Priming Effect of Misoprostol on Estrogen Pretreated Cervix in Postmenopausal Women

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ATMACA, R., KAFKASLI, A., BURAK, F. and GERMEN, A.T. *Priming Effect of Misoprostol on Estrogen Pretreated Cervix in Postmenopausal Women.* Tohoku J. Exp. Med., 2005, **206** (3), 237-241 —— Misoprostol, which is a prostaglandin E1 analogue, is effectively used in cervical priming in women both for labor induction and for gynecological procedures. Although its efficacy is well documented in reproductive age women, during postmenopausal period this efficacy is limited probably due to estrogen deficit. Our objective is to evaluate if estrogen deficit in postmenopausal women is important for the effect of misoprostol on cervical ripening before diagnostic procedures. In this study, 45 patients were randomly allocated to estrogen or placebo group. The study group received local estrogen cream and other group received chlindamycine phosphate cream as placebo. The patients were given oral misoprostol 24 and 12 hours before the procedure for uterine cavity evaluation. Cervix was dilated by using Heagar dilator up to 6 mm. Data were analyzed by Student *t*-test, Mann-Whitney's U-test, chi-square test and paired samples *t*-test where appropriate. Basal cervical widths for the estrogen and placebo groups were 4.4 ± 0.7 and 3.7 ± 0.7 mm, respectively ($p < 0.01$). Mean time required for dilatation of cervix was 44.4 ± 16.2 seconds for the estrogen group and 61.4 ± 18.3 seconds for the placebo group ($p < 0.01$). As a conclusion, misoprostol treatment alone is not effective to get cervical priming in postmenopausal women, and as shown in our study, pretreatment with local estrogen overcome the failure. To get a beneficial effect of misoprostol on cervical ripening, estrogenic activity is necessary and when pretreated with local estrogen, misoprostol ameliorates cervical priming in postmenopausal women. ——— misoprostol; postmenopausal women; cervical ripening; estrogen
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Careful evaluation of uterine cavity in postmenopausal women is mandatory in case of vaginal bleeding or visualization of increased endometrial thickness and irregular endometrial borders during sonographic examination since these findings raise the suspicion of endometrial malignancy. Although transvaginal ultrasound has great diagnostic values in detecting endometrial pathologies, most of the cases are not accurately diagnosed by only sonographic evaluation. Endometrial biopsy, sonohysterography and hysteroscopy are the most commonly used methods for accurate diagnosis.

Today, these mentioned methods are commonly practiced on outpatient clinics under with local anesthesia. Despite it is common and easily

practiced, it may be rather disturbing or complicated in postmenopausal women because of difficulties during dilatation of cervical canal.

Recently, authors had reported the use of misoprostol, which is a prostaglandin E1 analogue, for easier cervical dilation in nonpregnant women before hysteroscopic procedures (Preutthipan and Herabutya 2000; Thomas et al. 2002; Bisharah et al. 2003). Most of them had used misoprostol for cervical ripening in premenopausal period and all of them had reported favorable effects.

However, only a few studies had been reported on postmenopausal misoprostol use for cervical ripening and these studies had shown no beneficial effect (Ngai et al. 2001; Fung et al. 2002). Presence of beneficial effect of misoprostol only during premenopausal women questioned the possible effect of reproductive hormones on ameliorating activity of misoprostol on cervical ripening. In the present trial we tried to evaluate the role of estrogen and prostaglandin E1 (PGE1) on cervical ripening and for this purpose in the current trial we wanted to show whether pretreatment with estrogen enhances the effects of PGE1 on cervical dilatation in postmenopausal women.

MATERIAL AND METHOD

Ethical approval for the study was granted by departmental human subject ethics committee and a written consent was obtained from each patient enrolled in the study. Between November 2001 and February 2003, 45 women who need evaluation of uterine cavity because of postmenopausal bleeding or thickened or irregular endometrial echo, were participated in the study. Inclusion criteria were defined as (a) duration of menopause between 1 and 3 years, (b) more than 5 mm endometrial thickness assessed by sonographic evaluation and (c) irregular endometrial echo. Patient with following conditions were excluded from the study; (a) irregular and myometrial infiltrating endometrial echo, highly suspicious of malignancy, (b) abundant vaginal bleeding, (c) history of estrogen replacement therapy usage, (d) history of hypersensitivity or presence of contraindications to prostaglandins and (e) history of irritable bowel syndrome.

