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Can 400 µg vaginal Misoprostol be used as the cervical priming agent in menopausal women?

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Abstract

Objective : To investigate the efficacy of 400 µg of vaginal misoprostol for cervical priming in menopausal women before fractional curettage.

Methods : A total of sixty menopausal women with abnormal uterine bleeding were randomly assigned to receive either 400 µg of misoprostol or placebo vaginally 16 hours before fractional curettage. The main outcome measures were pre and post intervention - cervical width, other complications and side effects.

Results : Before intervention, mean cervical width in the misoprostol group (4.0 ± 1.2 mm.) did not statistically different from the mean cervical width in the placebo group (3.7 ± 1.7 mm.), P = 0.44. There was no statistical difference between the mean cervical widths after 16 hours of vaginal misoprostol (4.4 ± 1.4 mm.) and placebo (4.0 ± 0.7 mm.), P = 0.27. There was no severe side effects nor complications found in this study.

Conclusion : 400 µg vaginal misoprostol 16 hours prior to fractional curettage in menopausal women did not increase cervical width.

Key words : vaginal misoprostol, cervical priming, menopausal women

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Introduction

In some women with postmenopausal uterine bleeding, fractional curettage is an appropriate procedure for detecting pathology of endometrial tissue. The difficulty in dilatation of the cervical os may lead to many complications such as cervical tear, false tract and uterine perforation. This problem could be resolved by priming the cervical os before mechanical dilatation.

Misoprostol is a prostaglandin analogue for preventing peptic ulcer. It is cheap and easy to be stored in room temperature.[1] Misoprostol has shown to be an effective cervical priming agent for termination of pregnancy either by oral or vaginal administrations.[2-4] Most studies had shown that vaginal misoprostol can be used for termination of pregnancy in first trimester.[5-6] In 1998, Kuldip, et al. had reported that the optimal dose of vaginal misoprostol for preabortion cervical priming was 400 micrograms and the its efficacy was dose-dependent.[7]

In non-pregnant women, Ngai, et al. (1997) studied the effect of 400 micrograms oral misoprostol[8] and Preutthipan, et al. (1999) studied the effect of 200 micrograms vaginal misoprostol[9] They reported that misoprostol could prime and soften the cervix before hysteroscopy in non-pregnant women. Lekskulchai, et al. (2002) concluded that 400 micrograms was more effective than 200 micrograms vaginal misoprostol when administration 6 hours for cervical ripening before fractional curettage.[10] In menopausal women, Fung, et al. (2002)[11] and Bunnasathiansri, et al. (2004)[12] could not find the different effect between vaginal misoprostol and placebo for ripening the cervix. In contrast to the study of Darwish, et al. (2004), they shown that 200 micrograms vaginal misoprostol could prepare the cervix effectively before hysteroscopy in menopausal women.[13] We know that misoprostol when administered vaginally is more effective than administered orally for priming the cervix. In non HRT menopausal women, atrophic and dry vagina may effect on drug dissolving and need more time for absorption. So the aim of this study was to determine the efficacy of 400 micrograms vaginal misoprostol in longer period as 16 hours before fractional curettage in menopausal women.

Material and Method

From August 2004 to July 2006, menopausal women who presented with postmenopausal uterine bleeding and need fractional curettage were asked for accompanying in the study. The exclusion criteria included profuse bleeding, allergy to misoprostol, previous history of myocardial infarction, asthma and using HRT in last 6 months. A sample size of 60 women (30 women in each group) was calculated using two-tail alpha of 0.01 and a power of 0.9 assuming that the baseline cervical dilatation was 1 mm in the menopausal women and a change of 2 mm in baseline dilatation would be significant. The ideal sample size in each group was calculated as 19, and to allow for 10% of the unstable data, the number in each group was set at 30.

All 60 women were recruited and randomly allocated in to 2 groups. After signing the inform consent, all women were asked about preoperative symptoms such as abdominal pain, fever, headache, nausea and vomiting. Blood pressure, body temperature and preintervention cervical width were recorded by an intern. All women were advised to insert 2 tablets from the given opaque plastic bag into their posterior fornix before going to bed and record time of insertion on the bag. On the day of operation, they were asked to come back with the empty plastic bag. After 16 hours from the time recorded on the bag, any side effects such as abdominal pain, fever, nausea, vomiting and headache included blood pressure and body temperature were recorded. Prior to the procedure,

women were placed in the lithotomic position and part of the tablets which were not totally disintegrated were removed. Under the general intravenous anesthesia, the cervical width was measured using the largest Hegar dilator which can pass the cervical os without resistance. After fractional curettage was done, the women were observed in the operation room for at least 2 hours. SPSS 13.0 for windows (SPSS Inc, Chicago, Illinois) was used for statistical analysis. P < 0.05 was considered significant.

