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## GYNECOLOGY

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# Analgesic Effect of Lidocaine Spray during Endometrial Biopsy: A randomized controlled trial

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### ABSTRACT

**Objectives:** To investigate the effect of lidocaine spray applied on the cervical surface in pain reduction of patients undergoing endometrial biopsy using the Endosampler instrument.

**Materials and Methods:** A double-blinded, randomized controlled study was conducted in 100 women undergoing endometrial biopsy. Patients were randomly assigned to receive either lidocaine spray or placebo. Visual analog scale (VAS) was used to assess patients' pain at three points of the procedure (speculum insertion, cannula insertion and after speculum removal). The satisfaction of the procedure was evaluated by patients and doctors using five point Likert scale.

**Results:** Endometrial biopsy was successfully performed in 100 patients. The median VAS pain score during cannula insertion in the lidocaine group was 5.0 which was lower than 5.5 in the placebo group without statistical significance.

**Conclusion:** Lidocaine spray application on cervix before endometrial biopsy did not significantly reduce pain in patients who underwent this procedure.

**Keywords:** endometrial biopsy, lidocaine spray, pain score, randomized controlled trial

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## ผลของยาชาชนิดพ่นลิโดเคนในการบรรเทาความเจ็บปวดขณะทำการเก็บเยื่อโพรงมดลูก: การศึกษาแบบสุ่ม

มณีนุช ศรีมา, ชื่นกมล ชรากร, นวมลล เล็กสกุล, อาบอรุณ เลิศจรสุข

### บทคัดย่อ

**วัตถุประสงค์:** เพื่อศึกษาผลของการพ่นยาชาชนิดพ่นลิโดเคนที่ปากมดลูกในการลดความเจ็บปวดในผู้ป่วยที่เข้ารับการเก็บเยื่อโพรงมดลูกส่งตรวจด้วยเครื่องมือ Endosampler

**วัสดุและวิธีการ:** เป็นการศึกษาแบบสุ่ม โดยเปรียบเทียบกับยาหลอกในผู้ป่วยทั้งหมด 100 ราย ที่เข้ารับการเก็บเยื่อโพรงมดลูกส่งตรวจ โดยสุ่มผู้ป่วยออกเป็น 2 กลุ่ม กลุ่มหนึ่งได้รับการพ่นลิโดเคน (50 ราย) อีกกลุ่มหนึ่งได้รับยาหลอก (50 ราย) การประเมินคะแนนความเจ็บปวดทำโดยใช้ visual analog scale ใน 3 ช่วงเวลา ได้แก่ หลังใส่ speculum ขณะสอด cannula และหลังถอด speculum ความพึงพอใจต่อการทำหัตถการประเมินโดยผู้ป่วยและแพทย์ผู้ทำหัตถการโดยใช้ 5 point Likert scale

**ผลการศึกษา:** แพทย์สามารถทำหัตถการได้สำเร็จในผู้ป่วยทั้งหมด 100 ราย ค่ามัธยฐานของคะแนนความเจ็บปวดขณะสอด cannula ในกลุ่ม lidocaine คือ 5 (0-10) ซึ่งต่ำกว่าค่ามัธยฐานของคะแนนความเจ็บปวดขณะสอด cannula ในกลุ่มยาหลอก คือ 5.5 (0-10) แต่ไม่มีนัยสำคัญทางสถิติ (p value 0.78)

**สรุป:** การพ่นยาชาชนิดพ่นลิโดเคนที่ปากมดลูกก่อนการทำหัตถการเก็บเยื่อโพรงมดลูกส่งตรวจ ไม่สามารถลดความเจ็บปวดจากหัตถการดังกล่าวได้อย่างมีนัยสำคัญทางสถิติ

**คำสำคัญ:** การเก็บเยื่อโพรงมดลูก, ยาพ่นลิโดเคน, คะแนนความเจ็บปวด, การศึกษาแบบสุ่ม

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## Introduction

Endometrial biopsy is one of the most commonly performed procedures in gynecologic outpatient department. Many disorders were indicated for endometrial biopsy such as abnormal uterine bleeding, postmenopausal bleeding, anovulation, and abnormal cervical cytology<sup>(1)</sup>. Endometrial biopsy is a tool for the diagnosis of endometrial pathology with comparable sensitivity and specificity to fractional curettage<sup>(2)</sup>. In spite of its benefit, pain during the procedure was evident in previous studies. The pain score during this procedure ranged from 4.6 to 6.9 point out of 10<sup>(3-5)</sup>. Endometrial biopsy causes pain through cervical traction and dilatation as well as uterine contraction during the suction of endometrium.

Lidocaine spray is an effective local anesthesia used in gynecologic procedures such as loop electrosurgical excision procedure (LEEP)<sup>(6)</sup>, hysterosalpingography<sup>(7)</sup> and intrauterine device (IUD) insertion<sup>(8)</sup>. It is also easy to apply and non-invasive. Lidocaine spray causes a reversible blockade of impulse propagation by preventing the inward movement of sodium ions through the nerve membrane. So, it may reduce pain from cervical traction and dilatation but not from uterine contraction. Nowadays, the standard procedure of endometrial biopsy was performed without pain control. This research aimed to study the effect of cervical application of lidocaine spray on pain reduction during endometrial biopsy.

## Materials and Methods

This randomized, double-blinded, controlled trial was approved in June 2016 by the Committee on Human Rights Related to Research Involving Human Subjects of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University. Between June 2016 and June 2017, women with conditions indicated for endometrial biopsy at the gynecologic outpatient department were recruited.

The inclusion criteria were non-pregnant women who were consented for the office-endometrial biopsy. Women with contraindications for lidocaine administrations, such as hypersensitivity to lidocaine or amide type local anesthesia, cardiovascular diseases

(heart failure, arrhythmia and bradycardia), severe renal dysfunction, impaired hepatic function and a history of convulsion were excluded from the study. Additional exclusion criteria were uterine anomalies or myoma uteri that distorted the uterine cavity, cervical stenosis, acute cervicitis and pelvic inflammatory disease. Because experience and expectation affected people's pain perception<sup>(9)</sup>, women who had a prior experience with endometrial biopsy or an inability to evaluate pain by visual analog scale (VAS) were also excluded.

After the enrollment, demographic data of the participants was reviewed and analyzed according to the basic categories (e.g. age, underlying disease, number of gravidity, parity and delivery, menstrual history).

One hundred participants were randomly assigned into two groups. Group one received 4 puffs of 10% lidocaine spray (40 mg) applied on the cervix; while, group two received 4 puffs of placebo (normal saline) before endometrial biopsy. Randomization was accomplished by computer-generated block randomization. The randomized numbers were concealed in sealed opaque envelopes which would be opened by a research nurse. The spray bottles used in both groups were covered with the same stickers; consequently, they were identical. The operators, patients and pain evaluator were blinded.

Informed consent was obtained from all participants. Pain evaluation was rated by VAS using a plain 10 centimeter long line labelled on one edge with "worst pain" and another with "no pain". Participants were asked to mark the severity of pain on the line by themselves at 3 different times during the procedure: speculum insertion (VAS1), endosampler cannula insertion (VAS2) and after speculum withdrawal (VAS3). The pain evaluator measured the distance from the "no pain" side to the point which the patient marked in centimeter.

The procedure was standardized and performed by the residents and attending staff of the Department of Obstetrics and Gynaecology, Ramathibodi Hospital, Mahidol University.

After the patients were placed in lithotomy position, the operator inserted a sterile bivalve speculum and asked them to score VAS1 at once. Vagina and cervix were prepped with antiseptic solution; then, 4 puffs of

lidocaine or placebo spray were administered to the cervical surface thoroughly and left for three minutes. Three minute waiting time was the time recommended by the lidocaine spray's manufacturer. Moreover, as reported by Van der Burght M et al, 3 minutes was the duration of mean onset for lidocaine spray application on genital mucosa<sup>(10)</sup>. The cervical manipulation (with Allis or Tenaculum forceps) was optional. The Endosampler device® with a 3-mm diameter round tip cannula and a self-locking 10-ml syringe was utilized in all participants. While the inserted cannula was advanced to fundus, VAS2 was evaluated before the cannula was connected to the syringe. Endometrial tissue was aspirated systematically from fundus to the internal os throughout the cavity. The instrument and the speculum were removed and any bleeding was ceased. Afterwards, VAS 3 was acquired to represent immediate post procedural pain. The patients were observed for 10 minutes after the procedure. The participants were requested to notify doctors at any time during the procedure if there were any abnormal symptoms and the events would also be recorded. The operators and the participants were requested to complete questionnaires about the satisfaction after the procedure, using 5-point Likert scale.

Sample size calculation was based on the

endometrial biopsy-related pain score measured by a 10-cm VAS. Reference values (mean, standard deviation (SD)) were taken from the previous study conducted by Aksoy H, et al<sup>(11)</sup>. Assuming a 1-cm difference in VAS between the groups as a smallest effect with clinical importance, at least 44 subjects were required in each study group to detect a clinically significant difference between the two groups on a 10-cm VAS scale, with a power of 80% to verify the primary hypothesis and a type I error of 0.05. With the expected 10% dropout rate, we planned to recruit a total of 100 women (up to 50 subjects per study group).

Statistical analysis was performed with STATA software version 14.2. A comparison of the outcomes between the groups which were continuous variables was made by using the Mann-Whitney U test (in a non-parametric distribution) or Student's t test. For categorical variables, the Pearson chi square or Fisher's exact test, as appropriate, was used for comparison. P value less than 0.05 was considered statistically significant.

## Result

One hundred participants were recruited in this study (50 in each study group). (Fig. 1.) All of the participants successfully underwent the procedure.

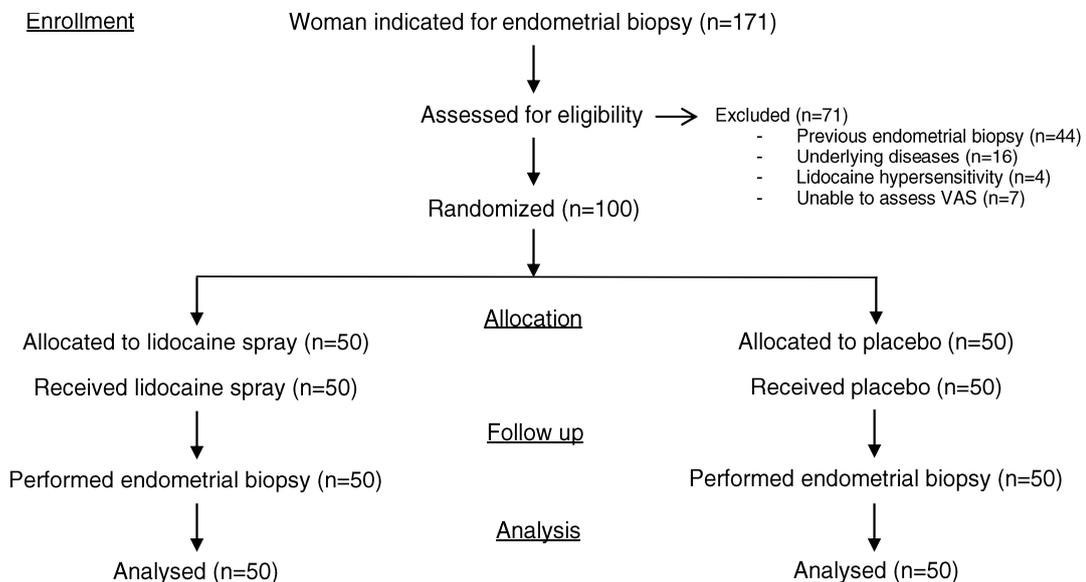


Fig. 1. Study flowchart.

Demographic characteristics of the patients were not statistically significant different between two groups. The most common indication for endometrial biopsy was menometrorrhagia. The use of instruments for cervical manipulation was comparable between the two groups. The mean operative time (from cannula insertion to removal of the speculum) was 3 minutes. No participant demonstrated any adverse reaction or complication in this study. The demographic data and baseline characteristics were demonstrated in Table. 1.

Table 2 demonstrates the VAS at 3 points of the procedure in the lidocaine and the placebo group. The median baseline pain score assessed by VAS

(speculum insertion) was 0.5 (0-8) in the treatment group and 0.3 (0-6.2) in the placebo group. The median pain score during cannula insertion was 5.0 (0-10) in the treatment group and 5.5 (0-10) in the control group (p = 0.78). The pain score in the lidocaine group was lower than the placebo group without statistical significance. The median pain score after the procedure (speculum withdrawal) was 2.9 (0-9.7) in the treatment group and 2.3 (0-10) in the control group. The mean patient satisfaction score was 4 ± 0.89 in the treatment group and 4 ± 0.71 in the control group. The mean satisfaction score of the doctors was 4 ± 0.77 in the treatment group and 4 ± 0.76 in the control group (Table 3).

**Table 1.** Demographic data.

Demographic data	Lidocaine N=50	Placebo N=50	p value
Age (years) (mean±SD)	49.32 ± 9.89	47.42 ± 10.67	0.35
Parity (median (range))	2 (0-4)	1 (0-3)	0.14
Nulliparity	12 (24)	18 (36)	0.27
Parous	38 (76)	32 (64)	
Previous vaginal delivery	33 (66)	26 (52)	0.22
Menopausal status			
Menopause	16 (32)	13 (26)	0.66
Premenopause	34 (68)	37 (74)	
Endometrial thickness (cms) (median (range))	0.96 (0.36-3)	1 (0.41-2.1)	0.80
Cervical manipulation			
No	29 (58)	35 (70)	0.29
Yes	21 (42)	15 (30)	
Cannulation attempt (median (range))	1 (1-5)	1 (1-5)	0.24
Operation time (min) (median (range))	3 (0.5-15)	3 (0.5-20)	0.39
Operator			
Residents	41 (82)	39 (78)	0.80
Attending staff	9 (18)	11 (22)	
Indication for endometrial biopsy			
Postmenopausal bleeding	15 (30)	12 (24)	0.24
Menometrorrhagia	35 (70)	35 (70)	
Others	0 (0)	3 (6)	

**Table 2.** Pain score at different stage of procedure.

Pain score* (0-10)	Lidocaine group N=50	Placebo group N=50	p value
VAS before insert cannula	0.5 (0-8)	0.3 (0-6.2)	0.44
VAS insert cannula	5.0 (0-10)	5.5 (0-10)	0.78
VAS after procedure	2.9 (0-9.7)	2.3 (0-10)	0.83
VAS difference (Insert cannula and before insertion)	3.5 (0-10)	3.6 (0-10)	0.73

\* data are presented in median (range) (cm.)

**Table 3.** Satisfaction of patients and doctors.

Satisfaction score* (0-5)	Lidocaine group N=50	Placebo group N=50	p value
Patient	4 ± 0.89	4 ± 0.71	0.80
Doctor	4 ± 0.77	4 ± 0.76	0.43

**Table 4.** Factors associated with pain perception and pain score during the procedure (VAS2).

Factors	N (%)		VAS2 (median (range))		p value
	Lidocaine group N=50	Placebo group N=50	Lidocaine group N=50	Placebo group N=50	
Parity					0.57
Nulliparity	12 (24)	18 (36)	6.6 (0.9-10)	5.5 (0-10)	
Parous	38 (76)	32 (64)	3.8 (0-10)	5.9 (0-9.9)	
Previous vaginal delivery					0.04
Yes	33 (66)	26 (52)	3.5 (0-10)	4.4 (0-9.8)	
No	17 (34)	24 (48)	6.2 (0.9-10)	6.5 (0-10)	
Menopausal status					0.24
Premenopause	34 (68)	37 (74)	3.6 (0.4-10)	5.5 (0-10)	
Menopause	16 (32)	13 (26)	6.0 (0-9.5)	6.5(0.2-9.5)	
Cervix manipulation					0.24
Yes	21 (42)	15 (30)	6.8 (0.9-10)	3.6 (0-9.8)	
No	29 (58)	35 (70)	3.8 (0.4-10)	5.6 (0-10)	
Operator					0.24
Residents	41 (82)	39 (78)	3.9 (0-10)	5.5 (0-9.9)	
Attending staff	9 (18)	11 (22)	6.8 (1.2-10)	6.6 (0.3-10)	

None of the patients requested for the analgesia during the 10 minutes observation period after the procedure and no analgesia was given. Factors relating to pain during endometrial biopsy were demonstrated in Table 4. Operator, cervical manipulation and patient's parity did not significantly affect pain score during the procedure. The history of vaginal delivery decreased the procedural pain. From demographic data, the number of nulliparous was not significantly different between the lidocaine and placebo groups.

## Discussion

Endometrial biopsy is a procedure frequently performed in the gynecologic outpatient department for the diagnosis of abnormal uterine bleeding. Even though the procedure is convenient to perform without the need for hospitalization or anesthesia, the pain during the operation is unavoidable. The mean pain score measured by VAS in the previous studies of endometrial sampling without pain control ranged from 4.6-6.9 cm<sup>(3-5)</sup>. Various methods of pain management have been studied, such as premedication with misoprostol<sup>(12)</sup>, non-steroidal anti-inflammatory drugs (NSAIDs)<sup>(13)</sup>, and paracervical nerve block<sup>(14)</sup>. The adverse effects from those analgesia were also focused. Misoprostol ingestion prior to the endometrial biopsy did not reduce discomfort and was associated with more side effects of nausea, diarrhea, cramping, abdominal pain, and vaginal bleeding<sup>(12)</sup>. Naproxen significantly decreased pain score during the endometrial biopsy but the adverse effect of nausea was noticed in the study of Somchit et al<sup>(13)</sup>. The paracervical nerve block reduced pain originating from cervical dilatation in the endometrial biopsy but provoked the adverse effect of vasovagal syncope<sup>(14)</sup>.

The spray form of lidocaine is the effective method for pain control in gynecologic procedure such as IUD insertion<sup>(8)</sup>, hysterosalpingography<sup>(7)</sup>, LEEP<sup>(6)</sup> and endometrial biopsy<sup>(11)</sup>. In the current study, the authors conducted a randomized controlled trial to study the effect of topical lidocaine spray to reduce pain during endometrial biopsy using Endosampler

instrument.

The result from the present study proclaimed no statistically significant difference in the VAS pain score, 5.0 in the lidocaine group, comparing with 5.5 in the placebo group. However, the pain scores in our study were more than those reported in Aksoy's study<sup>(11)</sup>, 3.51 in the lidocaine group and 5.11 in the placebo group. This discrepancy may be a consequence of the difference in population. There was a higher number of nulliparous women comprised in this study, 30% as compared to 3.3% in Aksoy's. The other possibility was the dissimilarity in the instruments. We used Endosampler; whilst, the previous study used Karman cannula. Women's pain perception was additionally affected by their cultures, experiences and tolerances which were difficult to standardize.

The strength of the present study was a randomized study conducted with concealment. The operators, patients and pain assessor were blinded regarding the group allocation. The technique of endometrial biopsy was standardized among operators. The protocol of pain evaluation was comprehensively described. The patient evaluated pain by themselves concurrently at the time of the pain perception which helped eliminate the recall bias of data. Furthermore, no adverse effect was reported in both study groups.

The limitation of the present study was a confined sample size to show significantly different pain between two groups. Besides, the procedural pain arising in the uterine cavity and from the contraction may not be managed by the application of lidocaine spray on the cervix. From the advantage of simplicity and safety of the lidocaine spray application, it might still be considered as an adjuvant pain control with other methods. Further studies with a higher number of participants and different dosage of lidocaine spray are needed to establish the potential effect of the lidocaine spray for pain control during endometrial biopsy.

## Conclusion

Lidocaine spray application on the cervix before endometrial biopsy did not significantly reduce pain in

patients who underwent this procedure.

## Potential conflicts of interest

The authors declare no conflict of interest.

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