Thai Journal of Obstetrics and Gynaecology
July 2018, Vol. 26, No. 3, pp. 198-204

GYNECOLOGY

Sublingual Misoprostol for Unsatisfactory Colposcopic Finding: A randomized controlled trial

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ABSTRACT

Objectives: To assess the effectiveness of 200 µg sublingual misoprostol for converting an unsatisfactory to satisfactory colposcopic finding.

Materials and Methods: Forty-two participants with abnormal cervical cytology and unsatisfactory colposcopic finding who underwent colposcopy between September 2016 and June 2017 were randomized into two groups; either misoprostol or placebo given sublingually. Second colposcopy was performed 2 hours later, and the conversion rate of unsatisfactory to satisfactory colposcopic finding of both groups was analyzed.

Results: Baseline characteristics were similar between two groups. Conversion rate of unsatisfactory to satisfactory colposcopic finding in participants who received sublingual misoprostol was statistically significant higher than placebo group (80.9% vs 38.1%, p = 0.011, relative risk = 2.1, 95% confidence interval 1.18-3.80). There was no significant difference in adverse effect between groups.

Conclusion: Two hundred micrograms of sublingual misoprostol, 2 hours before performing colposcopy can convert an unsatisfactory finding to a satisfactory one.

Keywords: unsatisfactory colposcopy, abnormal pap smear, sublingual misoprostol

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การใช้ยา misoprostol อมใต้ลิ้นกับยาหลอกในผู้ป่วยที่มีผลตรวจกล้องส่องขยายทางช่องคลอดเป็น unsatisfactory

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาประสิทธิภาพของยา misoprostol 200 ไมโครกรัม อมใต้ลิ้นในการเปลี่ยนแปลงผลตรวจกล้องส่องขยายทางช่องคลอดจาก unsatisfactory เป็น satisfactory

วัสดุและวิธีการศึกษา: ผู้เข้าร่วมวิจัยจำนวน 42 คน ที่ผลตรวจมะเร็งปากมดลูกผิดปกติและผลตรวจกล้องส่องขยายทางช่องคลอดเป็น unsatisfactory ที่เข้ามาตรวจที่ colposcopic clinic รพ.ขอนแก่น ในช่วงเดือนกันยายน 2559 ถึง มิถุนายน 2560 ได้รับการสุ่ม เป็น 2 กลุ่ม คือ กลุ่มที่ได้รับยา misoprostol อมใต้ลิ้น และกลุ่มที่ได้รับยาหลอกอมใต้ลิ้นเป็นเวลา 2 ชม. โดยเปรียบเทียบความสามารถในการเปลี่ยนปากมดลูกจาก unsatisfactory เป็น satisfactory

ผลการวิจัย: ผู้เข้าร่วมวิจัยทั้งสองกลุ่มมีลักษณะพื้นฐานไม่แตกต่างกัน ผู้เข้าร่วมวิจัยในกลุ่มที่ได้รับ misoprostol มีอัตราการเปลี่ยนปากมดลูกจาก unsatisfactory เป็น satisfactory มากกว่ากลุ่มที่ได้ยาหลอกอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 80.9 กับร้อยละ 38.1, p = 0.011, RR = 2.1, 95% CI 1.18-3.80) โดยไม่พบผลข้างเคียงที่รุนแรง

สรุป: ยา misoprostol 200 ไมโครกรัม อมใต้ลิ้นเป็นเวลา 2 ชม. ก่อนส่องกล้องขยายทางช่องคลอด มีความสามารถในการเปลี่ยนปากมดลูกจาก unsatisfactory เป็น satisfactory ในผู้เข้าร่วมวิจัยที่ตรวจพบความผิดปกติของปากมดลูกได้

คำสำคัญ: ผลส่องกล้องขยายทางช่องคลอดไม่เป็นที่น่าพอใจ, ผลตรวจมะเร็งปากมดลูกผิดปกติ, ยาไมโซพรอสตอลอมใต้ลิ้น

Introduction

Cervical cancer is the most common gynecologic cancer in Thailand[1]. Cervical cancer has a long pre-invasive period which can be detected by conventional Pap smear or liquid-based cytology[2]. An abnormal cytology must be further diagnosed using colposcopy[3]. An unsatisfactory colposcopic finding is defined as a transformation zone, such that the location of the common area of an abnormal lesion, is not be completely visualized[3-6]. The incidence of unsatisfactory colposcopy is between 10-15%. Invasive diagnostic procedures such as loop electrosurgical excision and/or endocervical curettage can be performed but this increases complications and morbidity[6].

