Can Vaginal Misoprostol Effectively Increase Rate of a Satisfactory Colposcopy? A Randomized Double-blind Placebo-controlled Trial*

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Objective: To evaluate the effectiveness of vaginal misoprostol in overcoming an unsatisfactory colposcopy in the patients who had abnormal cervical cytology and to evaluate side effects of vaginal misoprostol.

Methods: Sixty patients with an unsatisfactory colposcopy during the period of September 2007—November 2008 were recruited and randomly allocated to receive either two tablets of 200 μg misoprostol (400 μg) or two tablets of similar-looking placebo vaginally. Colposcopic re-examination was performed ~6 h later. The results and side effects before and 2 weeks after the colposcopic re-examination were recorded.

Results: Six out of 30 patients in the misoprostol group (20.0%) had a satisfactory colposcopic re-examination compared with 2 out of 27 patients (7.4%) in the placebo group without statistically significant difference ($P = 0.172$). Three patients in the placebo group dropped out due to not present at the appointment time. Six out of 30 patients (20.0%) and 1 out of 30 patients (3.3%) in the misoprostol group had side effects before and 2 weeks after the colposcopic re-examination orderly. Twenty-seven patients in the placebo group did not have any side effects before and 2 weeks after the colposcopic re-examination. All side effects occurred were minimal and well tolerated.

Conclusions: Four hundred micrograms of vaginal misoprostol were not proved to be effective in converting an unsatisfactory to a satisfactory colposcopy.

Key words: misoprostol — unsatisfactory colposcopy

INTRODUCTION

Cervical cancer is a major health problem in developing countries. In Thailand, a total of 6243 new cases are diagnosed and there are 2620 deaths from this malignancy in 2002 (1). The reason of high mortality rate is being diagnosed in an advanced stage of the disease. Pap smear and colposcopic examination are effective screening methods. Early detection of cervical cancer and pre-invasive disease with systematic referral for colposcopic examination and comprehensive treatment can reduce the incidence of cervical cancer and its mortality rate.

Since the 1920s, colposcopy has been used and now it becomes an accepted procedure worldwide as the most studied method for the detection of early cervical neoplasia (2). Accurate identification of the entire transformation zone and appropriate recognition of the colposcopic signs of cervical intraepithelial neoplasia and invasive cancer are essential steps in the colposcopic examination. One of the reasons...
for performing cervical conization is non-visualization of the entire transformation zone (360°) that means an unsatisfactory examination (2–4). So, the number of diagnostic conization procedures will be decreased by reducing unsatisfactory colposcopy (2,5). Approximately 10–15% of colposcopic examination is unsatisfactory (5).

Prostaglandins are known to cause cervical softening and dilation in the first, second or third trimester of pregnancy. Misoprostol (Cytotec®; Pharmacia Corporation, Searl, Chicago, IL, USA) is a stable, orally active, synthetic prostaglandin E1 analogue that is approved by The Food and Drug Administration (FDA) for the treatment and prevention of stomach ulcers (6). It is also used to induce labor and as an abortifacient. Both oral and vaginal misoprostol have been proved to be effective for cervical dilation before evacuation. Many clinical trials also show an effectiveness of vaginal misoprostol for a cervical priming effect in non-pregnant women before hysterectomy (7–9). Recently, there was a clinical trial showing that vaginal misoprostol is an effective and safe method to convert an unsatisfactory into a satisfactory colposcopy in the majority of the patients who had a suspicious cervix and post-coital bleeding with an inflammatory Pap smear indicated colposcopy (10). However, one of the common indications for colposcopy is an abnormal cervical cytology. Then the aims of the present study were to assess the effectiveness of misoprostol in overcoming an unsatisfactory colposcopy in the patients with an abnormal cervical cytology.