Results

From 60 women, the average age was 55.7 (45-72, SD = 5.96) years, mean of parity was 2.5 (0-8, SD = 1.66) and average time after menopause was 4.6 (1-17, SD = 3.8) years. Table 1 shows no differences in age, number of parity, time after menopause and hormonal therapy between misoprostol and placebo group.

Table 1 Characteristics of the women in the misoprostol group compare with the placebo group.

Characteristics	Misoprostol group	Placebo group	P-value*
Age (yr.+/-SD)	55.4+/-7.0	56.3+/-4.6	0.55
Parity (n+/-SD)	2.7+/-1.7	2.3+/-1.4	0.28
Time after menopause (yr.+/-SD)	4.5+/-3.9	4.9+/-3.7	0.69
HRT using conditions:			P-value**
Current HRT use	4	3	0.776
Quit HRT < 6 months	2	1	0.776
No HRT use/quit HRT > 6 months	24	26	0.776

*t-test, **Fisher's Exact test, HRT = Hormonal Replacement Therapy

Table 2 Comparison of cervical widths before and after 16 hours of intervention.

	Cervical width (mm.+/-SD, range)		
	Misoprostol group	Placebo group	P-value*
Pre - intervention	4.0+/-1.2, 0-5	3.7+/-1.7, 0-6	0.44
Post - intervention	4.4+/-1.4, 1-6	4.0+/-1.7, 0-6	0.27
P-value	< 0.0001	< 0.0001	

*t-test

From Table 2, mean cervical width before drug insertion was 4.0 ± 1.2(0-5) mm. in misoprostol group and 3.7 ± 1.7(0-6) mm. in placebo group. There was no statistically different between the pre-intervention cervical widths in both groups (P = 0.44). After 16 hours of drug administration, the average cervical width in misoprostol group (4.4 ± 1.4 mm.) was not statistically different from the average cervical width in the placebo group (4.0 ± 1.7 mm.) (P = 0.81) The post-intervention cervical width in misoprostol group was statistically higher than the pre-intervention cervical width in the same group (P < 0.0001). This result was similar to the placebo group. In 13 (43.3%) patients of the misoprostol group, some portion of the misoprostol tablets was present in the vagina after 16 hours of administration.

Table 3 Adverse side effects and intraoperative complications after 16 hours of interventions.

	Misoprostol group	Placebo group	P-value*
Nausea (n)	1	1	1.000
Headache (n)	0	0	
Abdominal cramping (n)	1	3	0.612
Diarrhea (n)	0	0	
Increased vaginal bleeding (n)	0	0	
Need for cervical dilatation	3	6	0.472
Intraoperative cervical tear	4	3	1.000

*Fisher's Exact test

Table 3 shows three women in misoprostol group and six in placebo group who need further cervical dilatation (P = 0.472). The intraoperative cervical tear was found in 4 and 3 women in misoprostol and placebo group, respectively (P = 1.000). Abdominal cramping was a common side effect in this study but there was no significant difference in the number of patients with abdominal cramping between these two groups (P = 0.612). Nausea was found in one patient in each group. No patients in this study need a medical treatment. There were no other complications from misoprostol administration and from curettage.

Discussion

In obstetrics, misoprostol is usually used for priming the cervix before termination of pregnancy. Moreover, there were a lot of studies showing the effectiveness of both oral and vaginal misoprostol for cervical ripening in non-pregnant women. In menopausal women, it had been shown that vaginal misoprostol 4 hours before operation could not prime and soften the cervix. This study tried to investigate that 400 micrograms vaginal misoprostol 16 hours may prime and soften the cervix effectively due to longer period of drug exposure and absorption.

From the results, we could not determine any efficacy of 400 micrograms vaginal misoprostol when administered 16 hours for cervical priming in menopausal women. Although after drug insertion we found the increasing in the cervical width of 0.4 mm. in misoprostol group and 0.3 mm. in placebo group but those increasing cervical width were not clinically significant. This would conclude that longer period of drug exposure could not help priming the cervix in menopausal women. The uterine cervix of the menopausal woman could not effectively absorb and response to misoprostol, even in patient with current HRT, due to atrophic change and decreased collagen content. Preparing the cervix with local estrogen may improve the efficacy of misoprostol and should be studied in the future.

References

1. RCOG, Misoprostol for all? Br J Obstet Gynaecol 1998;105:937-9.
2. Gemzell KD, ML, Rodriguez A, Spur BW, Womg PYK, Bygdman M. Comparison between oral and vaginal administration of misoprostol on uterine contractility. Obstet Gynecol 1999;93:275-80.
3. Jens JPC, SN, Lars H. Is misoprostol the treatment of choice for induced cervical ripening in early pregnancy termination? Acta Obstet Gynecol Scand 1995;74:809-12.

