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Randomized Comparative Study of 200 and 400 Micrograms Vaginal Misoprostol for Cervical Priming in Nonpregnant Nulliparous Women Undergoing Fractional Curettage

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ABSTRACT

Objective To compare the effectiveness of 200 and 400 µg of vaginal misoprostol inserted 6 hours prior to fractional curettage for pre - operative cervical dilatation.

Design Randomized comparative study.

Setting Department of Obstetrics and Gynecology at King Chulalongkorn Memorial Hospital.

Patients 50 non - pregnant nulliparous women with abnormal uterine bleeding and need to undergo outpatient fractional curettage.

Intervention Subjects were randomly assigned into two groups. In the first group, one tablet of 200 µg misoprostol was inserted in posterior fornix 6 hours prior to fractional curettage, two tablets were inserted in the second group. Cervical dilatation was assessed by Hegar dilator before and at 6 hours after misoprostol insertion.

Measurement and main results Baseline cervical dilatation were not significantly different before misoprostol insertion. The mean of difference between pre and post - treatment cervical dilatation in 400 µg misoprostol group was 3.80 ±1.29 mm and in 200 µg misoprostol group was 1.96±0.68 mm, respectively. The cervical dilation was significantly increased when compared with the 200 µg misoprostol group.($P < 0.001$) None of the patients had significant side effects.

Conclusion 400 µg vaginal misoprostol is more effective for pre - operative cervical dilatation in 6 hours than 200 µg vaginal misoprostol. No significant side effects were found in both groups.

Key words: Non - pregnant nulliparous women, vaginal misoprostol, fractional curettage, cervical dilatation

Women who presenting with abnormal uterine bleeding, sometimes need to undergone fractional curettage for detection of the endometrial pathology. Difficulty in entering the internal os may be the most common problem for nulliparous patients. The complications that related to this problem include cervical damage, creation of false tract and uterine perforation.[1]

Numerous studies have since demonstrated that the vaginal administration of prostaglandin given preoperatively, preceding vacuum aspiration during the first trimester, softens and dilates the cervix, thus

reducing the frequency of complications. Also, the vaginal use of prostaglandin E_2 3 hours prior to hysteroscopy in sterile patient, had reported to be effective for cervical dilatation and softening.[2] However, PGE_2 is too expensive and requires refrigeration.

Recently, misoprostol, a synthetic prostaglandin E_1 analogue that is inexpensive, stable in tropical climate, easy to transport and simple to administer, has been demonstrated to be effective for cervical priming by both oral[3] and vaginal administrations 10 - 12 hours[4] before hysteroscopy.

From the study of Zeiman et.al (1997), it showed that in pregnant women receiving vaginal misoprostol, the plasma concentration of misoprostol acid rose gradually, reached maximum value between 60 and 120 minutes, and declined slowly to an average of 61% of the peak value at 240 minutes after administration.[5] Therefore, we have carried out a randomized comparative study in 50 non - pregnant nulliparous women, who had abnormal uterine bleeding and assigned a 6 hours pre - treatment interval because we believed that vaginal misoprostol given 6 hours before fractional curettage would be adequate in non - pregnant nulliparous women. We have decided to compared the effectiveness between only two dosages, 200 and 400 µg because from a pilot study we had found that 400 µg of vaginal misoprostol could prime the cervix as effectively as 600 and 800 µg dosages.

The purpose of our study was to determine whether vaginal misoprostol is also effective when it is given 6 hours before fractional curettage and to determine the optimal dosage of vaginal misoprostol between 200 and 400 µg for pre - operative cervical dilatation.

Materials and methods

Patients : From November 1999 to March 2001, 50 women who had an indication for outpatient fractional curettage participated in the study. They were non - pregnant nulliparous and still in reproductive aged group. Exclusion criteria were the patient who had unstable vital signs or profused vaginal bleeding, previous history of cervical dilatation, and contraindications for misoprostol administration.

Ethical approval for the study was granted by the Ethical committee, Faculty of Medicine, Chulalongkorn University. After informed consent, the patients were randomized using numbered, sealed envelopes to receive either 200 µg or 400 µg misoprostol.