PATIENTS AND METHODS

From September 2007 to November 2008, after the research proposal was approved by the Ramathibodi Hospital Ethics Committee, we began collecting patients who had abnormal cervical cytology indication from our clinic. The definition of an unsatisfactory colposcopic examination was non-visualization of the entire transformation zone (360°) under endocervical speculum. Sample size in our study was calculated using the success rate of the Aggarwal’s study. An α error of 0.05 and a power of 90% were used. We added 20% of the number for expected loss follow-up. The final number of each arm was 29 patients. Therefore, we recruited 30 patients in each arm.

Sixty patients with an unsatisfactory colposcopy who met all the inclusion criteria including no history of previous hysterectomy and not received estrogen or other misoprostol treatment during study period were recruited. Exclusion criteria included pregnancy, history of hypersensitivity to prostaglandins, frank evidence of invasive cervical carcinoma and unwilling to cooperate in the study. Written informed consent was obtained from all subjects.

We used computer-generated random tables to make sample randomized numbers from 1 to 60. Sixty packs of drugs were prepared from the beginning, half of them contained two tablets of 200 μg misoprostol (400 μg, Cytotec®) each and another half contained two tablets of similar-looking placebo (pyridoxine) each. All the drugs removed the foil packages and put in the coded envelopes. All the patients were blinded and treated by inserting the tablets into the posterior vaginal fornix by the same physician in order from the coded envelopes. The patients were observed in the hospital for 6 h and the side effects of the drug were noted such as abdominal pain, perception of increase in body temperature, vaginal bleeding, headache or vomiting before a colposcopic re-examination.

The results of the re-examination were recorded in detail, including the visualization of the entire present squamocolumnar junction. The gynecologic oncologists who performed the re-examinations were blinded to the patient allocation. Two weeks later, all subjects were followed for clinical side effects. After the study was complete, all drug codes were revealed that each patient was allocated to the misoprostol or placebo group. We collected data on patient’s age, body mass index (BMI), parity, menopausal status, cervical cytology indication, number of satisfactory colposcopic re-examinations and also side effects.

Data were analyzed using the unpaired t-test, Pearson’s χ² test and Fisher’s exact test where appropriated, with P < 0.05 considered statistically significance. All analyses were performed with STATA version 10 (STATA corporation, Houston, TX, USA).

RESULTS

A total of 60 patients with an unsatisfactory colposcopy were recruited. The patients were divided into two groups by systematic randomization. During the study period, three patients of the control group did not participate at the appointment time, so 57 patients, 30 of the misoprostol group and 27 of the control group were completely participated as illustrated in Fig. 1.

The mean age of the misoprostol group was 49.7 ± 9.2 years which was not statistically different from that of 52.0 ± 7.6 years in the placebo group (P = 0.318). The mean BMI of the misoprostol and the placebo groups were 23.9 ± 3.2 and 24.3 ± 3.2 kg/m², respectively. The majority of the patients in both groups were non-obese (BMI < 25 kg/m²). Most of the patients in both groups were parous and menopause (Table 1).

Table 2 shows the frequency of the abnormal cervical cytologies of both groups. The majority of the patients were low-grade squamous intraepithelial lesion (LSIL) and there was not statistically significant difference (P = 0.204).

Six patients (20.0%) of the misoprostol group and two patients (7.4%) of the placebo group had satisfactory re-examination. The conversion rates of both groups were not statistically significant different (P = 0.172) (Fig. 2). All six patients in our study with successful conversion from an unsatisfactory to a satisfactory re-examination after they were treated by inserting vaginal misoprostol had BMI <
25 kg/m². Four out of six patients were parous and premenopause, and five out of six patients had LSIL indication.

Six patients of the misoprostol group had side effects before the re-examination and one patient had side effects at 2 weeks after the re-examination. The side effects included abdominal pain 13.3%, perception of increase in body temperature 10.0%, vaginal bleeding, headache and vomiting in 1 patient (3.3%). Only one patient had mild abdominal pain at 2 weeks after the re-examination. The placebo group did not have any side effects. Patients in the misoprostol group had more side effects before the re-examination than those in the placebo group.