Patients were randomized into two groups by means of a computer generated number table, consisting 22 patients in the first group and 23 in the second group. In the first group (estrogen group) patients were given local estrogen cream (Ovestin vaginal cream, Organon, Istanbul, Turkey) twice a day, applied by patient herself with a plastic applicator which was inserted in to vagina. In the second group (placebo group) patients were given local chlindamycine phosphate cream (Cleocin vaginal cream, Eczacibasi, Luleburgaz, Turkey) twice a day, applied by patient herself with a plastic applicator which was inserted in to vagina. The medications were given to patients by our department without any label indicating its content. All patients were checked with 3 days intervals in order to ensure medication was applied correctly. Duration of local application of estrogen and placebo cream was 14 days. Serum estradiol levels were measured in all patients before and after local estrogen application.

All patients were admitted to clinic the day before evaluation of uterine cavity and were given $400\,\mu g$ misoprostol (Cytotec, Searle, Chicago, IL, USA) (Tables 1 and 2) orally, 24 and 12 hours prior to the procedure.

Just before the procedure, cervical width and resistance was assessed by means of reversed dilatation method, starting from number 7 Hegar dilator.

With the women in a lithotomy position, number 7 Hegar dilator was inserted through cervical os. If dilator is not entered from cervical os, successively smaller Hegar dilator was tried until no resistance was met. The cervical width, assessed by the number of Hegar dilator, was noted. If the cervical width is smaller than 6 mm, it was dilated up the 6 mm using Hegar dilators in order to be able to perform curettage for endometrial sampling. Duration, from beginning of dilatation to the end of dilatation, was recorded in seconds.

To evaluate uterine cavity, we performed saline infusion sonohysterography. A sterile, disposable No: 8, guided urinary catheter (6 mm in width and 15 cm in length) was introduced through the cervical orifice until it reached the fundus. The speculum was withdrawn, and the ultrasound probe was introduced into the vaginal canal. A 50-ml syringe containing sterile normal saline was then attached to the catheter. Approximately 15 ml of saline was used for the procedure. After SIS, endometrial curettage with No: 0 curette was performed. Biopsy specimens were sent for pathological examination.

Data was analyzed by the student t-test for normally distributed data and Mann Whitney's U-test for skewed data. The discontinuous data was analyzed by chi-square test. Paired samples t test was used for intra group analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Forty five patients, 22 in estrogen group and 23 in placebo group were enrolled in the study. The mean ages of patients in the estrogen and placebo group were 48.7 ± 2.8 and 48.6 ± 1.9, respectively. Other demographic parameters, including parity, body mass index (BMI) and years of menopause were statistically similar in both groups and shown in Table 1. Operative findings of the two groups were shown in Table 2. The mean cervical baseline widths for the estrogen and placebo groups were 4.4 ± 0.7 mm and 3.7 ± 0.7 mm, respectively. The difference between estrogen treated group and placebo treated group were statistically significant ($p < 0.05$). Three patients in estrogen group and 1 patient in the placebo group did not require cervical dilatation ($p > 0.05$). The mean times needed to dilate cervix up to no 6 Hegar dilator for the estrogen and placebo groups were 44.4 ± 16.2 and 61.4 ± 18.3 seconds, respectively and the difference was statistically significant ($p < 0.05$). The serum estradiol levels before and after local estrogen application in estrogen group were 24.3 ± 0.4 ng/ml and 24.6 ± 0.3 ng/ml, respectively and the difference was statistically insignificant. 3 women in estrogen group and 3 women in placebo group had painful abdominal cramps after misoprostol intake. One patient in the estrogen group had diarrhea. There were 2 uterine perforations, occurred during cervical dilatation, in placebo group. No complication was observed in estrogen group. All patients were discharged 2 hours after the procedure except for 2 patients with uterine perforation.

DISCUSSION

Invasive procedures such as endometrial biopsy, sonohysterography and hysteroscopy are commonly performed on postmenopausal women in order to have an accurate diagnosis, particularly in cases of vaginal bleeding. Cervical dilatation is the most unpleasant part of these procedures both for premenopausal and postmenopausal women. Discomfort and complications due to cervical dilatation despite local anesthesia and precise techniques are serious problems postmenopausal women. Cervical stenosis, that is a frequent condition in postmenopausal period, is a major cause of these undesired effects. New techniques, premedications, analgesics and anestehisa methods to solve this problem are always investigated.

Prostaglandins are responsible for cervical

TABLE 1. *Patients' characteristics*

	Estrogen group $n = 22$ Mean ± S.D.	Placebo group $n = 23$ Mean ± S.D.	p
Age (years)	48.7 ± 2.8	48.6 ± 1.9	0.82
Parity	2.9 ± 1.0	3.0 ± 1.1	0.89
Duration of menopause (months)	23.6 ± 5.2	23.5 ± 4.6	0.91
BMI (kg/m^2)	26.9 ± 1.2	26.7 ± 1.1	0.88

BMI, body mass index.

