Thai Journal of Obstetrics and Gynaecology
January 2026, Vol. 34, No. 1, pp. 30-41.

GYNAECOLOGY

Lidocaine Gel Combined with Ibuprofen Versus Ibuprofen Alone for Pain Relief during an Endometrial Biopsy; A randomized controlled trial

Kemmanut Tueman, M.D.*,
Tanyalak Wongleucha, M.D.*

** Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen, Thailand*

ABSTRACT

Objectives: To study the effect of 2% lidocaine gel in conjunction with ibuprofen for pain relief during endometrial biopsy.

Materials and Methods: Women who met the eligibility criteria were randomly allocated into two groups. The intervention group received 2% lidocaine gel (3 mL), while the control group received the placebo gel (3 mL). Both groups received oral ibuprofen 400 mg 30 minutes before the procedure. The pain score in each step of the procedure, starting from speculum insertion, grasping the cervix, during endometrial biopsy, immediately after the procedure, and 10 minutes after the procedure, was assessed by a 10-cm visual analogue scale. Any adverse effects were also recorded.

Results: Eighty-six women, 43 in each group, were recruited during July to December 2024. Baseline characteristics, including age, parity, and menopausal status, were not different in both groups. The mean pain score during endometrial biopsy in the intervention group (3.30 ± 2.09) was significantly lower than in the control group (5.33 ± 2.01) (mean difference -2.03, 95% confidence interval -2.91 to -1.15, $p < 0.001$). Pain scores at each step of the procedure in the intervention group were lower than in the control group but not statistically different. Adverse effects were not found, and the satisfaction of both patients and physicians was satisfied.

Conclusion: The addition of 2% lidocaine gel was effective in reducing pain during endometrial biopsy when compared to ibuprofen alone.

Keywords: endometrial biopsy, lidocaine gel, ibuprofen, pain control.

Correspondence to: *Kemmanut Tueman, M.D., Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen, 40000, Thailand. E-mail: numphetty.mw@gmail.com*

Received: 2 February 2025, **Revised:** 20 November 2025, **Accepted:** 17 December 2025

การศึกษาผลของยาลิโดเคนเจลร่วมกับยาแก้อักเสบไอบูโพรเฟนเทียบกับการให้ยาแก้อักเสบไอบูโพรเฟนเพียงอย่างเดียวในการลดอาการปวด ระหว่างการเก็บเยื่อบุโพรงมดลูก: การศึกษาแบบสุ่ม

เขมณัฏฐ์ ถือมั่น, ธัญญลักษณ์ วงศ์ลือชา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของการใช้ยาลิโดเคนชนิดเจลร่วมกับการรับประทานยาแก้อักเสบไอบูโพรเฟนในการลดอาการปวด ระหว่างการเก็บเยื่อบุโพรงมดลูก*

วัสดุและวิธีการ: *เป็นการทดลองแบบสุ่มที่มีกลุ่มควบคุม โดยแบ่งกลุ่มสตรีที่มีเลือดออกจากช่องคลอดที่เข้าได้กับเกณฑ์ที่กำหนดเป็น 2 กลุ่ม คือ กลุ่มที่ได้รับยาลิโดเคนเจล (3 มล.) และกลุ่มได้รับยาหลอกชนิดเจล (3 มล.) โดยผู้เข้าร่วมวิจัยทั้งสองกลุ่มจะรับประทานยาแก้อักเสบ ไอบูโพรเฟน 400 มก.30 นาที และทาเจลบริเวณปากมดลูก 3 นาทีก่อนเริ่มทำหัตถการทั้งสองกลุ่ม และวัดระดับความเจ็บปวดโดยใช้มาตรวัด ความปวดตลอดการเก็บเยื่อบุโพรงมดลูก เริ่มตั้งแต่การใส่อุปกรณ์ถ่างช่องคลอด ขณะหนีบบริเวณปากมดลูก ในขณะทำหัตถการ และหลังจากทำ หัตถการเสร็จทันที และอีก 10 นาทีถัดมา โดยมีการติดตามอาการและอาการแสดงของภาวะไม่พึงประสงค์ตลอดการทำหัตถการ*

