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## GYNAECOLOGY

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# Effect of Lidocaine Gel for Pain Relief during Endometrial Sampling: A double-blinded randomized controlled trial

Napat Likkasittipan, M.D.\*,  
Budsaba Wiriyasirivaj, M.D.\*

\* Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

### ABSTRACT

**Objectives:** To investigate the effect of 2% lidocaine gel for pain relief during endometrial sampling procedures compared with placebo.

**Materials and Methods:** This double-blinded randomized, prospective, placebo-controlled study was performed at an out-patient gynecology clinic, tertiary teaching hospital, Bangkok, Thailand from September 2018 to April 2019. Sixty women who were indicated for endometrial tissue sampling were randomly assigned to either lidocaine group, which received 2% lidocaine gel 1 milliliter applied at cervical os and 2 milliliters pushed into cervical canal 3 minutes before the procedure, or placebo group which received placebo gel administered in the same manner. Pain scores, using 10 centimeter-visual analog scale, were assessed at baseline, when inserting the speculum, during Wallach Endocell® insertion, during endometrial aspiration, immediately after aspiration, and 10 minutes after procedure. Adverse symptoms and signs were also observed.

**Results:** Mean pain score during endometrial aspiration was significantly lower in the lidocaine group (n = 29) compared with placebo (n = 29) ( $2.92 \pm 2.40$  and  $4.47 \pm 2.06$ , respectively;  $p = 0.011$ ). Mean pain score at baseline, during Wallach Endocell® insertion, immediately after aspiration, and 10 minutes after procedure were not statistically significantly different between groups ( $1.52 \pm 2.25$ ,  $3.13 \pm 2.81$ ,  $1.89 \pm 2.23$ , and  $0.62 \pm 1.32$  in the lidocaine group, and  $1.69 \pm 2.07$ ,  $4.20 \pm 2.35$ ,  $2.95 \pm 2.33$ , and  $0.93 \pm 1.36$  in the placebo group, respectively ( $p > 0.05$ )). There were no adverse symptoms and signs observed.

**Conclusion:** The 2% lidocaine gel applied at the cervical surface and internal cervical canal was effective for pain relief during endometrial sampling.

**Keywords:** endometrial sampling, endometrial biopsy, lidocaine gel, pain control.

**Correspondence to:** Budsaba Wiriyasirivaj, M.D., Department of Obstetrics and Gynaecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, 681 Samsen Road, Dusit, Bangkok, 10300, Thailand. Email: wboosaba@yahoo.com

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# ผลของยา利多เคนเจลในการลดความเจ็บปวดระหว่างการเก็บเยื่อโพรงมดลูก: การศึกษาแบบสุ่มปกปิดสองทางมีกลุ่มควบคุม

ณพัชร ลิขสิทธิ์พันธุ์, บุษบา วิริยะศิริเวช

## บทคัดย่อ

**วัตถุประสงค์:** เพื่อศึกษาประสิทธิผลของ利多เคนเจลความเข้มข้น 2% ในการลดระดับความเจ็บปวดเปรียบเทียบกับยาหลอกในการเก็บเยื่อโพรงมดลูก

**วัสดุและวิธีการ:** การศึกษาแบบสุ่มปกปิดสองทางไปข้างหน้า มีกลุ่มควบคุม ทำการศึกษาตั้งแต่เดือนกันยายน พ.ศ. 2561 ถึงเดือนเมษายน พ.ศ. 2562 จำนวน 60 คน ซึ่งมีข้อบ่งชี้ในการเก็บเยื่อโพรงมดลูก ทำการแยกกลุ่มผู้ป่วยออกเป็นสองกลุ่มแบบสุ่ม โดยกลุ่มที่ 1 จะได้รับ利多เคนเจลความเข้มข้น 2% จำนวน 30 คน ส่วนกลุ่มที่ 2 จะได้รับยาหลอกจำนวน 30 คน เช่นกัน ผู้ป่วยจะได้รับการวัดระดับความเจ็บปวดโดยใช้เครื่องมือชื่อ visual analog scale โดยทำการวัดระดับความเจ็บปวดพื้นฐานขณะใส่เครื่องมือต่างช่องคลอด จากนั้นจึงทำการฉีดเจ็ลป้ายบริเวณปากมดลูกส่วนหน้าปริมาตร 1 มิลลิลิตร และในช่องปากมดลูกปริมาตร 2 มิลลิลิตร รอเวลา 3 นาที วัดระดับความเจ็บปวดขณะสอดเครื่องมือ Wallach Endocell® ขณะดูดเก็บเยื่อโพรงมดลูก ขณะถอยเครื่องมือออกพ้นปากมดลูกทันที และหลังจากการทำหัตถการ 10 นาที โดยเฝ้าระวังอาการและอาการแสดงของภาวะไม่พึงประสงค์ตลอดการทำหัตถการ