### DISCUSSION

Many investigators have tried to find methods or interventions to convert an unsatisfactory to a satisfactory colposcopy in patients who had abnormal cervical cytology. The success rate with various methods used in previous studies varies from 60% to 94% (11–14). However, most of them were non-randomized, prospective interventional studies. For example, Stern et al. (11) studied 18 women with abnormal cervical cytologic findings and unsatisfactory colposcopy underwent cervical dilatation with Dilapan® (Gynotech), a hydrotropic dilator with a success rate of 94%, but all the patients included were pre-menopause. Also, placing a hydrotropic sponge in the cervix (Lamicel®), using osmotic dilators (11,13), was not effective in a randomized trial. Another study was conducted by Saunders et al. (14) who used 30 mg of ethinyl estradiol daily for 10 days, so it converted 70% of unsatisfactory into satisfactory colposcopy compared with 23% in placebo group with statistically significant difference. However, the disadvantage with estrogen is that it needs at least 5–10 days for good results, and it also causes nausea and vomiting and potentially adverse effects on the coagulation system.

Since 1997, misoprostol has been used prior to operative hysteroscopy in the doses varying from 200 to 400 μg for 6–12 h with successful results for cervical ripening and dilatation with minimal side effects (8,9,15). Only one study has been conducted so far involving the use of misoprostol in cases of unsatisfactory colposcopy with the rate of...

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**Table 1. Demographic profiles**

<table>
<thead>
<tr>
<th>Demographic profiles</th>
<th>Misoprostol group (n = 30)</th>
<th>Placebo group (n = 27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.7 ± 9.2</td>
<td>52.0 ± 7.6</td>
<td>0.318</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 ± 3.2</td>
<td>24.3 ± 3.2</td>
<td>0.614</td>
</tr>
<tr>
<td>&lt;25</td>
<td>23 (76.6)</td>
<td>18 (66.6)</td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>7 (23.3)</td>
<td>9 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>5 (16.6)</td>
<td>8 (29.6)</td>
<td>0.244</td>
</tr>
<tr>
<td>Parous</td>
<td>25 (83.3)</td>
<td>19 (70.3)</td>
<td></td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-menopause</td>
<td>10 (33.3)</td>
<td>10 (37.0)</td>
<td>0.771</td>
</tr>
<tr>
<td>Post-menopause</td>
<td>20 (66.7)</td>
<td>17 (62.9)</td>
<td></td>
</tr>
</tbody>
</table>

Data were presented as mean ± SD and n (%). BMI, body mass index.

**Table 2. Indication for colposcopy**

<table>
<thead>
<tr>
<th>Indication for colposcopy</th>
<th>Misoprostol group (n = 30)</th>
<th>Placebo group (n = 27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US, ASC-H</td>
<td>7 (23.3)</td>
<td>6 (22.2)</td>
<td>0.204</td>
</tr>
<tr>
<td>LSIL</td>
<td>11 (36.6)</td>
<td>11 (40.7)</td>
<td></td>
</tr>
<tr>
<td>HSIL</td>
<td>10 (33.3)</td>
<td>5 (18.5)</td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>2 (6.6)</td>
<td>1 (3.7)</td>
<td></td>
</tr>
<tr>
<td>AGC</td>
<td>0 (0)</td>
<td>4 (14.8)</td>
<td></td>
</tr>
</tbody>
</table>

Data were presented as n (%). ASC-US, atypical squamous cell of undetermined significant; ASC-H, atypical squamous cell favor neoplasia; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; AGC, atypical glandular cell.

**Figure 1.** The study profile.

**Figure 2.** Number of patients who were converse from an unsatisfactory to a satisfactory colposcopy (n = 57), P value = 0.172.
conversion to a satisfactory colposcopy 78.9% compared with 30.0% in the placebo group with statistically significant difference \( (P = 0.004) \), yet they were only 10.2% who had abnormal cervical cytology indications (10).