ผลการศึกษา: *จำนวนอาสาสมัครในงานวิจัยนี้มีทั้งสิ้น 86 คน แบ่งเป็นกลุ่มละ 43 คน เก็บข้อมูลระหว่างเดือนกรกฎาคม ถึง เดือนธันวาคม พ.ศ.2567 ข้อมูลพื้นฐานของผู้เข้าร่วม เช่นอายุ จำนวนบุตร และสถานะวัยหมดประจำเดือนไม่แตกต่างกันอย่างมีนัยสำคัญระหว่างสองกลุ่ม ระดับความเจ็บปวดระหว่างการเก็บเยื่อบุโพรงมดลูกในกลุ่มที่ได้ยาลิโดเคนเจลคู่กับยาแก้อักเสบไอบูโพรเฟนน้อยว่ากลุ่มที่ได้ยาหลอกชนิดเจล ร่วมกับยาแก้อักเสบไอบูโพรเฟนอย่างมีนัยสำคัญ (3.30 ± 2.09 และ 5.33 ± 2.01 ตามลำดับ, ส่วนต่างเฉลี่ย -2.03, 95% confidence interval (-2.91-(-1.15)), $p < 0.001$) คะแนนความเจ็บปวดในแต่ละขั้นตอนของหัตถการมีแนวโน้มต่ำกว่าในกลุ่มทดลองแต่ยังไม่พบความแตกต่างกัน ทางนัยสถิติทั้งสองกลุ่มไม่พบอาการไม่พึงประสงค์จากการใช้ยาลิโดเคนเจล และระดับความพึงพอใจของผู้ป่วยอยู่ในเกณฑ์ดี*

สรุป: *การใช้ลิโดเคนเจลร้อยละ 2 ทาบริเวณปากมดลูก ร่วมกับไอบูโพรเฟนสามารถลดความเจ็บปวดระหว่างการเก็บเยื่อบุโพรงมดลูกได้อย่างมีประสิทธิผล เมื่อเทียบกับการใช้ไอบูโพรเฟนอย่างเดียว*

คำสำคัญ: *การเก็บเยื่อบุโพรงมดลูก, ลิโดเคนเจล, ไอบูโพรเฟน, การลดความเจ็บปวด*

Introduction

Abnormal uterine bleeding (AUB) is characterized by irregularity, excessive volume, altered frequency, or prolonged duration, occurring in the absence of pregnancy[1]. The etiologies of abnormal uterine bleeding are categorized by International Federation of Gynecology and Obstetrics and American College of Obstetricians and Gynecologists using the PALM-COEIN acronym, with endometrial cancer included among them[2]. The prevalence of endometrial cancer among premenopausal women with AUB was 10.5%[3]. Although one study found that only a subset of premenopausal women with AUB—those with obesity, tamoxifen use, or endometrial thickness greater than 10 mm—had a significantly increased risk for endometrial hyperplasia or carcinoma, with the risk markedly increased when more than one factor was present, this study had a low endometrial hyperplasia/endometrial cancer prevalence[4]. Thus, if they indicated an endometrial biopsy[5], they also required tissue to exclude malignancy.

The causes of abnormal uterine bleeding can be found using a variety of techniques, including endometrial biopsy and ultrasound, particularly transvaginal ultrasound, which is helpful for postmenopausal women. Endometrial biopsy plays a primary role in determining carcinoma, premalignant lesions, and other pathology-related bleeding. The endometrial biopsy can be performed using various office aspirators, hysteroscopy (either in-office or inpatient), or by fractional curettage, but currently the first line of treatment is an office endometrial biopsy[5].

Overall, high accuracy is achieved for diagnosing endometrial cancer when a sufficient sample is obtained using an endometrial biopsy, which has a sensitivity of 70.9% and a specificity of 97.2%[6]. One study found that endometrial biopsy had more sensitivity than fractional curettage for detecting high-grade malignancy, at 91.6% and 73.6%[3], respectively. And it has numerous advantages, including the fact that it can be performed as an outpatient procedure and rarely requires general anesthesia or intravenous sedation[7].

Endometrial biopsy is performed with endometrial suction devices, which are divided into low-pressure and high-pressure devices. In Khon Kaen Hospital, we have used the MedGyn Endosampler, a low-pressure device with a 3 mm curette and a 10-cc syringe, to reduce patients' discomfort. However, it can still cause moderate to severe pain during an endometrial biopsy, and pain is the most significant obstacle to the successful completion of the procedure[7].

The mechanism of pain during endometrial biopsy comes from two pathways: the first one from uterine cramping caused by inflammatory cytokines such as prostaglandins, and the second one from stimulation of the uterovaginal plexus, which supplies the lower part of the uterus and vagina. The cervix is the transitional zone between them; therefore, it has the most abundant nerve supply[8-12].

Several recent studies evaluated pain management during endometrial biopsy, including paracervical nerve block, non-steroidal anti-inflammatory drugs (NSAIDs), intrauterine lidocaine, and topical anesthetics such as lidocaine spray or gel applied to cervical areas[7]. However, a standard guideline for pain reduction during endometrial biopsy is still lacking, and the results are inconclusive.

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are nonselective, reversible cyclooxygenase inhibitors, so they can inhibit prostaglandin synthesis. The onset of action of ibuprofen is 30–60 minutes, and the duration of analgesia is about 6–8 hours. Several studies had studied NSAIDs for relief of pain during the endometrial biopsy, but the results were inconclusive[8, 13].