**ผลการศึกษา:** ระดับความเจ็บปวดขณะดูดเก็บเยื่อโพรงมดลูกในกลุ่มที่ได้รับ利多เคนเจลความเข้มข้น 2% ( $n = 29$ ) น้อยกว่ากลุ่มที่ได้รับยาหลอก ( $n = 29$ ) อย่างมีนัยสำคัญ ( $2.92 \pm 2.40$  และ  $4.47 \pm 2.06$  ตามลำดับ,  $p = 0.011$ ) ระดับความเจ็บปวดไม่มีความแตกต่างกันในขณะใส่เครื่องมือต่างปากมดลูก ขณะสอดเครื่องมือ Wallach Endocell® ขณะถอยเครื่องมือออกพ้นปากมดลูกทันที และหลังจากการทำหัตถการ 10 นาที ( $1.52 \pm 2.25$ ,  $3.13 \pm 2.81$ ,  $1.89 \pm 2.23$ , และ  $0.62 \pm 1.32$  ในกลุ่มที่ได้รับยา利多เคนเจล และ  $1.69 \pm 2.07$ ,  $4.20 \pm 2.35$ ,  $2.95 \pm 2.33$ , และ  $0.93 \pm 1.36$  ในกลุ่มที่ได้รับยาหลอกตามลำดับ,  $p > 0.05$ ) ไม่พบอาการและอาการแสดงของภาวะไม่พึงประสงค์ในการทำวิจัย

**สรุป:** การใช้利多เคนเจลความเข้มข้น 2% ป้ายบริเวณผิวปากมดลูกและในโพรงปากมดลูกสามารถลดความเจ็บปวดขณะทำการเก็บเยื่อโพรงมดลูกได้

**คำสำคัญ:** การเก็บเยื่อโพรงมดลูก, ลิดเคนเจล, การลดความเจ็บปวด

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## Introduction

Endometrial sampling (ES) is a common procedure for pathological evaluation of many gynecological disorders, including abnormal uterine bleeding, postmenopausal bleeding, abnormal cytology and infertility<sup>(1)</sup>. The majority of pain or discomfort during the procedure may arise during dilatation of the cervix for insertion of the catheter device and during endometrial aspiration<sup>(2)</sup>. Although flexible devices cause less pain than conventional methods of ES, nearly half of the patients experience moderate to severe pain during the procedure<sup>(3)</sup>.

There have been several studies about pain control during ES, such as taking non-steroidal anti-inflammatory drugs (NSAIDs) orally 30 minutes before the procedure<sup>(4)</sup>, or paracervical block with lidocaine<sup>5</sup>. The new approach for pain relief using a topical anesthetic agent on the cervical surface, such as lidocaine spray<sup>6,7</sup> or lidocaine gel before the procedure, has been studied<sup>(8,9)</sup>; however, the results are inconclusive and currently there is no standard guideline for pain control during ES.

In 2016, a randomized placebo-controlled trial to investigate the efficacy of 10% lidocaine spray on pain relief during ES, found that 5 puffs of lidocaine spray on cervical surface significantly decreased pain score during the procedure<sup>(7)</sup>. However, the disadvantage is the cost of lidocaine spray, which is twice that of the gel, and the need for spray nozzle sterilization before each used.

2% lidocaine gel is another form of topical anesthetic agent that is a sterile aqueous product with rapid onset and long duration (30 minutes), enough for pain control during ES and cheaper than the spray, thus it is considered a more feasible option. In 2013, a randomized placebo-controlled trial, found that cervical application of 2% lidocaine gel did not significantly reduce pain or anxiety during ES<sup>(8)</sup>, whereas, another randomized placebo-control trial in 2016, found that cervical lidocaine gel significantly decreased the pain score during ES<sup>(9)</sup>.

