Thai Journal of Obstetrics and Gynaecology
January 2023, Vol. 31, No. 1, pp. 40-47.

GYNAECOLOGY

Lidocaine Prilocaine Cream versus Intracervical Injection for Pain Relief during Loop Electrosurgical Excision Procedure

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ABSTRACT

Objectives: To compare the effectiveness between lidocaine prilocaine cream versus intracervical injection for pain relief during loop electrosurgical excision procedure (LEEP).

Materials and Methods: Sixty women who underwent LEEP at Khon Kaen Hospital were enrolled in a single, blinded, non-inferiority randomized controlled trial. The participants were randomly allocated into two groups; group 1 received lidocaine prilocaine cream applied to the cervix (n = 30), and group 2 intracervical injection (n = 30) before performing LEEP. The pain score was measured at speculum placement, during anesthetization, during the procedure, immediately after, and 30 min after the procedure, using the 10-cm visual analogue scale (VAS). In addition, we recorded adverse events and additional analgesia.

Results: Baseline characteristics were similar between groups. The mean pain score during LEEP among groups was not significantly different between intracervical injections (control group) (5.53 ± 0.46, 95% confidence interval (CI) 4.60-6.47 vs. 4.59 ± 0.44, 95%CI 3.68-5.50, p = 0.145). The mean pain score during anesthetization with lidocaine prilocaine cream (intervention group) was significantly lower than with the intracervical injection (1.20 ± 0.29, 95%CI 0.60-1.80 vs. 3.62 ± 0.48, 95%CI 2.64-4.60, p < 0.001). No serious adverse events occurred.

Conclusion: Lidocaine prilocaine cream was not significantly different intracervical injection for pain relief during LEEP and provided better pain relief during anesthetization (than in the control group) without serious adverse events.

Keywords: loop electrosurgical excision procedure, LEEP, lidocaine prilocaine cream, intracervical injection, visual analog scale.

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Received: 28 September 2021, **Revised:** 20 December 2021, **Accepted:** 22 December 2021

ผลของการทาครีมยาชาเปรียบเทียบกับการฉีดยาที่ปากมดลูกเพื่อลดความเจ็บปวดในการตัดปากมดลูกด้วยห่วงไฟฟ้า

กชนิภา แพทยานันท์, ชินวัฒน์ ศรีนิล

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลการลดความเจ็บปวดในผู้ป่วยที่เข้ารับการทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้า โดยการทาครีมยาชาเปรียบเทียบกับการฉีดยาชาที่ปากมดลูก*

วัสดุและวิธีการ: *สตรีที่เข้ารับการทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้าที่โรงพยาบาลขอนแก่น จำนวน 60 คน ถูกสุ่มแบ่งเป็นสองกลุ่ม คือ กลุ่มที่ 1 ได้รับการทาครีมยาชาที่ปากมดลูก และกลุ่มที่ 2 ได้รับการฉีดยาชาที่ปากมดลูกก่อนทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้า สตรีทั้งสองกลุ่มได้รับการประเมินความเจ็บปวดขณะใช้เครื่องมือถ่างขยายช่องคลอด ขณะฉีดยาชาที่ปากมดลูกหรือทาครีมยาชาที่ปากมดลูก ระหว่างทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้า หลังทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้าเสร็จทันที และหลังทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้าเสร็จนาน 30 นาที โดยใช้เครื่องมือวัดความเจ็บปวดประกอบด้วยเส้นตรงยาว 10 เซนติเมตร รวมถึงมีการประเมินภาวะแทรกซ้อนจากการใช้ยาและความต้องการยาแก้ปวดชนิดอื่นเพิ่มเติม*