Pre - treatment evaluation

Measurements of blood pressure, temperature and pulse rate were carried out. Any discomforts such as abdominal pain, nuasea, diarrhea and headache were recorded. The gynecologic examination was performed before misoprostol administration, including measurement of the cervical canal, during which the largest Hegar which could be passed through the cervical canal without resistance was recorded. Patients who had a cervical canal through a Hegar No. 4 could pass were excluded.

All had a vaginal suppository inserted into the posterior fornix 6 hours prior to fractional curettage. The tablets were moistened with water before insertion and women were instructed to remain recumbent for at least 3 hours post - administration.

Post - treatment evaluation

Any side effects such as nausea, vomiting, abdominal pain, diarrhea and virtigo as well as vaginal bleeding were asked and recorded. Blood pressure, temperature and pulse rate were recorded again.

A gynecological examination was again carried out 6 hours after insertion, when particular attention was paid to the cervical softeness, bleeding, and lesions. In addition, calibration of the cervical canal was performed, and the largest possible Hegar dilator which could be inserted without resistance was noted. If a Hegar No. 4 could not be inserted into the cervical canal, then mechanical dilatation was carried out prior to operation.

Fractional curettage was performed under a paracervical blockade. Following the operation, the

patients were remained in the department for 1 - 2 hours before being discharged. All were offered control examination 1 week after the operation, a pelvic examination was performed at this time and the side effects were assessed again.

Assessment of response

No. of Hegar dilator indicates the length of cervical diameter in millimetre and the largest No. of Hegar dilator that could pass through the cervical canal without resistance both before and after drug insertions were recorded and calculated for the difference in baseline cervical dilatation, the main outcome indicator.

Occurrence and severity of side effects were compared include temperature and blood pressure.

Statistical analysis

From a pilot study with a type I error of 0.05 and a power of 0.90, 22 patients were required for each group. Assuming a 10% default at follow up the number chosen was 25; therefore the total sample size was 50.

Variables that were normally distributed were presented as mean and standard deviation. Data were analyzed using the unpaired t - test with $p < 0.05$ considered statistically significant in the differences between two groups. Pre - treatment and post - treatment data were analyzed using paired t - test.

Results

As shown in Table 1, there was no statistically significant difference between two treatment groups when they were comparable with regard to age, body weight and height. All were suffered from abnormal uterine bleeding that need fractional curettage.

There was no significant difference in the baseline of cervical width prior to treatment in both groups.(Table II, P = 0.746) The mean cervical dilatation following the insertion for 6 hours of 200 µg and 400 µg misoprostol were 3.36±1.19 and 5.28±1.74, respectively. One patient in 200 µg group had no cervical change while 13 patients in 200 µg group and 4 patients in 400 µg group need further dilatation of the cervical canal. A softening of the uterine cervix had taken placed in these patients thus facilitating dilatation. The mean difference between pre - and post - cervical dilatation in 400 µg group (3.80 mm.) was statistically significant higher than that of 200 µg group (1.96 mm.).(P <0.001)

There was no clinically and statistically significant change in blood pressure and body temperature in both groups. Only mild abdominal pain was complained from one patient in 200 µg group and two in 400 µg group before treament but it was not increased in severity after the operation completed. Other side effects such as nausea, vomiting, chilling and headache were not be detected from all patients. And at one week follow up visit, none had any delayed side effects.

Table 1. Patient characteristics

Characteristics	Misoprostol 200 µg (n = 25)	Misoprostol 400 µg (n = 25)	P - value
Age (y)	36.7 (7.7)	36.6 (6.7)	0.980
Height (cm)	156.3 (2.5)	154.3 (4.4)	0.149
Weight (kg)	62.5 (13.3)	56.8 (9.2)	0.175

* mean (SD)

Table 2. Statistical comparison in two treatment groups

Cervical dilatation	200 µg group (mean ± SD)	400 µg group (mean ±SD)	P - value
Pre - treatment cervical width	1.40 ± 0.82	1.48 ±0.92	0.746
Post - treatment cervical width	3.36 ± 1.19	5.28 ±1.74	< 0.001
Difference between post - pre	1.96 ± 0.68	3.80 ±1.29	< 0.001

mean = mm.

Discussion

The previous investigation in 1988 shows that vaginal Meteneprost (9 - deoxo - 16.16, dimethyl - 9 - methylene PGE_2) can soften and dilate the non-pregnant cervix[2]. Later in 1997, S.W.Ngai et al. showed that oral misoprostol could prime the uterine cervix prior to hysteroscopy in non - pregnant women.