Therefore, this study aimed to investigate the effect of 2% lidocaine gel on cervical surface for pain relief during ES compared with placebo.

## Materials and Methods

This double-blinded randomized, prospective, placebo-controlled study was performed in a tertiary teaching hospital, Bangkok, Thailand, between September 2018 and April 2019. The study was approved by Vajira International Review Board (COA055/61) and registered at <http://www.thaiclinicaltrials.gov> (TCTR20181219004) according to the standards set by the International Committee of Medical Journal Editors and the World Health Organization. The sample size calculation was determined based on result of the study by Karaca et al<sup>(9)</sup>. With the power of 80% and ensuring the inclusion of at least 30% of nulliparous women plus 10% for incomplete data, sample sizes of 30 cases per group were needed. The randomization was performed by computer generated random number. The study population comprised of women who had an indication for ES, were aged more than 18 years old, had no previous lidocaine allergy, and who gave informed consent. Exclusion criteria were: uterine anomaly, massive vaginal bleeding, taken analgesic drugs before the procedure, received misoprostol for cervical dilatation, cardiac arrhythmia, coronary heart disease, severe hepatic disease and unable to use visual analog scale (VAS). All study subjects were given the careful information and gave an opportunity for the questions then signed informed consents. Participants' clinical data such as age, weight, height, underlying disease, parity, and indication for ES, were recorded.

The catheter device for procedure is a Wallach Endocell<sup>®</sup>, soft and flexible endometrial suction curettage device. It has 3.4 millimeters outer diameter, 3.1 millimeters inner diameter, and 24.3 centimeters in length.

A total of 60 women were included in this study. Participants were randomized into two groups. 2% lidocaine and placebo gel were prepared identically in a 3 ml syringe with sterile technique by a research assistant who was blind to the assignment. The operators who performed the procedure were residents of Obstetrics and Gynecology department, Faculty of Medicine, Vajira Hospital, who had the same experiences.

Patients, operators and pain recorders were blind to the nature of gel. The pain score was assessed using 10-cm VAS. The operators asked subjects for pain scores in each step and the research assistances recorded the pain scores.

The ES was performed while the participant was in lithotomy position. A speculum was inserted into the vagina to identify the cervix, and baseline pain score was assessed at this time point (P0). Vagina and cervix were cleaned with povidone-iodine solution. Participants randomized to group 1 received 2% lidocaine gel, 1 ml applied on anterior cervical surface and 2 ml pushed into cervical canal, while those randomized to group 2 received placebo gel in the same manner. After waiting 3 minutes for analgesic action, the Wallach Endocell® was inserted into the cervical canal and VAS was assessed (P1). If the equipment could not pass through the cervix, the tenaculum was used to grasp the anterior lip of the cervix to tract the uterus. After passing the Wallach Endocell® into the uterine cavity, ES was performed using corkscrew twisting motion and aspiration curettage. The procedure was repeated 3 times to ensure tissue adequacy. VAS was assessed during aspiration curettage (P2). The equipment was then removed from the uterine cavity and pain was assessed using the VAS immediately after removal (P3).

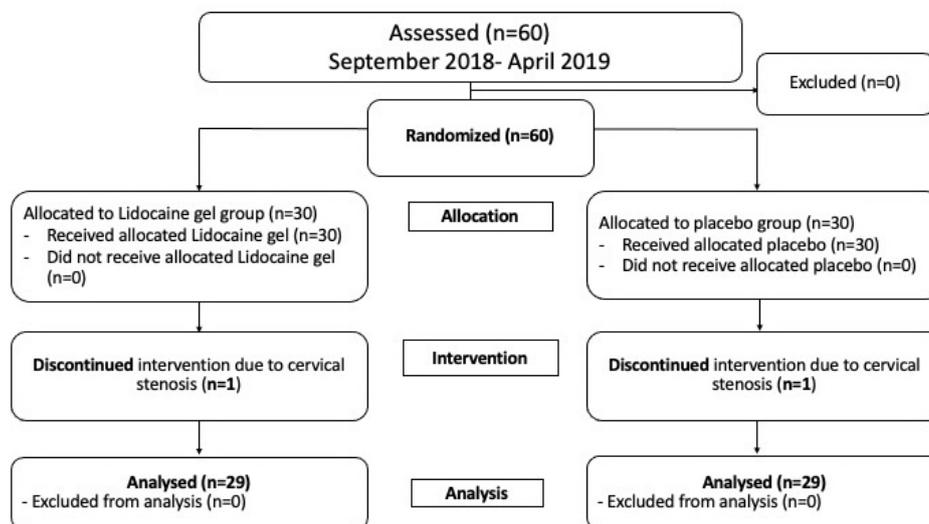
Pain score was assessed again with the VAS at 10 minutes after the procedure (P4). The adverse effects related to lidocaine gel and the procedure, such as sweating, syncope, nausea, bradycardia, hypotension, and vasovagal symptoms were observed.