Misoprostol is a prostaglandin E1 that is used to soften the cervix of non-pregnant women[7-8]. Previous studies reported the effectiveness of vaginal misoprostol in converting an unsatisfactory to a satisfactory colposcopic finding[9-12]; however, vaginal misoprostol took 4-6 hours for drug administration before performing the colposcopy[9,12]. The long waiting time is inconvenient and impractical in an outpatient setting. Sublingual misoprostol 1 hour prior to vacuum aspiration was significantly more effective in softening the cervix than the vaginal route[13]. There has been no study about the effectiveness of sublingual misoprostol for converting unsatisfactory to satisfactory colposcopic findings. This study was thus conducted to assess the efficacy of sublingual misoprostol to convert an unsatisfactory to a satisfactory colposcopic finding.

Materials and Methods

A double blind, randomized, controlled trial was conducted at Khon Kaen Hospital, Thailand between September 2016 and June 2017. This study was approved by the Khon Kaen Hospital Institutional Review Board for Human Research. All participants were informed about the study and signed the informed consent form before enrollment.

We included participants 18 years or over with an abnormal Pap smear, equivocal types (i.e., Atypical Squamous cell of Undetermined Significance, ASCUS; Atypical Glandular cell, (not otherwise specified, NOS), Low Grade Squamous Intraepithelial Lesion, LSIL) with unsatisfactory colposcopic finding and no history of previous hysterectomy. We excluded participants with a history of hypersensitivity to prostaglandins, having gross cervical mass, having had a prior surgical procedure of the cervix (i.e. conization or LEEP).

The unsatisfactory colposcopic finding defined as a transformation zone could not be completely visualized. An unsatisfactory colposcopy could be found among women with a premenopausal or postmenopausal status; thus both conditions were included in the study, and balanced by randomization.

Eligible participants were randomized by computer generated block of four into two groups; misoprostol and placebo. The random numbers were put into sequentially sealed opaque envelopes. Participants in the study group received 1 tablet of 200 µg sublingual misoprostol and the control group received 1 tablet of sublingual placebo. The second colposcopy was performed 2 hours after drug administration after which the conversion rate was recorded. Side effects such as fever, nausea and vomiting, abdominal pain, diarrhea, and shivering were recorded 4 hours after drug administration. The primary outcome was the conversion rate from an unsatisfactory to a satisfactory colposcopic finding. The secondary outcomes were adverse effects (i.e., fever, nausea, vomiting, abdominal pain, diarrhea, and shivering).

The sample size was calculated based on an error value of 0.05 and a power of 80%. We used the proportion from the pilot study to calculate the sample size (viz., a conversion rate of 80% and 30% in the intervention and control group, respectively). The total number of participants was 42 (21 in each group).

Statistical analysis

Categorical variables were analyzed using the Chi-square test or Fisher's exact test. Continuous

variables were analyzed using the Student t-test or the Mann-Whitney U-test depending on the data distribution. The primary outcome was presented as the relative risk with a 95% confidence interval. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using STATA version 13.

Results

Forty-two participants who had an unsatisfactory colposcopy (i.e., the transformation zone could not be completely visualized) were randomly assigned into two groups (21 per group) (Fig. 1). Demographic data including age, body mass index (BMI), underlying diseases, history of drug allergy, menopausal status, parity, anti-HIV test, number of partner were similar in both groups (Table 1). There have more cases of postmenopausal women than premonapausal women in both groups (15 of 21 in each group). The cervical cytology was not different between groups (Table 2). The conversion rate of unsatisfactory to satisfactory colposcopic finding in the misoprostol group was significantly higher than in the placebo group (80.9% vs. 38.1%, and the relative risk (RR) was 2.1, (95% CI 1.18-3.80), p = 0.011). (Table 3)

The adverse effect 'abdominal pain' was found in 3 of 21 (14.29%) and 2 of 21 (9.52%) in the study and control group, respectively. Other adverse effects were also found such as 1 bleeding per cervical os and 1 palmar rash in study group. There were no other serious adverse effects detected. (Table 4)

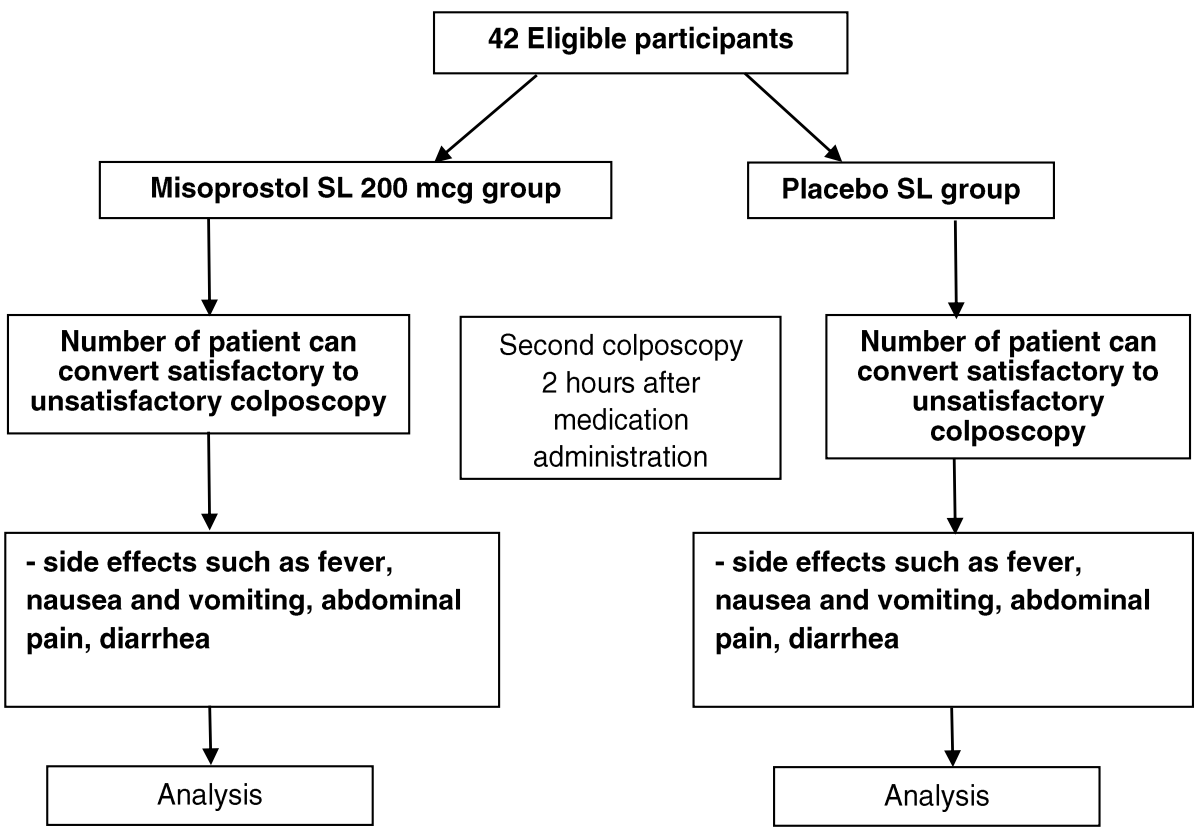

Fig. 1. Participants flow diagram.
(SL, sublingual; mcg, microgram)

Table 1. Demographic data of participants.

Characteristic	Study group (misoprostol) (n=21)	Control group (placebo) (n=21)	p value
Age, years (mean ± SD)	42.9 ± 11.5	36.7 ± 11.2	0.10
BMI, kg/m^2 (mean ± SD)	23.5 ± 3.7	22.8 ± 4.4	0.49
Underlying disease, n (%)	7 (33.3)	4 (19.1)	0.48
Drug allergy, n (%)	1 (4.7)	1 (4.7)	1.00
Parity			
- Multiparous (vaginal birth), n (%)	19 (90.5)	13 (61.9)	0.58
Anti HIV, n (%)			
Menopause status	4 (19.1)	4 (19.1)	0.58
- Postmenopausal age, n (%)	15 (71.4)	15 (71.4)	1.00
Multiple partner, n (%)	13 (61.9)	14 (66.7)	0.57

BMI : Body mass index; SD : Standard deviation; HIV : Human immunodeficiency virus; n : number of patients

Table 2. Cervical cytology.

Cervical cytology	Study group (misoprostol) (n = 21)	Control group (placebo) (n = 21)	p value
ASCUS	8	11	0.354
LSIL	13	9	
AGC NOS	0	1	

ASCUS : Atypical squamous cells of undetermined significance; LSIL : Low grade squamous intraepithelial lesion;
AGC NOS : Atypical glandular cells, not otherwise specified; n : number of patients

Table 3. Primary outcomes.

Colposcopic examination	Study group (misoprostol) (n=21)	Control group (placebo) (n=21)	RR	95%CI	p value
Satisfactory, n (%)	17 (80.95)	8 (38.10)	2.1	1.18-3.80	0.011
Unsatisfactory, n (%)	4 (19.05)	13(61.90)			

RR : Relative risk; 95%CI : Confidence interval; n : number of patients

Table 4. Secondary outcomes.

Side effect	Study group (n = 21)	Control group (n = 21)	p value
Fever n,%	0	0	1.000
N/V n,%	0	0	
Abdominal pain n,%	3 (14.29)	2 (9.52)	
Diarrhea n,%	0	0	
Chills and shivering n,%	0	0	
Bleeding per cervical os n,%	1 (4.76)	0	
Palmar rash n,%	1 (4.76)	0	

N/V : nausea and vomiting; n : number of patients

Discussion

Our findings support the hypothesis that 200 µg misoprostol sublingual 2 hours prior to colposcopy was able to convert an unsatisfactory to a satisfactory colposcopic finding. The conversion rate of the misoprostol group was 80.9% compared to 38.1% in the placebo group (p = 0.011, RR 2.1, 95%CI 1.18-3.80). This finding was consistent with Aggarwal et al[9], whose study was different from ours in dosage and route of administration (i.e., they used 400 µg misoprostol). By comparison, Tungmunsakulchai et al[12], used a lower dose of 200 µg misoprostol, which had a shorter waiting time (4 hours) before the next colposcopy. Tungmunsakulchai et al[12], found that the effectiveness was not significantly different from the findings of Aggarwal et al. and it had fewer adverse effects.

In our study, a dose of 200 µg of misoprostol 2 hours before a second colposcopy was chosen because Aronsson et al[14], showed that sublingual misoprostol was rapidly absorbed and peak plasma levels were reached significantly faster compared with the vaginal route.

Regardless menopausal status, current study had higher incidence of postmenopausal women in both group than Tungmunsakulchai et al[12], however the result was no difference.

Although a previous study showed greater adverse effects from the sublingual route of misoprostol than the vaginal route, we did not find any serious or life-threatening adverse effects. Notwithstanding, a small number of non-serious adverse effects (i.e., abdominal pain and vaginal bleeding) were documented after sublingual administration of misoprostol in both groups[9,14].

Although the second colposcopy was performed 2 hours after drug administration, which is shorter than in previous studies, the conversion rate of unsatisfactory to satisfactory colposcopic finding was still appreciable higher[9,12].

The strength of the present study was that it was a randomized controlled trial and there were no dropouts. Sublingual misoprostol 200 µg taken 2 hours before coloscopy was a useful preparation for converting an unsatisfactory to a satisfactory colposcopic finding in the outpatient setting and could thus reduce morbidity from overtreatment. Among post-menopausal participants, the morphology of cervical epithelium was more difficult to convert to a satisfactory colposcopic finding than among pre-menopausal women. Further study is needed to elucidate the mechanism among post-menopausal women.

Conclusion

Two hundred microgram sublingual misoprostol, 2 hours before performing colposcopy can convert an unsatisfactory to a satisfactory cloposcopic finding.

Acknowledgements

The authors thank (a) the patients for their participation (b) Khon Kaen Hospital for its support, and (c) Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript.

Potential conflicts of interest

The authors declare no conflict of interest.

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