ผลการศึกษา: *ข้อมูลลักษณะพื้นฐานทางประชากรศาสตร์ของทั้งสองกลุ่มไม่แตกต่างกัน คะแนนความเจ็บปวดระหว่างการทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้าในกลุ่มที่ทาครีมยาชาที่ปากมดลูก (กลุ่มทดลอง) ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติกับกลุ่มฉีดยาชาที่ปากมดลูก (กลุ่มควบคุม) (ค่าเฉลี่ยคะแนนความเจ็บปวด ± ส่วนเบี่ยงเบนมาตรฐานของกลุ่มทดลอง และกลุ่มควบคุมมีค่า 5.53 ± 0.46, 95%CI 4.60-6.47 เทียบกับ 4.59 ± 0.44, 95%CI 3.68-5.50, p = 0.145) แต่พบว่า คะแนนความเจ็บปวดระหว่างการให้ยาบรรเทาความเจ็บปวดก่อนทำหัตถการในกลุ่มที่ทาครีมยาชาที่ปากมดลูก (กลุ่มทดลอง) น้อยกว่ากลุ่มฉีดยาชาที่ปากมดลูก (กลุ่มควบคุม) (ค่าเฉลี่ยคะแนนความเจ็บปวด ± ส่วนเบี่ยงเบนมาตรฐานของกลุ่มทดลอง และกลุ่มควบคุมมี 1.20 ± 0.29, 95%CI 0.60-1.80 เทียบกับ 3.62 ± 0.48, 95%CI 2.64-4.60, p < 0.001) อย่างมีนัยสำคัญทางสถิติ และไม่พบภาวะแทรกซ้อนที่รุนแรงในทั้งสองกลุ่ม*

สรุป: *ประสิทธิภาพในการบรรเทาความเจ็บปวดระหว่างการทำหัตถการตัดปากมดลูกด้วยห่วงไฟฟ้าในกลุ่มที่ทาครีมยาชาที่ปากมดลูกไม่แตกต่างจากกลุ่มควบคุม แต่การทาครีมยาชาที่ปากมดลูกสามารถลดความเจ็บปวดระหว่างให้ยาบรรเทาความเจ็บปวดก่อนทำหัตถการได้อย่างมีนัยสำคัญทางสถิติ และไม่พบภาวะแทรกซ้อนที่รุนแรงจากการใช้ยา*

Introduction

Since 1990, loop electrosurgical excision procedure (LEEP) has been used worldwide for the diagnosis and treatment of cervical intraepithelial neoplasia (CIN 2-3)[1-3]. The procedure is an invasive cervical procedure requiring effective pain control. Pain during LEEP is thought to result from heat generated during the excision. The generator combines high-frequency, low-voltage electric current that arcs between the loop (electrode) and the tissue it contacts. When current heats the cellular water content to boiling, cellular disruption and vaporization occurs, forming the plane of excision[4]. Several anesthetic techniques are used for pain relief during LEEP, including intracervical injection[5], topical anesthesia[6-7], and paracervical block (P.B.)[8]. Local anesthesia can be used to prevent pain; however, the standard of local anesthesia when performing LEEP remains unclear[4].

Lidocaine intracervical injection is routinely performed at Khon Kaen Hospital but it is invasive and causes bleeding that may interfere with colposcopic inspection. Lidocaine prilocaine cream is a new anesthetic agent widely used for local pain control for various procedures. Its advantages include non-invasive, easy-to-use, and less systemic absorption. It is also used for pain control in gynecologic procedures. The author was thus interested in conducting research comparing the effectiveness of pain control between the two anesthetic techniques.

The 5% Emla® cream comprises two local anesthetics - lidocaine 25 mg/g and prilocaine 25 mg/g. When 5% Emla® cream is applied onto a mucous membrane, absorption is rapid, so occlusive dressings are unnecessary. The onset of action is 5 min after application. The total maximum dosage is 20 g and the maximum recommended duration of exposure is 4 h. The percentage of absorption depend on skin surface blood flow[9,10]. One study reported that lidocaine prilocaine cream applied onto the uterine cervix before hysterosalpingogram (HSG) can relieve pain during the procedure. The cervical intervention was the most painful step during the procedure, and lidocaine prilocaine cream decreased the pain during this step[12]. It has also been used locally on the uterine cervix before laser ablation and hysteroscopy and was found to reduce pain[13,14].

The objective of the current study was to evaluate the efficacy of lidocaine prilocaine cream vs. intracervical injection for pain reduction during loop electrosurgical excision procedure (LEEP). The primary outcome was mean pain score during LEEP, and the secondary outcomes were (a) mean pain score (i) during speculum placement, (ii) during anesthetization, (iii) immediately after the procedure, (iv) 30 min after the procedure, (b) adverse events; and, (c) the need for additional analgesia.

Materials and Methods

The present study was a randomized, single-blinded, placebo-controlled trial. The Khon Kaen Hospital Institutional Review Board for Human Research reviewed and approved the study (KEF63018). All participants had the study explained to them and signed informed consent before enrolling.

We recruited 60 women 18 years or older who underwent LEEP at Khon Kaen Hospital between December 2020 and August 2021 after being diagnosed with cervical intraepithelial neoplasia. We excluded women with coagulopathy, neurological diseases with impaired sensation, cardiac arrhythmia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, lidocaine hypersensitivity, and those who were pregnant.

The participants were randomized into two groups using a computer-generated block of four: the study group - lidocaine prilocaine cream, and the control group - intracervical injection. The randomization list was kept in a sealed opaque envelope. Gynecologic oncologists performed LEEP.

The participants were first placed in a lithotomy position, and the operative area was cleaned and draped. Next, a sterile bivalve speculum was inserted into the vaginal canal to evaluate the uterine cervix. The operator determined the proper loop size to be used (1, 1.5, 2, 2.5, to 3 cm in diameter) based on the size, extent of the cervical lesion, and contour of the cervix under colposcopy. The study group received

5 g of 5% lidocaine prilocaine cream applied onto the cervix and external os using a cotton swab. The control group received 2% lidocaine with 1:100,000 epinephrine injected submucosally 1.8 ml (36 mg) at 3, 6, 9, and 12 o'clock of the ectocervix. After waiting for 5 min, LEEP was performed. The pain score was recorded using a 10-cm long, unmarked continuous horizontal line as a visual analog scale (VAS) for five different time points (speculum placement, during anesthetization, during excision, immediately after the procedure, and 30 min after the procedure). Patients were informed that the far-left point represented "no pain" and the far-right point represented "unbearable pain." They were then asked to mark the vertical line across the VAS five times to determine their pain levels. All participants could ask for additional analgesia when needed.

Vital signs and adverse events-i.e., lightheadedness, palpitation, numbness of lips, and tinnitus - were recorded by a nurse until 30 min after the procedure. Additional analgesia was also recorded. The primary outcome was the pain score during LEEP. The secondary outcomes were (a) the pain score (i) during speculum placement, (ii) during anesthesia, (iii) immediately after the procedure, (iii) 30 min after the procedure, (iv) 30 min after the procedure; (b) adverse effects; and, (c) the need for additional analgesia. In addition, baseline characteristics were recorded, including age, body mass index (BMI), parity, cervical cytology results, loop diameter, underlying disease, operative time, and pain score after applying the speculum.

The sample size was calculated based on data from the pilot study with 80% power at the 5% significance level with up to 10% dropout.

$Z_{\alpha/2} = 1.96$, $Z_{\beta} = 0.84$, 80% power

Pilot study: $\mu 1 = 5.38$, $\mu 2 = 6.29$

alpha = 0.05, beta = 0.2

$$\text{n/ group} = \frac{2\,(Z_{\alpha/2} + Z_{\beta})^2\,\delta^2}{(\mu_1 - \mu_2)^2}$$

The total sample size was thus 60 participants (30 in each group). Data were analyzed using STATA version 13. Continuous variables were analyzed using the student t-test and presented as means ± standard deviation (SD). Categorical variables were analyzed using the Chi-square or Fisher's exact test and presented as percentages. A p value < 0.05 was considered statistically significant.