The data were analyzed using STATA 14 statistical software. Continuous variables were analyzed by student's t-tests and presented as descriptive statistics (mean ± standard deviation). Multilevel linear regression was used to compare overall pain score between groups. Statistical significance was determined as a p value < 0.05.

## Results

A total of 60 patients were enrolled and randomly assigned into two groups of 30 cases. One participant in each group was excluded due to failure to pass the device into the uterine cavity because of cervical stenosis; thus, there were 29 participants in each group for the analysis (Fig. 1).

Table 1 shows clinical characteristics of participants in each group. Mean age, body mass index, parity, previous vaginal delivery, menopausal status, indication for endometrial sampling, tenaculum use and tissue adequacy were not significantly different between groups.



**Fig. 1.** The flowchart of participants during the study period.

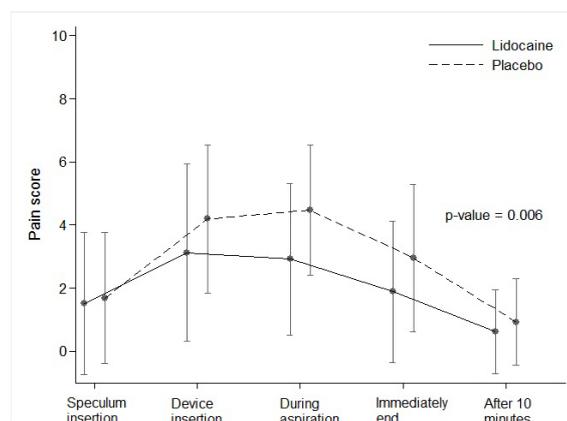
**Table 1.** Clinical characteristics of the participants in each group.

Characteristics	Lidocaine group (n=29)	Placebo group (n=29)	p value
Age (years)	51.90 ± 11.62	54.14 ± 13.71	0.505
Weight (kg)	64.06 ± 11.27	67.62 ± 13.32	0.161
Height (cm)	156.14 ± 5.20	157.83 ± 6.21	0.266
BMI (kg/m <sup>2</sup> )	26.24 ± 4.14	27.14 ± 5.11	0.464
Parity			0.269
- Nulliparous	8 (27.6%)	12 (41.4%)	
- Multiparous	21 (72.4%)	17 (58.6%)	
Previous vaginal delivery			0.791
- No history	12 (41.4%)	13 (44.8%)	
- History	17 (58.6%)	16 (55.2%)	
Menopause	10 (34.5%)	15 (51.7%)	0.185
Indication for endometrial sampling			
- Abnormal uterine bleeding age ≥ 35 years	18 (62.1%)	17 (58.6%)	
- Postmenopausal bleeding, ET ≥ 4 mm	9 (31.0%)	12 (41.4%)	
- Vaginal bleeding with tamoxifen taking	2 (6.9%)	0 (0.0%)	
Tenaculum used	12 (41.4%)	10 (34.5%)	0.588
Pathological adequacy	27 (93.1%)	24 (82.8%)	0.423

Data were presented as mean ± standard deviation or n (%), ET: endometrial thickness

Fig. 2 and Table 2 show pain scores at each time point of ES. The baseline pain score was not different between lidocaine group (1.52 ± 2.25) and placebo group (1.69 ± 2.07) (p = 0.762). Lidocaine gel application significantly lowered the overall pain score of ES compared with placebo (coefficient -0.41) (p = 0.006, linear mixed model). Mean pain score during aspiration curettage was significantly

less in the lidocaine group (2.92 ± 2.40) than in the placebo group (4.47 ± 2.06) (p = 0.011). There was no significant difference of pain score between lidocaine group and placebo group during device insertion (3.13 ± 2.81 vs 4.20 ± 2.35, p = 0.122), immediately after the procedure (1.89 ± 2.23, vs 2.95 ± 2.33, p = 0.080), and 10 minutes after the procedure (0.62 ± 1.32 vs 0.93 ± 1.36, p = 0.382).



**Fig. 2.** Mean pain scores at each time point of endometrial sampling procedure.

**Table 2.** Pain score in each step of endometrial sampling between groups.

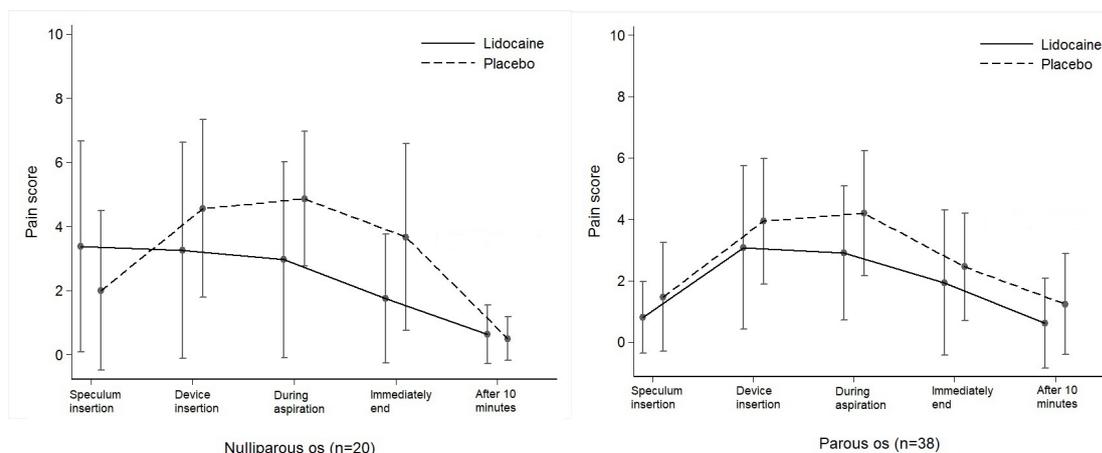
Pain score (mean ± S.D.)	Lidocaine group (n=29)	Placebo group (n=29)	p value
Speculum insertion	1.52 ± 2.25	1.69 ± 2.07	0.762 <sup>a</sup>
Wallach Endocell® insertion	3.13 ± 2.81	4.20 ± 2.35	0.122 <sup>a</sup>
During aspiration	2.92 ± 2.40	4.47 ± 2.06	0.011 <sup>a</sup>
Immediately after sampling	1.89 ± 2.23	2.95 ± 2.33	0.080 <sup>a</sup>
10 minutes after procedure	0.62 ± 1.32	0.93 ± 1.36	0.382 <sup>a</sup>
Overall pain score	-0.41 (-0.62 to -0.19)	-0.17 (-0.39 to 0.04)	0.006 <sup>b</sup>

SD: standard deviation

<sup>a</sup> student's t-test, <sup>b</sup> linear mixed model

Fig. 3 and Table 3 show the pain scores at each time point of ES procedure in nulliparous cervical os (n = 25) and parous cervical os (n = 33). In both subgroups, the lidocaine group was significantly lower pain score

than the placebo group (p < 0.001 in nulliparous os and p = 0.003 in parous os). However, there was no significant difference in pain scores at each time point between lidocaine group and placebo group.



**Fig. 3.** Mean pain scores at each time point of endometrial sampling procedure.

**Table 3.** Pain score in each step between group of nulliparous and parous cervical os.

Pain score (mean ± S.D.)	Nulliparous os (n=25)		p value	Parous os (n=33)		p value
	Lidocaine group (n=29)	Placebo group (n=13)		Lidocaine group (n=17)	Placebo group (n=16)	
Speculum insertion	2.42 ± 3.03	1.84 ± 2.44	0.608 a	0.88 ± 1.21	1.56 ± 1.79	0.209 <sup>a</sup>
Wallach Endocell® insertion	2.98 ± 2.88	4.61 ± 2.66	0.151 a	3.23 ± 2.84	3.85 ± 2.08	0.483 <sup>a</sup>
During aspiration	2.83 ± 2.57	4.74 ± 2.06	0.050 a	2.98 ± 2.35	4.25 ± 2.09	0.113 <sup>a</sup>
Immediately after sampling	1.75 ± 1.83	3.54 ± 2.82	0.076 a	1.98 ± 2.53	2.48 ± 1.80	0.522 <sup>a</sup>
10 minutes after procedure	0.50 ± 0.80	0.46 ± 0.66	0.896 a	0.71 ± 1.61	1.31 ± 1.66	0.295 <sup>a</sup>
Overall pain score	-0.32 (-0.47 to -0.17)	-0.23 (-0.38 to -0.08)	<0.001 <sup>b</sup>	-0.20 (-0.32 to -0.08)	-0.10 (-0.22 to 0.02)	0.003 <sup>b</sup>