TABLE 2. *Operative findings of estrogen group and placebo group*

	Estrogen group $n = 22$ Mean ± S.D.	Placebo group $n = 23$ Mean ± S.D.	p
Baseline cervical width (mm)	4.4 ± 0.7	3.7 ± 0.7	0.01
Time to dilate cervix (seconds)	44.4 ± 16.2	61.4 ± 18.3	0.01
Number of patients needed cervical dilatation	19	22	0.27

ripening before labor and El-Refaey et al. (1996) reported the first treatment of oral misoprostol for the management of the third stage of labour in an observational study. Since then misoprostol has attracted widespread attention because of its strong uterotonic and cervical ripening effects (Goldberg et al. 2001). These beneficial effects on cervical ripening makes it also a desirable agent for helping cervical dilatation on non-pregnant women. Ngai et al. (1997) had reported misoprostol usage on non-pregnant women. Following this study many reports had supported its beneficial effects on cervical dilatation. All of these studies were done on premenopausal women. Ngai et al. (2001) had also reported misoprostol usage on postmenopausal women before hysteroscopy and observed no beneficial effect on cervical dilatation.

Mechanism of cervical ripening had not been clearly defined but it has increased substantially after Danforth et al. (1960) had reported it. It has been suggested that pro inflammatory cytokines (Sennstrom et al. 2000), connective tissue remodeling regulated by prostaglandins, relaxin and gonadal steroids (Norman et al. 1993) may have role on this process. Ding et al. (1990) had reported increased in vitro hydrolytic activity in cervical tissue after administration of PGE1 in first trimester pregnancy. Local application of PGE2 has also been demonstrated by Norman et al. (1993) to induce connective tissue remodeling. Although prostoglandins have important role in cervical ripening, Ngai et al. (2001) had failed to show beneficial effect of misoprostol on postmenopausal women.

This may be either due to change in cervical tissue collagen component (more fibrotic and less elastic) and lesser effect of prostaglandin on these components or due to deficiency of gonadal steroids. Rajabi et al. (1991) had showed that estradiol have stimulative effect on procollagenase transcription via a prostaglandin dependent pathway in cervical fibroblasts in guinea pig. Also it is believed that PGE2 interacts with gonadal steroid receptors and results in production of collagenases (Norman et al. 1993). It is speculated that the favorable effect of PGE2 on cervical re-

modeling had not been observed in Ngai's study (2001) since estrogen is deficient in postmenopausal women. Assuming this hypothesis is correct, in our study we had pretreated cervix with local estrogen derivatives before PGE1 application.

Our results showed a significant difference between estrogen pretreated group and placebo pretreated group in terms of cervical dilatation and cervical ripening as demonstrated by easier dilatation of cervix and basal cervical width. Although cervical dilatation was easier, there was no statistically significance in the number of patients needed cervical dilatation. This finding also supports that misoprostol was effective in cervical ripening but not in spontaneous cervical dilatation. Our study indicate that beneficial effect of misoprostol on cervical ripening is seen only in the case of presence of estrogenic activity.

Another explanation of ineffectiveness of misoprostol on postmenopausal cervix may be inappropriate absorption on postmenopausal women. In many studies which have evaluated the effect of misoprostol on cervical ripening, undissolved misoprostol tablets in vagina were reported and this may be a factor for ineffectiveness of vaginal misoprostol treatment. Fung et al. (2002) did not show a significant difference in the incidence of undissolved medication when the drug was administered overnight, and about 5 hours are necessary for drug absorption with the assumption that the active ingredient drug was released while the tablet remained in vagina. In order to eliminate this possibility of inappropriate absorption, we have used enteral route for the administration of misoprostol.

Estrogen treatment in postmenopausal women with presumed endometrial abnormality that may be due to a malignancy is the questionable part of our study. But short duration of treatment, type of estrogen (estriol) and the route of estrogen administration eliminated the risk of its undesirable effects on endometrium and also safety of local estriol application on endometrium had been already reported (Vooijs and Geurts 1995). Furthermore there was no change in serum estradiol levels before and after local estrogen treat-

ment in our study and local estrogen treatment did not cause a hyperestrogenemic state which may be harmful.

As a conclusion, misoprostol is an effective drug for cervical ripening in pregnant and pre-menopausal women but its efficacy is limited in postmenopausal period. In order to use misoprostol to have an easier cervical dilatation before diagnostic procedures, the presence of estrogenic activity is necessary and in such cases, pretreatment with local estrogen may be beneficial in ameliorating the effects of misoprostol.

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