Results

Sixty women were indicated as needing to undergo LEEP at Khon Kaen Hospital. All of the participants were recruited into the study and randomly allocated into two groups - the study group (lidocaine prilocaine cream) (n = 30) and the control group (intracervical injection) (n = 30). No dropouts occurred during the study, so the data from all 60 women were included and analyzed (Fig. 1).

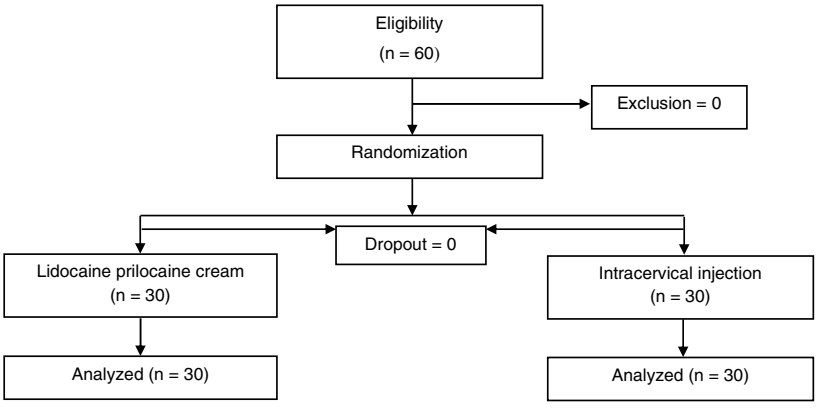

Fig. 1. Study flow diagram.

Both groups had similar demographics and characteristics, including age, BMI, menopausal status, parity, cervical cytology results, final histology, loop diameter, underlying diseases, operation time, and pain score after applying the speculum (Table 1).

Table 1. Demographics and characteristics of the cases.

	Lidocaine Prilocaine cream (n = 30)	Intracervical injection (n = 30)	p value
Age, y, Mean ± SD	38.87 ± 9.53	42.00 ± 10.71	0.236[c]
BMI, Mean ± SD, cm/m^2	23.22 ± 4.10	24.69 ± 3.66	0.149[c]
Menopausal status, n (%)			0.278[a]
Pre-menopause	27 (90.0)	24 (80.0)	
Menopause	3 (10.0)	6 (20.0)	
Parity, n (%)			0.739[a]
Nullipara	6 (20.0)	5 (16.7)	
Multipara	24 (80.0)	25 (83.3)	
Cervical cytology results			0.762[b]
ASC-H	3 (10.0)	6 (20.0)	
LSIL	7 (23.3)	4 (13.3)	
HSIL	17 (56.8)	15 (50.0)	
Cancer	1 (3.3)	1 (3.3)	
AIS	0 (0.0)	0 (0.0)	
AGC	1 (3.3)	2 (6.7)	
Other	1 (3.3)	2 (6.7)	
Final histology, n (%)			0.385[b]
CIN-1	2 (6.6)	3 (10.0)	
CIN-2	6 (20.0)	11 (36.7)	
CIN-3	17 (56.8)	12 (40.0)	
AGC	3 (10.0)	3 (10.0)	
AIS	0 (0.0)	0 (0.0)	
CIS	0 (0.0)	1 (3.3)	
Cancer	2 (6.6)	0 (0.0)	
Loop diameter, cm, Mean ± SD	1.70 ± 0.50	1.72 ± 0.43	0.891[c]
Underlying diseases, n (%)			
Hypertension	1 (3.33)	4 (13.3)	0.161[a]
Diabetes mellitus	1 (3.33)	3 (10.0)	0.301[a]
HIV	2 (6.6)	2 (6.6)	1.000[a]
Allergy	1 (3.3)	3 (10.0)	0.301[a]
Operative time, min, Mean ± SD	14.13 ± 1.63	10.50 ± 0.77	0.050[c]
Pain score after applied speculum Mean ± SD	1.64 ± 0.39	1.73 ± 0.40	0.877[c]

chi-square test[a], Fisher's Exact test[b], student t-test[c]

