginal misoprostol application. Termination of pregnancy using misoprostol is known to have a lower rate of complication and lower cost. The authors used misoprostol vaginal suppository every 6 hours for 3 consecutive doses. With a dosage of 600 g, they expected to observe a high rate of success at 24 hours and a decrease in the length of hospital stay. Moreover, the authors used misoprostol 400 g as a comparison expecting the same success rate with a lower dosage.

In the present study, complete abortion was observed at a significantly higher rate with 600 g (56.9%) compared to 400 g misoprostol (38.3%). The mean induction to abortion time was 8.85 $\pm$ 4.68 and 9.15 $\pm$ 6.09 hours, respectively. The present study showed a successful abortion rate of 81.5% when using misoprostol 600 g. However, the present study showed a lower rate of complete abortion (56.9%) when using misoprostol 600 g compared to a higher rate of 71.66% reported by Herabutya et al[13]. However Wong et al[15] reported a success rate of 60.8% observed at 24 hours using misoprostol 400 g, lower than the present study (71.7%). Their success rate increased to 75.7% once observation was extended for 48 hours. This is similar to the present study. The similar rate of complete abortion at 24-hours in the two studies was 41.9% and 38.3%, respectively.

Kovavisarach and Sathapanachai[14], studied the effectiveness of vaginal misoprostol 400 g with only one dose in patients with a gestational age of less than 12 weeks. That study found that it can induce complete abortion as high as 63%. The present study showed a rate of complete abortion of only 38.3% when applying the same dosage of misoprostol.

Jain et al[16] studied the effectiveness of misoprostol 200 g vaginal suppository every 6 and 12 hours in the second trimester of pregnancy and discovered that the success rate of complete abortion at 48 hours was 87.2% and 89.2%, respectively. This may conclude that the shorter time interval from 12 hour to 6 hour did not increase the rate of abortion. Furthermore, misoprostol 400 g vaginal suppository was found by Zieman et al[17] to have the highest drug level in 80 minutes and persisted for 4 hours. Following this theory, a shorter interval of misoprostol application should lead to a higher success rate but this was not so as shown by Jain et al.

The side effects of misoprostol were compared between the two groups in the present study, eg. fever, abdominal pain, excessive bleeding per vagina and diarrhea were found to be no statistically significant different ($p > 0.05$). Excessive bleeding per vagina was observed in four patients; two patients in each group. They were evaluated both clinically and by pelvic examination and all four patients were diagnosed with incomplete abortion. They were then given a blood transfusion and were observed closely for hemodynamic stability for the curative treatment. Dilatation and curettage was done and termination of pregnancy was completed without further complication.

Conclusion

The present study demonstrated that misoprostol can be used to terminate pregnancy with an acceptable rate of success however, it was discovered that lesser time interval in misoprostol application did not result in an increased rate of complete abortion rate but, somewhat, increased the rate of incomplete abortion. Therefore, less time interval for misoprostol application may lead to a higher chance to terminate

pregnancy by dilatation and curettage. Dosage of misoprostol, route of administration, frequency and time interval for administration are still not fully understood properly thus future study of the drug efficacy and efficiency should be completed.

In conclusion, intravaginal misoprostol 600 g is significantly more effective than 400 g for termination of early pregnancies without significant difference in side effects between the two groups. However, the optimal dosage regimens and application times need more study with a large number of Thai women. The authors believe that misoprostol can be used for pregnancy termination as an alternative to dilatation and curettage.

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เปรียบเทียบประสิทธิผล ของไมโสพรอสตอล ขนาด 400 และ 600 ไมโครกรัมเหน็บทางช่องคลอด ในการยุติการตั้งครรภ์ในอายุครรภ์ที่น้อยกว่า 20 สัปดาห์

วิบูลย์ เรืองชัยนิคม, เอกราช พงษ์พิษณุ, จามิกร เภกะสุต, สราวุธ สารภักดิ์

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบประสิทธิผล และอาการข้างเคียงที่เกิดขึ้น จากการ ใช้ยาไมโสพรอสตอล ขนาด 400 และ 600 ไมโครกรัม เหน็บทางช่องคลอดในการทำให้เกิดการแท้งครบในหญิงตั้งครรภ์ที่ต้องยุติการตั้งครรภ์ในอายุครรภ์ที่น้อยกว่า 20 สัปดาห์*

ชนิดของการวิจัย: *การวิจัยเชิงทดลองที่แบ่งตัวอย่างโดยการสุ่ม*

สถานที่ที่ทำการวิจัย: *โรงพยาบาลภูมิพลอดุลยเดช พอ.บนอ.*

วัสดุและวิธีการ: *หญิงตั้งครรภ์ จำนวน 125 ราย ผู้มีอายุครรภ์น้อยกว่า 20 สัปดาห์ ที่มารับการรักษาที่โรงพยาบาลภูมิพลอดุลยเดช ตั้งแต่วันที่ 1 มิถุนายน พ.ศ. 2546 ถึง 31 พฤษภาคม พ.ศ. 2547 ได้รับความเห็นชอบให้ยุติการตั้งครรภ์จากแพทย์ผู้ดูแลรักษา และได้รับความยินยอมจากหญิงตั้งครรภ์และครอบครัว แบ่งกลุ่มตัวอย่างออกเป็น 2 กลุ่ม โดยวิธีสุ่ม กลุ่มที่หนึ่ง 60 ราย เหน็บไมโสพรอสตอล ทางช่องคลอด ขนาด 200 ไมโครกรัม จำนวน 2 เม็ด ทุก 6 ชั่วโมง 3 ครั้ง ส่วนกลุ่มที่สอง 60 ราย เหน็บไมโสพรอสตอลทางช่องคลอด ขนาด 200 ไมโครกรัม จำนวน 3 เม็ด ทุก 6 ชั่วโมง 3 ครั้ง สังเกตและประเมินผลภายใน 24 ชั่วโมง*

ตัววัดที่สำคัญ: *อัตราการแท้งครบ และอาการข้างเคียงที่เกิดขึ้นจากการใช้ไมโสพรอสตอล ขนาด 400 และ 600 ไมโครกรัม เหน็บทางช่องคลอด ใน 24 ชั่วโมง*

ผลการศึกษา: *จากการศึกษาพบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในลักษณะทั่วไปของกลุ่มประชากรตัวอย่างทั้ง 2 กลุ่ม กลุ่มที่เหน็บยาไมโสพรอสตอล ขนาด 600 ไมโครกรัม มีอัตราแท้งครบใน 24 ชั่วโมง ร้อยละ 56.92 สูงกว่ากลุ่มที่ใช้ยาไมโสพรอสตอล ขนาด 400 ไมโครกรัม ซึ่งมีอัตราแท้งครบ ร้อยละ 38.33 อย่างมีนัยสำคัญทางสถิติ ($p < 0.05$) แต่อาการข้างเคียงที่เกิดขึ้นจากการใช้ยา เช่น ไข้, ปวดท้องน้อย, เลือดออกมากทางช่องคลอด, ถ่ายเหลว ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ($p > 0.05$)*

สรุป: *ไมโสพรอสตอล เหน็บทางช่องคลอด ขนาด 600 ไมโครกรัม ทุก 6 ชั่วโมง 3 ครั้ง สามารถทำให้เกิดแท้งครบได้ดีกว่า ขนาด 400 ไมโครกรัม อย่างมีนัยสำคัญทางสถิติ โดยที่อาการข้างเคียงจากการใช้ยาไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ*