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Misoprostol versus Placebo for Unsatisfactory Colposcopic Finding: A Randomized Controlled Trial

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ABSTRACT

Objective: To assess the effectiveness of vaginal misoprostol for converting unsatisfactory to satisfactory colposcopy.

Materials and Methods: Forty women with abnormal cervical cytology and unsatisfactory colposcopy who underwent colposcopic examination at colposcopic clinic Khon Kaen Hospital, between May, 2009 and June, 2010. Patients were randomly allocated to received either 200 µg misoprostol or placebo vaginally, and colposcopic examination were taken 4 hours later. The percentage of conversion to satisfaction result and the adverse effects were recorded.

Result: There were 20 women in each misoprostol and placebo group. One patient was excluded from each group because of follow up problem. In misoprostol group, 13 out of 19 patients (68.4%) were converted into satisfactory colposcopy result compared with five out of 19 patients (26.3%) in placebo group. This effect was statistically significant difference (P=0.009). No serious adverse effects was reported in both groups.

Conclusions: Two hundred micrograms of vaginal misoprostol was effective and safe to convert unsatisfactory to satisfactory colposcopy result.

Keywords: misoprostol, transformation zone, unsatisfactory colposcopy

Introduction

Colposcopy is accepted as a routine procedure for evaluating precancerous lesion in women with abnormal cervical cytology. Approximately 10-15% of patients had unsatisfactory colposcopy (the entire transformation zone could not be completely visualized[1]. The unnecessary invasive procedure such as cold-knife conization, loop electrosurgical excisional procedure, which increase acute and long-term complications such as blood loss, infection, risk from anesthetic drugs, abortion, preterm labor and cervical incompetence, should be prevented[1]. Various methods have been tried for converting unsatisfactory to satisfactory colposcopy including physical manipulation by cotton-tipped applicator, mechanical methods (osmotic or hygroscopic dilator), and pharmacological methods with ethinyl estradiol or Goserelin[2-7]. However, the effectiveness of these methods is still unclear.

Misoprostol, a prostaglandin E1 derivative, is

widely used for both obstetric and gynecologic procedures such as induction of labor, cervical dilatation for hysteroscopy and endometrial biopsy[8-13]. The purpose of the present study was to evaluate the effectiveness of misoprostol for converting unsatisfactory colposcopy to satisfactory colposcopy and its adverse effects.

Materials and Methods

This double-blind randomized, placebo-controll trial was conducted between May, 2009 and June, 2010 at colposcopic clinic, Khon Kaen Hospital. Forty patients who had abnormal cervical cytology with unsatisfactory colposcopy were enrolled. Unsatisfactory colposcopy was defined as the entire transformation zone could not be completely visualized. Exclusion criteria were history of hypersensitivity to prostaglandins, pregnancy and evidence of invasive cervical carcinoma on colposcopic examination, gross cervical mass and prior surgical procedure of cervix, i.e. cold-knife conization and loop electrosurgical excisional procedure (LEEP).

All participants signed their informed consent after a full explanation about the procedure. Forty women were randomly allocated to received forty identical coded packages containing 200 µg of misoprostol or placebo (produced by pharmacologists of the Department of Pharmacology, Khon Kaen University). Computer-generated randomization was used and allocation concealment by sequentially opaque envelopes. The first colposcopic examination was done and vaginal tablet was inserted. After four hours, the second colposcopic examination was performed by the same colposcopist. Main outcome was the number of women who had successfully converted unsatisfactory colposcopy result to satisfactory colposcopy result.

Adverse effects were also recorded by the nurses who were standardized at the time of the second colposcopy was performed. These outcomes were measured at first colposcopic examination and then 4 hours after intervention. This study was approved by Khon Kaen Hospital Ethics Committee.

Statistical Analysis

Chi-square or Fisher's exact test was used for categorical variables. Student t-test or non-parametric test was used for continuous variables. A p-value < 0.05 was considered statistically significant. The sample size was calculated based on 80% power and 0.05 error. The conversion rate was from 0.8 to 0.3.

Results

Forty women with unsatisfactory colposcopy result were randomly allocated into two groups, 20 women in each group. The study group received 200 µg misoprostol and the control group, received placebo vaginally 4 hours prior to re-colposcopy.

Characteristics of age, occupation, parity, underlying disease, history of sexual transmitted disease including HIV infection were similar in both groups but more number of postmenopausal women in control group (Table1). The referral Pap smears are shown in Table 2. The degree of cytologic abnormalities were not significantly difference between both groups (p= 0. 698). One patient in each group was dropped out after drug administration. The remaining 38 women were recruited. In the study group, 13 patients out of 19 patients (68.4%) had converted the unsatisfactory colposcopy result into satisfactory colposcopy result compared with only 5 out of 19 patients (26.3%) in control group with statistically significant difference (P=0.009) as shown in Table 3. According to adverse effects, abdominal pain was statistically significant higher in study group than control group (P=0.002). However, the patients did not require additional analgesia. For other adverse effects, there was no statistically significant difference between both groups (Table 4). There was no vomiting in both groups.

Table 1. Characteristics of patients.

Characteristics	Study group (n = 20)	Control group (n = 20)	p-value
Mean age, (years)	43.8	49.5	0.143
Postmenopausal women, n (%)	4(10)	10(25)	0.048
Multipara, n (%)	17(42.5)	18(45)	0.282
HIV infection, n (%)	1(2.5)	1(2.5)	0.756

n = number of patients

Table 2. Referral Pap smear.

Cervical cytology	Study group (n = 20)	Control group (n = 20)	p-value
ASCUS	8	5	0.698
ASC-H	1	2	
LSIL	3	2	
HSIL	6	8	
AGC-NOS	0	1	
AGC-FN	0	1	
SCCA	2	1	

ASCUS = atypical squamous cells of undetermined significance; ASC-H = atypical squamous cells cannot exclude high-grade lesions; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; AGC-NOS = atypical endocervical cells, not otherwise specified; AGC-FN = atypical endocervical cells, favor neoplasic; SCCA = squamous cell carcinoma

Table 3. Colposcopic finding in post-intervention status.

Colposcopic examination	Study group (n = 19)	Control group (n = 19)	95% CI	p-value
Satisfactory	13	5	1.15 - 5.85	0.009
Unsatisfactory	6	14		

Table 4. The adverse effects.

Side effect	Study group (n = 19)	Control group (n = 19)	p-value
Fever	3	1	0.302
Abdominal pain	8	0	0.002
Nausea	3	0	0.115
Diarrhea	2	2	0.243

Discussion

Two hundred microgram of misoprostol vaginal tablet was effective for converting the unsatisfactory to satisfactory colposcopy result. The rate of conversion in misoprostol group was 68% (13 out of 19) compared with 26% in placebo group (5 out of 19). Adverse effects were minor and no serious effect was observed, except slightly abdominal pain which was higher in misoprostol group. The additional analgesia was not required. However, the numbers of postmenopausal women in control group were significant higher than study group. Half of them can be converted to satisfactory colposcopy result themselves (5 out of 10), whereas the menopause status had effect to physical properties of cervix, the cervix of pre-menopause women trend to be softening than menopausal cervix.

The present study was consistent with Aggarwal et al who found that the misoprostol was significantly converted unsatisfactory to satisfactory colposcopy result (p=0.004)[8]. However, they used the higher dose of misoprostal (400 µg) and longer waiting time (6 hours). In the study, 200 µg misoprostol was chosen because of less serious adverse effects (abdominal pain, nausea, fever, and diarrhea). Its effectiveness was not different from higher dose but less adverse effects.

However, we found that abdominal pain in the study group was significantly higher than in control group but none of them were serious symptoms. From prior studies[2-7], various methods had been used to convert unsatisfactory to satisfactory colposcopy but their effectiveness were inconclusive. Although, the study performed second colposcopy at four hours after drug administration, the convertion rate was still appreciable and practical on outpatient basis. Only one in each group was dropped out after drug administration (5%).

We did not control for menopausal status which may effect the outcome. In postmenopausal woman, the squamocolumnar junction moves into endocervical canal and tends to be more difficult to convert to the satisfactory colposcopy than premenopausal group. Follow up investigation and management after conversion of colposcopy result, such as invasive procedure, should be taken into account for the further study.

In conclusion, misoprostal was effective and safe for converting unsatisfactory to satisfactory colposcopy result.

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การใช้ misoprostol กับยาหลอก ในผู้ป่วยที่ผลตรวจกล้องส่องขยายทางช่องคลอดเป็น unsatisfactory

ฤทัยรัตน์ ตั้งมั่นสกุลชัย, มาลีชาติ ศรีพิพัฒนะกุล

วัตถุประสงค์ *: เพื่อศึกษาผลของ misoprostol ในการเปลี่ยนจาก unsatisfactory เป็น satisfactory ในการตรวจด้วยกล้องส่องขยายทางช่องคลอด*

วัสดุและวิธีการ *: สตรีที่ผลเซลล์วิทยาปากมดลูกผิดปกติ ที่เข้ารับการตรวจด้วยกล้องส่องขยายทางช่องคลอด ระหว่างเดือนพฤษภาคม ปี 2552 ถึง เดือนมิถุนายน ปี 2553 โรงพยาบาลขอนแก่น สุ่มแบ่งเป็นสองกลุ่ม เพื่อรับยา misoprostol หรือยาหลอกเหน็บช่องคลอด unsatisfactory เป็น satisfactory และบันทึกผลแทรกซ้อนจากการใช้ยา*

ผลการรักษา *: สตรี 40 คน ได้รับ misoprostol 200 ไมโครกรัม และยาหลอกกลุ่มละ 20 คน มีหนึ่งคนในแต่ละกลุ่ม ไม่สามารถติดตามผลได้ ร้อยละ 64.8 ในกลุ่ม misoprostol เปลี่ยน unsatisfactory เป็น satisfactory เทียบกับร้อยละ 26.3 ในกลุ่มยาหลอก ซึ่งแตกต่างกันอย่างมีนัยสำคัญ (P=0.009) และไม่พบภาวะแทรกซ้อนรุนแรง*

สรุป *: misoprostol 200 ไมโครกรัม เหน็บทางช่องคลอดสามารถเปลี่ยนจาก unsatisfactory เป็น satisfactory อย่างมีประสิทธิภาพและปลอดภัย*