SD: Standard deviation, BMI: body mass index, ASC-H: atypical squamous cells cannot excluded HSIL, LSIL: low grade squamous intraepithelial lesion, HSIL: high grade squamous intraepithelial lesion, AIS: adenocarcinima in situ, AGC: atypical glandular cells, CIS: carcinoma in situ, CIN: cervical intraepithelial lesion, HIV: human immunodeficiency virus

The primary and secondary outcomes are presented in Table 2. The mean pain score was not significantly different between the study and control group during LEEP (5.53 ± 0.46, 95%CI 4.60 - 6.47 vs. 4.59 ± 0.44, 95%CI 3.68 - 5.50, p = 0.145); immediately after the procedure (1.45 ± 0.40, 95% CI 0.64 - 2.26 vs. 1.26 ± 0.31, 95%CI 0.62 - 1.90, p = 0.708); and 30 min after the procedure (2.13 ± 0.40, 95%CI 1.31 - 2.96 vs. 1.52 ± 0.36, 95%CI 0.79 - 2.25, p = 0.257).

Table 2. Primary and secondary outcomes.

VAS pain score	Lidocaine Prilocaine cream (n=30)	Intracervical injection (n=30)	Mean different	95% CI	p value
during anesthetization					< 0.001[c*]
mean ± SD	1.20 ± 0.29	3.62 ± 0.48	-2.41	-3.54 - 1.29	
(95% CI)	(0.60 - 1.80)	(2.64 - 4.60)			
During excision					0.145[c]
mean ± SD	5.53 ± 0.46	4.59 ± 0.44	0.94	-0.33 - 2.22	
(95% CI)	(4.60 - 6.47)	(3.68 - 5.50)			
Immediate after procedure					0.708[c]
mean ± SD	1.45 ± 0.40	1.26 ± 0.31	0.19	-0.82 - 1.20	
(95% CI)	(0.64 - 2.26)	(0.62 - 1.90)			
30 minutes after procedure					0.257[c]
mean ± SD	2.13 ± 0.40	1.52 ± 0.36	0.62	-0.46 - 1.70	
(95% CI)	(1.31 - 2.96)	(0.79 - 2.25)			
Cervical view					0.011[c*]
mean ± SD	98.00 ± 6.10	93.00 ± 8.37	5.00	1.22 - 8.78	
(95% CI)	(95.72 - 100.28)	(89.88 - 96.12)			

student T-test[c], significant p < 0.05*

VAS: visual analog scales, CI: confidence interval, SD: standard deviation

The mean pain score during anesthetization was significantly lower in the study group than in the control group (1.20 ± 0.29, 95%CI 0.60 - 1.80 vs. 3.62 ± 0.48, 95%CI 2.64 - 4.60, p < 0.001); and the cervical view was significantly better in the study group than in the control group (98.00 ± 6.10, 95%CI 95.72 - 100.28 vs. 93.00 ± 8.37, 95%CI 89.88 - 96.12, p = 0.011).

Only one woman in the study group experienced dizziness after applying the lidocaine prilocaine cream. One participant in the study group requested additional analgesia (Table 3).

Table 3. Adverse events and additional analgesia.

	Lidocaine Prilocaine cream (n=30)	Intracervical injection (n=30)	p value
Adverse events, n (%)			
Dizziness	1 (3.3)	0 (0.0)	0.500[b]
Additional analgesia, n (%)	1 (3.3)	0 (0.0)	0.500[b]
Bleeding, n (%)	2 (6.6)	0 (0.0)	0.246[b]

Fisher's Exact test[b]

Discussion

The mean pain score during LEEP in the lidocaine prilocaine cream group was not significantly different from that of the intracervical injection group (5.53± 0.46 vs. 4.59 ± 0.44). Adverse effects were not significantly different between the groups.