Recently, Preutthipan and Herabutya demonstrated that 9 - 10 hours after 200 µg misoprostol vaginal suppository was more effective than placebo for cervical dilatation in non - pregnant nulliparous women.[4]

In our practice for OPD patient, the shorter operating time gives more comfortable for the patient and vaginal misoprostol has more long - lasting stimulation effect on the cervix than oral administration, so we conducted this clinical trial to determine the optimal dosage of vaginal misoprostol for 6 hours before fractional curettage. And we found that 400 µg of vaginal misoprostol could soften and dilate the cervical os more effective than 200 µg. Compared to the previous study, the mean cervical dilatation after 6 hours of 400 µg vaginal misoprostol, 5.28 mm., was slightly lower than that of after 12 hours 400 µg oral misoprostol, 6.0 mm.(Ngai et al.1997)[3]

Because the misoprostol tablets are not prepared for vaginal use and local factors such as acidic media are different between the patients. Most of the patients in both groups had the particulate remnants of tablets remained in the posterior fornices, albeit in varying proportion. This showed that there had large interpatient variation in tablet dissolution. Two of the 400 µg group had minimal change in the cervical dilatation and also had significant remnants remained in the vagina. This incomplete dissolution of tablet may decreased the drug absorption. And to decrease this variation, a further study needs to carry out under the specific local factors such as preparing in powder form and wetted with water or with acetic acid before insertion.

No side effects were observed in both groups. These results differ from those of Preutthipan and Herabutya (1999) who showed a relatively high frequency of side effects after vaginal misoprostol administration, paricularly mild lower abdominal pain and slight vaginal bleeding.[4] We believed that these because the incidence of the side effects could be lower when the treatment interval was shortened. However, as our sample size was relatively small, a more extensive study needs to be carried out to confirm these results. At the follow up visit 1 week later no signs of any side effects nor cervical lesion were observed.

In conclusion, a 400 µg vaginal misoprostol is more effective than 200 µg when administered 6 hours prior to fractional curettage but the further study needs to underwent in the bigger sample size and use specific local factors to decrease the variations of drug absorption.

Reference

1. Anthony GS, Fisher J, Coutts JR, Calder AA. Forces required for surgical dilatation of the pregnant and non - pregnant human cervix. Br J Obstet Gynaecol 1982; 89 (11) : 913 - 6.
2. Hald F, Kristoffersen SE, Gregersen E. Prostaglandin vaginal suppositories in non pregnant women requiring cervical dilatation prior to hysteroscopy. Acta Obstet Gynecol Scand 1988 ; 67 : 219 - 22.
3. Ngai SW, Chan YM, Liu KL, Ho PC. Oral misoprostol

for cervical priming in non - pregnant women. Hum Reprod 1997 ; 12 : 2373 - 5.
4. Preutthipan S, Herabutya Y. A randomized controlled trial vaginal misoprostol for cervical priming before hysteroscopy. Obstet Gynecol 1999 ; 94 : 427 - 30.
5. Zieman M, Fong SK, Benowitz NL.. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol 1997 ; 90 : 88 - 92.
6. 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 ; 5 : 1220 - 2.
7. Singh K, Fong YF, Prasad RNV, Dong F. Randomized trial to determine optimal dose of vaginal misoprostol for preabortion cervical priming. Obstet Gynecol 1998; 92 : 795 - 8.
8. Singh K, Fong YF, Prasad RNV, Dong F. Does an acidic medium enhance the efficacy of vaginal misoprostol for pre - abortion cervical priming. Hum Reprod 1999; 14 : 1635 - 7.
9. Singh K, Fong YF, Prasad RNV, Dong F. Evacuation interval after vaginal misoprostol for preabortion cervical priming. Obstet Gynecol 1999 ; 94 : 431 - 4.
10. RCOG . Misoprostol for all ? Br J Obstet Gynaecol 1998 ; 105 : 937 - 9.
11. Danielsson GK, Marions L, Rodriguez A, Spur BW, Wong PYK, Bygdeman M. Comparison between oral and vaginal administration of misoprostol on uterine contractility. Obstet Gynecol 1999 ; 93 : 275 - 80.