A topical anesthetic agent like 2% lidocaine gel inhibits sodium influx into the cell membrane, thereby blocking the action potential of the peripheral nerve fibers so that pain can be reduced. The onset of action is short, as it begins after only about 3–5 minutes. Several studies have studied the analgesic effect of 2% lidocaine gel in endometrial biopsy [14-16], but the results have been inconclusive.

From the findings above, only one mechanism cannot reduce pain during endometrial biopsy. This research aimed to study the effect of 2% lidocaine gel in conjunction with ibuprofen for pain relief during endometrial biopsy.

Materials and Methods

From July to December 2024, this study was conducted as a double-blind, randomized, prospective, placebo-controlled trial. The participants were women who visited the Gynecology Outpatient Clinic at Khon Kaen Hospital in Khon Kaen, Thailand. The study has been registered at http://www.thaiclinicaltrials.gov (TCTR20240620003) in accordance with the standards established by the International Committee of Medical Journal Editors and the World Health Organization and has received approval from the Khon Kaen Hospital Institutional Review Board for Human Research (reference number: KEF67009).

The inclusion criteria were women ≥ 18 years old who had indicated endometrial biopsy: AUB in women aged 35 years or older, or women age < 35 years old with risk factors including a history of unopposed estrogen exposure, failed medical management, or persistent AUB; and other indications including AUB in women taking tamoxifen or postmenopausal bleeding. The exclusion criteria were a history of lidocaine allergy, previous history of NSAIDs allergy, history of gastric ulcer, gastritis or gastrointestinal bleeding, asthma, uncontrolled hypertension, bleeding disorders, kidney disease, liver disease, glucose-6-phosphate dehydrogenase deficiency, cardiac arrhythmias, coronary heart disease, uterine anomaly, or massive vaginal bleeding, receiving misoprostol for cervical dilation, cervical stenosis, ongoing vaginal, cervix or pelvic infection, combination with endocervical biopsy, inability to pass an instrument into the endometrial cavity, inability to provide consent or participate in postoperative evaluation due to dementia, cognitive impairment or language barrier, and inability to use the visual analogue scale (VAS). Informed consent was obtained from all participants before conducting the procedure.

Participants were randomly assigned to one of two groups: 2% lidocaine gel with ibuprofen (intervention group) or placebo gel with ibuprofen (control group), by a computer-generated random number sequence using a block of four. A pharmacist, who was not involved in the study, prepared the study medications under sterile conditions. The 2% lidocaine gel and the placebo gel (a water-based hydroxyethyl-cellulose gel [Q-C, I.T.O. Chemical (1979) LTD.] with other excipients per manufacturer) were packaged in identical 3 mL syringes. The procedures were performed by trained gynecology residents or attending gynecologists from the Obstetrics and Gynecology Department at Khon Kaen Hospital. Participants were instructed to rate their pain level on a 10-cm VAS. Pain scores were recorded by drawing a line at each step of the procedure and collected by the first nursing assistant, who was not involved in performing the procedure or in the randomization process.

Before the procedure, all the participants received an identical protocol, which included a pelvic examination and a pelvic ultrasound performed by a gynecologist to determine endometrial thickness; those who met the eligibility criteria were randomly assigned. Allocation concealment was maintained by using seals and opaque envelopes. Patients, operators, and pain recorders were all blinded.

The opaque envelopes were opened by the second nursing assistant, who was not involved in

outcome assessment. The envelopes contained the unnamed solution (either 2% lidocaine gel or placebo gel), sealed in an opaque medication envelope, along with ibuprofen.

All participants in both groups received 400 mg of oral ibuprofen 30 minutes before the procedure. Endometrial biopsy was performed using a MedGyn Endosample, with a semi-rigid cannula with a 3 mm diameter and a 10-cc syringe as the catheter device. Thirty minutes later, participants were placed in the lithotomy position for the procedure. The speculum was placed into the vagina to identify the cervix; the pain score (P0) was recorded at this time as the baseline pain score. The vagina and cervix were sterilized with a povidone-iodine solution.

Participants in the intervention group received 3 mL of 2% lidocaine gel applied to the anterior and posterior cervical surfaces using a wooden Ayre spatula. In comparison, those in the control group received 3 mL of placebo gel applied in the same manner. Applications were performed by gynecology residents or attending staff who were not otherwise involved in the study. After waiting three minutes for the onset of the analgesic effects, the anterior lip of the cervix was grasped with the tenaculum to track the uterus, and the pain score was assessed using the VAS at this time point (P1). The uterine sound was inserted into the uterine cavity to record the depth of the uterus, followed by insertion of the MedGyn endosampler. An endometrial biopsy was done by a corkscrew twisting technique and aspiration curettage; the pain score was assessed using the VAS during endometrial biopsy (P2). After the removal of all equipment, the pain score was evaluated using the VAS immediately (P3). The participants' vital signs, as well as the adverse effects associated with lidocaine gel, such as palpitation, hypotension, dyspnea, drowsiness, and signs of uterine perforation such as severe pelvic pain, were monitored until ten minutes after the procedure, and the pain score was assessed again with the VAS (P4).

All primary and secondary outcomes were recorded. The primary outcome was the pain score during endometrial biopsy (P2). The secondary outcomes were the pain score during speculum insertion (P0), during the grasping of the cervix with the tenaculum (P1), immediately after the removal of all equipment (P3), and at ten minutes after the procedure (P4), as well as the satisfaction score of the patients with the pain, the satisfaction score of the physicians with the smoothness, histological findings, additional anesthesia, and the side effects of lidocaine gel.

The study was based on a pilot study involving 30 participants; each group consisted of 15 women. The mean pain score during endometrial biopsy in the intervention group was 3.36 with a standard deviation (SD) of 2.05, while in the control group the mean pain score during endometrial biopsy was 4.86 with a SD of 1.99. With a power of 90%, a significance level of 0.05, and a dropout rate of 10%, the sample size was calculated, and the study required a total population of 86 participants, with 43 in each group. Randomization was performed using a computer-generated random number sequence, using a block of four.

The data were analyzed using SPSS version 18 based on an intention-to-treat analysis. Continuous data were analyzed using the student's t-test for normally distributed data or the Mann-Whitney U test for data that was not normally distributed and were presented as descriptive statistics (mean ± SD or median ± interquartile range, as appropriate). Categorical data were analyzed by the chi-square test or Fisher's exact test if the expected count was less than five and presented as count number and percentage (n, %). The difference in pain scores between the two groups was compared using analysis of longitudinal data (linear mixed-effects model). Statistical significance was determined as a p value less than 0.05.

Results

Between July and December 2024, all 86 eligible women had indications for an endometrial biopsy; no one was excluded. The 86 cases were randomly assigned: 43 to the 2% lidocaine gel with ibuprofen group (intervention group) and 43 to the placebo gel with ibuprofen group (control group). There were no dropouts (Fig. 1).

Baseline characteristics were comparable between groups (Table 1). The mean age was 47.8 ± 7.9 years in the intervention group and 46.6 ± 6.9 years in the control group. AUB was the most common indication for biopsy.

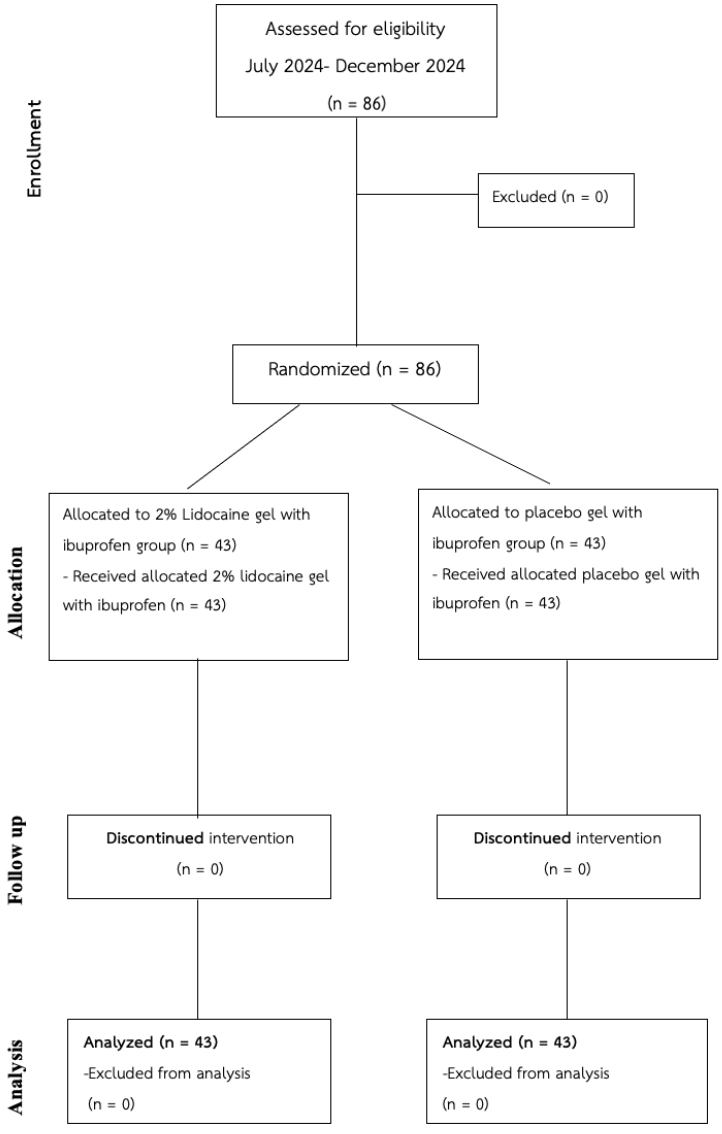

Fig. 1. Study flow.

Table 1. Baseline characteristics.

	Intervention group (n = 43)	Control group (n = 43)	p value
Age (years), mean ± SD	47.8 ± 7.9	46.6 ± 6.9	0.395[a]
BMI (kg/m^2), mean ± SD	26.4 ± 4.8	26.8 ± 5.3	0.711[a]
Underlying disease, n (%)			0.063[b]
Yes	9 (20.9)	18 (41.9)	
DM	3 (7.0)	3 (7.0)	
Hypertension	5 (11.6)	7 (16.3)	
Others			
- Hyperthyroid	2 (4.7)	1 (2.3)	
- Allergic Rhinitis	0 (0.0)	1 (2.3)	
- Autoimmune disease	1 (2.3)	3 (7.0)	
- Breast Cancer	0 (0.0)	3 (7.0)	
No	34 (79.1)	25 (58.1)	
Parity, n (%)			0.518[b]
Nulliparous	4 (9.3)	7 (16.3)	
Multiparous	39 (90.7)	36 (83.7)	
Menopausal status, n (%)			0.298[b]
Premenopausal	31 (72.1)	36 (83.7)	
Postmenopausal	12 (27.9)	7 (16.3)	
Previous vaginal delivery, n (%)			0.518[c]
Yes	39 (90.7)	36 (83.7)	
No	4 (9.3)	7 (16.3)	
Previous procedure at cervix or uterus, n (%)			0.770[b]
Yes	6 (14.0)	8 (18.6)	
- Endometrial biopsy	1 (2.3)	5 (11.6)	
- Curettage	4 (9.3)	1 (2.3)	
- Manual vacuum aspiration	1 (2.3)	1 (2.3)	
- Cervical biopsy	2 (4.6)	1 (2.3)	
- Intrauterine device insertion	0 (0.0)	1 (2.3)	
No	37 (86.0)	35 (81.4)	
Indication for endometrial sampling, n (%)			
Abnormal uterine bleeding	29 (67.4)	35 (84.1)	0.217[b]
Postmenopausal bleeding	13 (30.2)	7 (16.3)	0.202[b]
Endometrial hyperplasia	1 (2.3)	1 (2.3)	1.000[c]
Gynecologic disease, n (%)			0.666[b]
Yes	21 (48.8)	24 (55.8)	
Adenomyosis	6 (14)	11 (25.6)	
Myoma uteri	16 (37.2)	13 (30.2)	
Others			
Endometrial Hyperplasia	1 (2.3)	0 (0.0)	
Endometriosis	1 (2.3)	0 (0.0)	
No	22 (51.2)	19 (44.2)	
Endometrial thickness (cm.), median (IQR)	0.4 (0.3,0.7)	0.5 (0.3,0.8)	0.193[d]
Depth of uterus (cm.) median (IQR)	8 (7,9.5)	7 (7,9)	0.403[d]

[a] student's t-test, [b] chi-square, [c] Fisher's exact test, [d] Mann-Whitney U test
BMI: body mass index, SD: standard deviation, IQR: interquartile range

There was no difference in baseline pain scores between the intervention group (1.04 ± 1.43) and the control group (1.13 ± 1.48) (mean difference -0.09, p = 0.779) (Table 2). When compared with the baseline pain score, the mean pain score at each procedural step is presented in Table 3 and Fig. 2. During endometrial biopsy, the mean change in pain score was significantly lower in the intervention group (2.26, 95%CI 1.69-2.83) compared with the control group (4.21, 95%CI 3.64-4.78), with a mean difference of 1.95 (95%CI 1.14-2.76, p < 0.001). The intervention group consistently showed lower mean change in pain scores than the control group during tenaculum grasping, device insertion, immediately post-procedure, and ten minutes post-procedure; these differences did not reach statistical significance.

Table 2. Pain score in each step of endometrial sampling procedure.

VAS pain score, mean ± SD	Intervention group (n = 43)	Control group (n = 43)	Mean difference (95%CI)	p value
Speculum insertion (P0)	1.04 ± 1.43	1.13 ± 1.48	- 0.09 (-0.71-0.53)	0.779
Grasping tenaculum (P1)	2.16 ± 1.86	2.81 ± 2.14	- 0.65 (-1.51-0.21)	0.137
During endometrial biopsy (P2)	3.30 ± 2.09	5.33 ± 2.01	-2.03 (-2.91-(-1.15))	< 0.001
Immediately after procedure (P3)	2.21 ± 1.92	3.03 ± 2.26	- 0.83 (-1.72-0.07)	0.077
10 minutes after procedure (P4)	0.68 ± 0.95	1.13 ± 1.56	-0.46 (-1.00-0.10)	0.109

SD: standard deviation, CI: confidence interval

Table 3. Mean pain score compared with baseline

Pain score	Intervention group (n = 43) mean change (95%CI)	p value	Control group (n = 43) mean change (95%CI)	p value	Different mean change (95%CI)	p value
Grasping tenaculum (P1)	1.12 (0.55-1.69)	< 0.001	1.68 (1.11-2.25)	< 0.001	0.56 (-0.25-1.37)	0.176[e]
During endometrial biopsy (P2)	2.26 (1.69-2.83)	< 0.001	4.21 (3.64-4.78)	< 0.001	1.95 (1.14-2.76)	< 0.001[e]
Immediately after procedure (P3)	2.17 (0.60-1.74)	< 0.001	1.87 (1.30-2.45)	< 0.001	0.71 (-0.10-1.52)	0.088[e]
10 minutes after procedure (P4)	-0.36 (-0.93-0.21)	0.221	0.01 (-0.57-0.58)	0.988	0.36 (-0.45-1.17)	0.380[e]

[e] linear mixed-effects model
CI: confidence interval

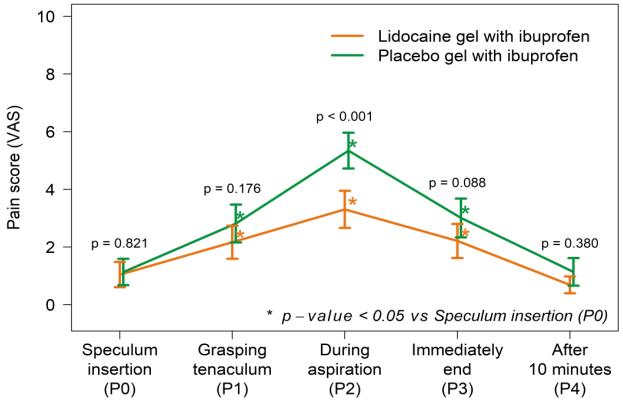

Fig. 2. A Linear mixed-effects model of mean change pain score during each step of endometrial biopsy.

VAS: visual analogue scale

No participants required additional analgesic, and no adverse effects related to lidocaine or the procedure were observed in this study. Both patient and physician satisfactions were high in both groups, with the majority reporting complete satisfaction. Histopathological findings of the endometrial samples did not differ significantly between the groups, with proliferative endometrium being the most common result (Table 4, 5).

Table 4. Other secondary outcomes.

	Intervention group (n = 43)	Control group (n = 43)	p value
Satisfaction of patient, n (%)			0.233[c]
Completely satisfied	38 (88.4)	32 (74.4)	
Satisfied	3 (7.0)	8 (18.6)	
No idea	2 (4.7)	3 (7.0)	
Dissatisfied	0 (0.0)	0 (0.0)	
Completely dissatisfied	0 (0.0)	0 (0.0)	
Satisfaction of physician, n (%)			0.228[c]
Completely satisfied	39 (90.7)	34 (79.1)	
Satisfied	4 (9.3)	8 (18.6)	
No idea	0 (0.0)	1 (2.3)	
Dissatisfied	0 (0.0)	0 (0.0)	
Completely dissatisfied	0 (0.0)	0 (0.0)	

[c] Fisher's exact test

Table 5. Histopathological findings.

	Intervention group (n = 43)	Control group (n = 43)	p value
Pathological findings, n (%)			
Proliferative endometrium	18 (41.9)	24 (55.8)	0.281b
Secretory endometrium	7 (16.3)	2 (4.7)	0.156c
Endometrial cancer	1 (2.3)	2 (4.7)	1.000c
Others			
- Acute endometritis	1 (2.3)	0 (0.0)	1.000c
- Benign endometrial tissue	3 (7.0)	3 (7.0)	1.000c
- Chronic endometritis	3 (7.0)	2 (4.7)	1.000c
- Endometrial polyp	2 (4.7)	3 (7.0)	1.000c
- Glandular and stromal breakdown	4 (9.3)	2 (4.7)	0.676c
- High grade squamous intraepithelial lesion (CIN3)	1 (2.3)	0 (0.0)	1.000c
- Inactive endometrium	0 (0.0)	2 (4.7)	0.494c
- Inaccessible simple	1 (2.3)	1 (2.3)	1.000c
- Necrotic tissue	1 (2.3)	0 (0.0)	1.000c
- Progestational effect	1 (2.3)	2 (4.7)	1.000c

[b] chi-square; [c] Fisher's exact test
CIN: cervical intraepithelial neoplasia

Discussion

Because AUB is a common condition in about 14-25% of reproductive-age women[17] and malignancy is found in around 5.3%[18], identifying the causes of AUB in high-risk women is essential. Currently, office endometrial biopsy stands as the first-line diagnostic method. However, a significant barrier to the successful execution of this procedure is pain perception[7].

The baseline pain score did not differ between the intervention group (1.04 ± 1.43) and the control group (1.13 ± 1.48). No statistically significant difference in pain scores was seen during tenaculum grasping, device insertion, immediately post-procedure, and ten minutes post-procedure between the intervention and the control groups. The highest pain scores occurred during the aspiration phase. Although the pain scores during speculum insertion, grasping of the cervix, immediately post-procedure, and ten minutes post-procedure were lower in the intervention group than in the control group, the difference was not statistically significant.

A significant reduction in pain was found only during the aspiration step. While the mean difference of approximately 2 cm on the VAS may not reach the threshold for clinical significance, the shift from moderate to mild pain may still be meaningful for patient comfort, particularly in outpatient gynecologic settings.

Evidence from previous studies supports the use of multimodal analgesia. Unlu et al[19] demonstrated that paracervical cream combined with NSAIDs or intrauterine lidocaine with NSAIDs significantly reduced pain during hysterosalpingography compared with single-agent regimens. Their findings aligned with our study, in which the combined use of topical anesthetic and NSAIDs resulted in the lowest pain scores. Similarly, Dogan et al[20] reported that intrauterine lidocaine with NSAIDs was superior to single-agent analgesia during endometrial biopsy.

Studies using single analgesic agents have yielded mixed results. Karaca et al[14] and Likkasittipan et al[16] found that cervical application of 2% lidocaine gel reduced pain during biopsy, whereas Kozman et al[15] reported no benefit. Similarly, other topical local anesthetic agent, such as lidocaine spray assessed by Sripha et al[21] and by Korsuwan et al[22], also showed inconsistent effects. NSAID-only regimens have variable outcomes: Tanprasertkul et al[8] found no significant benefit with etoricoxib, whereas Somchit et al[13] found that naproxen significantly reduced pain. A systematic review and meta-analysis by Charoenkwan et al[7] examined various methods of pain control including NSAIDs, paracervical block, intrauterine lidocaine, and topical anesthetics, but concluded that evidence remains inconclusive. Our findings support the concept that single-agent analgesia may be insufficient because pain from endometrial biopsy results from both inflammatory and cervical nerve pathways[8–12]. Combining NSAIDs, which reduce prostaglandin-mediated inflammation, with local cervical anesthesia may therefore provide more comprehensive analgesia. The pain scores of the intervention group and the control group during speculum insertion or tenaculum grasping were not statistically significantly different, consistent with the results of a prior study[14]. The pain scores immediately after the procedure (P3) and ten minutes afterward (P4) in the intervention group and the control group were not significantly different, as ibuprofen has an analgesic duration of approximately 6–8 hours and 2% lidocaine gel has a duration of local analgesia of 30 minutes to 12 hours or more.

Furthermore, no adverse events resulted from the lidocaine gel or the procedure reported, and both the patients and physicians expressed complete satisfaction with this study.

In an outpatient setting, lidocaine gel applied to the cervix in conjunction with oral ibuprofen could reduce pain during endometrial biopsy. Additionally, lidocaine gel and ibuprofen are readily available in hospitals, and preparation is uncomplicated. This should be considered by physicians for their clinical practice.

Strengths of this study included its prospective, double-blind, randomized, placebo-controlled design with adequate statistical power and no loss to follow-up. Pain was assessed at multiple time points, allowing for dynamic evaluation and appropriate repeated-measures analysis using a linear mixed-effects model. Additionally, the multimodal analgesic regimen was easy to administer and suitable for outpatient settings.

However, several limitations should be acknowledged. This was a single-center study, limiting generalizability. Pain was assessed using the VAS, a subjective but validated measure[23, 24]. Future studies should explore the lowest effective doses of lidocaine gel and ibuprofen, evaluate their use in more challenging populations such as nulliparous or postmenopausal women[25], and include multicenter trials comparing various analgesic techniques.

Conclusion

The combination of analgesic drugs with 2% lidocaine gel and ibuprofen showed effectiveness for relieving pain during endometrial biopsy compared to ibuprofen alone without any serious adverse events, supporting its use in routine clinical practice.