Although there has not been any study on the efficacy of lidocaine prilocaine cream for pain reduction during LEEP, previous studies on cervical and uterine interventions provided relevant comparisons. Liberty et al[10] reported on the effect of applying lidocaine prilocaine cream on the uterine cervix for pain relief after performing hysterosalpingography (HSG) in 84 women who underwent HSG as part of an infertility evaluation. Liberty et al[11] found that cervical instrumentation in the lidocaine prilocaine-treated patients was associated with significantly less pain than the placebo (3.3 ± 2.9 vs. 4.9 ± 2.7, p = 0.02).

Tavakolian et al[14] reported on the effect of lidocaine prilocaine cream on the uterine cervix to determine intrauterine device (IUD) insertion pain among 92 women who underwent IUD insertion. Tavakolian et al[14] found that lidocaine prilocaine cream significantly reduced pain during the use of a tenaculum compared with placebo (1.52 ± 1.85 vs. 4.30 ± 2.40, p < 0.001). In addition, the mean pain score during insertion of a hysterometer in the lidocaine prilocaine cream group was associated with significantly less pain than the placebo group (3.11 ± 2.53 vs. 5.20 ± 2.31, p < 0.001).

Williams et al[15] reported on the use of lidocaine-prilocaine cream for vulvar biopsy among 106 women undergoing vulvar biopsy. They found the cream significantly reduced pain before vulvar biopsy compared with a lidocaine injection (2 (0, 17) vs. 17 (5, 38), p = 0.02) with no significant difference pain at vulva biopsy (6 (1, 50) vs. 3 (0, 15), p = 0.47). Our study results thus agreed with these three previous studies[10, 14,15], indicating that lidocaine prilocaine cream reduced pain during LEEP.

Based on the current study, the difference in pain scores did not exceed the margin of clinical significance with less pain during anesthetization and significantly improved the cervical view. A better cervical view is key to the success of the procedure. Bleeding from intracervical injection might cause a poor cervical view and affect the adequacy of the procedure.

Besides the primary outcome, we found that the pain scores at speculum placement, immediately after LEEP, and 30 min after LEEP were not significantly different between groups. Lidocaine prilocaine cream produced the most prolonged duration of analgesia (about 45 min) and reduced pain scores (30 min after LEEP).

One of the participants in the lidocaine prilocaine cream group requested additional analgesia. There was no significant difference in adverse events between the two groups. Only one participant in the study experienced dizziness after the application of the lidocaine prilocaine cream. The symptom was mild and resolved within a few minutes without medical treatment. Zilbert[12] reviewed the effect of using lidocaine prilocaine cream for pain relief during minor gynecological procedures and found that it was well-tolerated and adverse reactions were generally mild, local, and transient.

Post-procedure bleeding was not significantly different between groups. However, two participants in the lidocaine prilocaine cream group noticed post-procedure bleeding. The mechanism of the post-procedure bleeding might be from the absence of any vasoconstriction effect of adrenaline.

The mean difference in operative time was 3.63 min, which was not significantly different between the lidocaine prilocaine cream and intracervical injection group (14.13 ± 1.63 and 10.50 ± 0.77, p = 0.05, respectively). This longer operative time might be due to the waiting time after lidocaine prilocaine cream application but not from any adverse event(s) after the intervention.

The study's strengths were that (a) it was randomized controlled trial, and (b) no patients dropped out. The limitations of the study were that (a) it was a single centre, blind intervention; and, (b) it lacked a cost-effectiveness analysis.

Conclusion

Compared with intracervical injection, lidocaine prilocaine cream (a) not significantly reduced pain during LEEP; (b) significantly reduced pain during anesthetization; and, (c) provided a better cervical view without any serious adverse event.

Acknowledgement

The authors thank (a) the staff of the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Khon Kaen Hospital for their assistance and support; (b) the participants for their cooperation; and, (c) Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript.

Potential conflicts of interest

The authors declare no conflicts of interest.

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