4. Ngai SW, Tang OS, Lao T, Ho PC, Ma HK. Oral misoprostol versus placebo for cervical dilatation before vacuum aspiration in first trimester pregnancy. Hum Reprod 1995;10: 1220-2.
5. Cem F, MT, Seval T. Effect of vaginal misoprostol application for cervical softening in pregnancy interruption before ten weeks of gestation. Acta Obstet Gynecol Scand 1996;75: 54-6.
6. Singh K, Fong Y, Prasad RN, Dong F. Evacuation interval after vaginal misoprostol for preabortion cervical priming. Obstet Gynecol 1999;94:431-4.
7. Singh K, Fong YF, Prasad RN, Dong F. Randomised trial to determine optimal dose of vaginal misoprostol for preabortion cervical priming. Obstet Gynecol 1998;92:795-8.
8. Ngai SW, Chan YM, Lui KL, Ho PC. Oral misoprostol for cervical priming in non-pregnant women. Hum Reprod 1997;12:2373-5.
9. Preutthipan SC, Herabutya Y. A randomised controlled trial of vaginal misoprostol for cervical priming before hysteroscopy. Obstet Gynecol 1999;94:427-30.
10. Lekskulchai O, Manothai S. Comparison between 200 and 400 microgram of vaginal misoprostol for cervical ripening in nulliparous women before F&C. Thai J Obstet Gynecol 2002;14: 45-9.
11. Fung TM, LM, Wong SF, Ho LC. A randomised placebo-controlled trial of vaginal misoprostol for cervical priming before hysteroscopy in postmenopausal women. BJOG 2002;109:561-5.
12. Bunnasathiansri S, Herabutya Y, O-Prasertsawat PT. Vaginal misoprostol for cervical priming before dilatation and curettage in postmenopausal women: A randomised controlled trial. J Obstet Gynaecol Res 2004;30:221-5.
13. Darwish AM, Ahmad AM, Mohammad AM. Cervical priming prior to operative hysteroscopy: a randomized comparison of laminaria versus misoprostol. Hum Reprod 2004;19:2391-4.

บทคัดย่อ

ประสิทธิภาพของการใช้ยาไมโสพรอสตอลขนาด ๔๐๐ ไมโครกรัม เหน็บทางช่องคลอดเพื่อช่วยในการเตรียมปากมดลูกของหญิงวัยหมดประจำเดือนก่อนการขูดมดลูก

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วัตถุประสงค์ : เพื่อศึกษาถึงประสิทธิภาพของยาไมโสพรอสตอลขนาด ๔๐๐ ไมโครกรัมในการเตรียมปากมดลูกของหญิงวัยหมดระดูก่อนการขูดมดลูก

วิธีการวิจัย : หญิงวัยหมดระดูที่มีภาวะเลือดออกผิดปรกติจากโพรงมดลูกจำนวน ๖๐ คน ถูกคัดเลือกแบบสุ่มแบ่งเป็น ๒ กลุ่ม คือ กลุ่มที่ได้รับการเหน็บยาไมโสพรอสตอลขนาด ๔๐๐ ไมโครกรัม และกลุ่มที่ได้รับการเหน็บยาหลอกทางช่องคลอดเป็นเวลา ๑๖ ชั่วโมงก่อนการขูดมดลูก โดยประเมินความแตกต่างของขนาดของการเปิดขยายปากมดลูกก่อนและหลังการเหน็บยา ภาวะแทรกซ้อน และผลข้างเคียงต่างๆ ที่เกิดขึ้น

ผลการวิจัย : ก่อนการเหน็บยา พบว่าค่าการเปิดขยายเฉลี่ยของปากมดลูก ในกลุ่มที่ได้รับยาไมโสพรอสตอล (๔.๐ ± ๑.๒ มม.) ไม่มีความแตกต่างอย่างมีนัยสำคัญจากค่าการเปิดขยายเฉลี่ยในกลุ่มที่ได้รับยาหลอก (๓.๗ ± ๑.๗ มม.) (P = 0.44) และไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ในค่าเฉลี่ยของการเปิดขยายของปากมดลูกหลังการเหน็บยา ๑๖ ชั่วโมงของยาไมโสพรอสตอล (๔.๔ ± ๑.๔ มม.) และยาหลอก (๔.๐ ± ๐.๗ มม.) รวมทั้งไม่พบภาวะแทรกซ้อนหรือผลข้างเคียงอย่างรุนแรงในการศึกษานี้

สรุป : การเหน็บยาไมโสพรอสตอลขนาด ๔๐๐ ไมโครกรัมเป็นเวลา ๑๖ ชั่วโมงก่อนการขูดมดลูกในหญิงวัยหมดระดูไม่เพิ่มการเปิดขยายของปากมดลูก