In our study, a dose of 400 \( \mu \text{g} \) of misoprostol was chosen, as it has shown to be successful with minimal side effects in the previous studies in non-pregnant patients. The vaginal route of drug administration was used because systemic bioavailability is three times greater compared with the oral route (16), and the gastrointestinal adverse effects are greatly reduced (15). The misoprostol tablet has maximum absorption in 4–6 h after vaginal insertion, so a time interval of 6 h is chosen between the drug administration and the colposcopic re-examination. We did not find any changes in the morphology of the cervical epithelium and the colposcopic findings between prior examinations and the re-examinations (Fig. 3).

The analysis of demographic profiles of the patients in both groups including age, BMI, parity, menopausal status and the cervical cytology indication was not different. The rate of vaginal misoprostol and placebo in conversion of an unsatisfactory to a satisfactory colposcopy was only 20.0% and 7.4%, respectively. There were some variations of the results in both examinations and in different gynecologic oncologists who performed the examinations (17). If the procedure was performed by only one gynecologic oncologist in the whole study, this would decrease any variations in the results. However, in our clinic, all gynecologic oncologists randomly performed the examinations for each patient.

From the previous study, Aggarwal et al. (10) concluded that patients who had a pinhole type of cervical os did not response to misoprostol and patients who had a slit-like external os were subsequently converted to satisfactory examination after they were treated by inserting misoprostol vaginally. In our study, there were different characteristic criteria of the sampling patients. First, the patients in the misoprostol group had the mean age of 49.7 years which is older in comparison with the mean age of 42.3 years in the responders of the previous study (10). Second, the majority of the patients in our study were post-menopause and might have a pinhole type of cervical os as a result of hormonal deficit. We did not collected data about the type of cervical os, so further trials in separated groups of different types of cervical os were suggested. Lastly, the previous study included the patients with a suspicious cervix or post-coital bleeding with an inflammatory Pap smear which were common in reproductive aged patients or who had a slit-like external os, but our study did not include these mentioned criteria. So, the result of our study was not successful in conversion of an unsatisfactory to a satisfactory colposcopy.

It might be implied that vaginal misoprostol 400 \( \mu \text{g} \) could be effective by softening, dilatation and effacement of the cervix to convert to satisfactory examination in <25 \( \text{kg/m}^2 \) BMI, parous and premenopausal patients. In post-menopausal patients, the higher dose (>400 \( \mu \text{g} \) of misoprostol) might be effective. However, we found no correlation between BMI, parity, menopausal status, cervical cytology indication and a satisfactory examination by vaginal misoprostol insertion. Because of small numbers of our patients, the power of 0.1558 was detected in the study. So, further trials in separated groups of pre- and post-menopausal patients with different doses and appropriate numbers of patients with the power of 0.8 were suggested.

The mild side effects such as abdominal pain, perceived increase in body temperature, vaginal bleeding, headache and vomiting at 6 h after vaginal misoprostol insertion were found in a small number of patients. There were no severe or life-threatening side effects.

In conclusion, 400 \( \mu \text{g} \) of vaginal misoprostol was not effective in converting an unsatisfactory to a satisfactory colposcopy in the patients who had abnormal cervical cytology with minimal side effects at 6 h after vaginal insertion. However, the 20% rate of conversion after vaginal misoprostol insertion may be of clinically significant benefits in reducing conization procedures in further trial.

**Figure 3.** (a) Before vaginal insertion of misoprostol, cervix of a patient who had a slit-like external os showed non-visualized squamo-columnar junction. (b) Six hours after vaginal insertion of misoprostol, cervix of the same patient was converted from an unsatisfactory to a satisfactory colposcopy in view of visualization of the entire transformation zone both upper and lower lips after 3\% dilute acetic acid is applied.
Conflict of interest statement

None declared.

References