<sup>a</sup> student's t-test, <sup>b</sup> linear mixed model

## Discussion

In this randomized controlled trial, the authors found that the pain score during ES in the lidocaine group was significantly lower than the placebo group ( $p = 0.011$ ), and the overall pain score in the lidocaine group was lower than the placebo group ( $p = 0.006$ ). We evaluated the pain score by VAS when inserting the speculum, device insertion, during aspiration, immediately after curettage, and 10 minutes after curettage. Pain scores were at their maximum during device insertion and aspiration curettage. Although the pain scores during device insertion, immediately after procedure and 10 minutes after procedure in the lidocaine group were lower than in the placebo group but there was no statistical significance.

A previous study by Karaca et al, showed that cervical 2% lidocaine gel was effective for decreasing pain during Pipelle endometrial biopsy<sup>(9)</sup>, whereas a study by Kozman et al, showed that an application of 2% lidocaine gel to the cervix did not significantly reduce the pain when compared with placebo<sup>(6)</sup>. These findings supported the results of Karaca et al, but contradicted the results of Kozman et al. Our study used the Wallach Endocell<sup>®</sup> device and the study by Karaca et al, used the Pipelle device, both of which are flexible devices whereas the study of Kozman et al, used the Vabra device. The study by Kozman used Vabra applicator which is a solid device that can cause more pain than the flexible one<sup>(10)</sup>. Thus, the topical analgesia on the cervix might not be effective at relieving pain caused by solid devices when compared with flexible ones. Pain scores at other steps of the procedure in the lidocaine group were lower than the placebo group; however, they were not statistically significant as same as the previous study.

ES or biopsy is the most common procedure for collecting endometrial tissue in out-patient departments<sup>(1,11)</sup>. It is known that the instruments and procedures are painful and adequate analgesia for pain relief is required<sup>(12)</sup>. A previous study by Wanijasombutti et al in 2013 reported that 20% of patients had moderate to severe pain during the procedure<sup>(13)</sup>. This pain perception is due to uterovaginal or Frankenhauser

plexus supplying the upper vagina, cervix and uterus which derives from the parasympathetic plexus (sacral spinal nerve 2-4)<sup>14</sup> that is blocked sodium influx through the cell membrane for action potential by lidocaine<sup>(15)</sup>. The 2% lidocaine gel is simple and convenient topical analgesic agent for applying the mucosa to relieve pain in many procedures with rapid onset. Compare with the lidocaine spray, lidocaine gel is easy for use and may cheaper than the spray.

For the subgroup analysis of women with nulliparous and parous cervical os, there was no significant difference in pain scores at each time point between lidocaine group and placebo group. This might be because the sample sizes of each subgroup were too small.

Lidocaine gel application at the cervical os could reduce the pain score in most patients that done the ES and clinician should consider for use in clinical practice. The lidocaine gel can also be easily found in various hospitals and the drug preparation is not complicated. The strength of our study was that it was a double-blinded, randomized, placebo-controlled trial with adequate power to support the results. The limitation was that this study used Wallach Endocell<sup>®</sup>, other different diameter devices might need different dosage of analgesia. Future studies are needed to find more effective doses of 2% lidocaine gel, especially in special populations who have a tendency for difficult procedures such as nulliparous and menopausal women, or to compare it with other pain management modalities for ES.

## Conclusion

The 2% lidocaine gel applied at the cervical surface and internal cervical canal was an effective and convenient option for pain relief during endometrial sampling.

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fundings had no role in the study design, data collection and analysis, decision to publish or preparation of manuscript.

## Potential conflicts of interest

The authors declare no conflict of interest.

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