Acknowledgements

The authors sincerely thank the obstetrics and gynecology team, the nursing staff at Khon Kaen Hospital, and the participants for their help and cooperation.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. American College of Obstetricians and Gynecologists. Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. Obstet Gynecol 2019;133:e148–59.
2. Rindfleisch K, Falleroni J, Schrager S. Abnormal uterine bleeding in reproductive-aged women. J Clin Outcomes Manag 2015;22:83–94.
3. Khomphaiboonkij U, Jarruwale P. Accuracy of pre-operative endometrial sampling for the detection of high grade endometrial cancer. Thai J Obstet Gynaecol 2015;23:158–64.
4. Suwanwanich M. Risk assessment of endometrial hyperplasia and cancer in premenopausal women with abnormal uterine bleeding. Thai J Obstet Gynaecol 2024;32:149–55.
5. Berek JS, Hillard PJA, editors. Berek & Novak's gynecology. 16th ed. Philadelphia: Wolters Kluwer Health; 2012.
6. Gou J, Li ZY. Accuracy of endometrial biopsy by Pipelle: a systematic review and meta-analysis. Ann Oncol 2019;30:ix84–5.
7. Charoenkwan K, Nantasupha C. Methods of pain control during endometrial biopsy: a systematic review and meta-analysis of randomized controlled trials. J Obstet Gynaecol Res 2020;46:9–30.
8. Tanprasertkul C, Pongrojpow D. Efficacy of etoricoxib for pain relief during endometrial biopsy: a double blind randomized controlled trial. J Med Assoc Thai 2008;91:13–8.
9. Yaron M, Legardeur H, Barcellini B, Akhoundova F, Mathevet P. Safety and efficacy of a suction cervical stabilizer for intrauterine contraceptive device insertion: results from a randomized controlled study. Contraception 2023;123:110004.
10. Goldthwaite LM, Baldwin MK, Page J, Micks EA, Nichols MD, Edelman AB, et al. Comparison of interventions for pain control with tenaculum placement: a randomized clinical trial. Contraception 2014;89:229–33.
11. Liberty G, Gal M, Halevy-Shalem T, Michaelson-Cohen R, Galoyan N, Hyman J, et al. Lidocaine-prilocaine (EMLA) cream as analgesia for hysterosalpingography: a randomized controlled trial. Hum Reprod 2007;22:1335–9.
12. Davies A, Tom MA, Baskett F, Robert MB, Richardson E, Nagele F, et al. Analgesia for outpatient hysteroscopy: a randomized controlled trial. Fertil Steril 1997;67:1019–42.
13. Somchit W, Lertkhachonsuk AA, Vallipakorn SAO. Naproxen for pain relief during endometrial biopsy: a randomized controlled trial. J Med Assoc Thai 2015;98:631–5.
14. Karaca I, Yapca OE, Adiyeke M, Toz E, Karaca SY. Effect of cervical lidocaine gel on pain during Pipelle endometrial sampling. Eurasian J Med 2016;48:189–91.
15. Kozman E, Collins P, Howard A, Akanmu T, Gibbs A, Frazer M. The effect of intrauterine 2% lignocaine gel on pain perception during Vabra endometrial sampling: a randomized trial. BJOG 2001;108:87–90.

16. Likkasittipan N, Wiriyasirivaj B. Effect of lidocaine gel for pain relief during endometrial sampling: a randomized controlled trial. Thai J Obstet Gynaecol 2021;29:273–80.
17. Whitaker L, Critchley HO. Abnormal uterine bleeding. Best Pract Res Clin Obstet Gynaecol 2016;34:54–65.
18. Farzaneh F, Ashtiani AJ, Hashemi M, Hosseini MS, Arab M, Ashrafganjoei T, et al. Endometrial cancer in women with abnormal uterine bleeding: data mining classification methods. Caspian J Intern Med 2023;14:526–33.
19. Unlu BS, Yilmazer M, Koken G, Arioz DT, Unlu E, Baki ED, et al. Comparison of four different pain relief methods during hysterosalpingography: a randomized controlled study. Pain Res Manag 2015;20:107–11.
20. Dogan E, Celiloglu M, Sarihan E, Demir A. Anesthetic effect of intrauterine lidocaine plus naproxen sodium in endometrial biopsy. Obstet Gynecol 2004;103:347–51.
21. Sripha P, Phaliwong P. Effectiveness of lidocaine spray in reducing pain during cervical manipulation: a randomized controlled trial. Thai J Obstet Gynaecol 2018;26:190–7.
22. Korsuwan P, Wiriyasirivaj B. Lidocaine spray for pain control during office-based endometrial biopsy: a randomized placebo-controlled trial. Thai J Obstet Gynaecol 2018;26:262–9.
23. Haefeli M, Elfering A. Pain assessment. Eur Spine J 2006;15 Suppl 1:S17–24.
24. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, et al. Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage 2011;41:1073–93.
25. Visser NCM, Breijer MC, Herman MC, Bekkers RLM, Veersema S, Opmeer BC, et al. Factors attributing to the failure of endometrial sampling in women with postmenopausal bleeding. Acta Obstet Gynecol Scand 2013;92:1216–22.