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Lidocaine Spray for Pain Control during Office-based Endometrial Biopsy: A randomized placebo-controlled trial

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ABSTRACT

Objectives: To evaluate effectiveness of 10% lidocaine spray for pain relief during office-based endometrial biopsy

Materials and Methods: Fifty women who indicated for endometrial tissue sampling by Wallach endocell® participated in this randomized, double blinded, placebo-controlled study. The procedures were performed at out-patient gynecology clinic, Department of Obstetrics and Gynecology, Vajira hospital, Bangkok, Thailand, from July 2016 to April 2017. Participants were simple randomly assigned to either lidocaine group which they will receive 5 puff of 10% lidocaine solution spray (50 mg), four puff to cervical surface and one puff towards internal os, or placebo group which they will receive 5 ml placebo solution spray administered in the same manner. Pain score was measured intraoperation, immediate after, 15 minutes and 30 minutes post-operation, using a 10 cm-visual analog scale (VAS-10).

Results: Lidocaine spray application during office-based endometrial biopsy significantly lowered the overall pain score compared with placebo (coefficient -3.27, $p < 0.001$, multilevel linear regression). Mean pain score during procedure was 3.56 ± 1.50 in the lidocaine group (n=25) and 7.28 ± 1.02 in the placebo group (n=25) ($p < 0.001$). The mean pain score immediate after, at 15 and 30 minutes after the procedure was 3.04 ± 1.31, 0.80 ± 1.41 and 0.08 ± 0.40 in the lidocaine spray group respectively and 7.08 ± 1.19, 3.92 ± 1.47 and 1.92 ± 1.41 in the placebo group respectively ($p < 0.001$).

Conclusion: 10% lidocaine spray applied at cervical surface and internal cervical os was effective for pain relief during and immediate after office-based endometrial Biopsy.

Keywords: endometrial biopsy, lidocaine spray, pain control, analgesia

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การใช้ Lidocaine spray ในการระงับอาการปวดระหว่างการดูดเนื้อเยื่อบุโพรงมดลูกที่ห้องตรวจผู้ป่วยนอก: การทดลองแบบสุ่มและมีกลุ่มควบคุม

ปวีร์ กอสุวรรณ, บุษบา วิริยะสิริเวช์

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของการพ่น 10% Lidocaine spray เพื่อลดความเจ็บปวดขณะเก็บดูดชิ้นเนื้อเยื่อบุโพรงมดลูก*

วัสดุและวิธีการ: *สตรีที่มีข้อบ่งชี้ในการเก็บชิ้นเนื้อโพรงมดลูกจำนวน 50 ราย ที่มารับการตรวจที่ห้องตรวจผู้ป่วยนอก ภาควิชาสูตินรีเวช คณะแพทยศาสตร์วชิรพยาบาล เข้าร่วมการศึกษา โดยใช้อุปกรณ์ Wallach Endocell® เก็บตรวจชิ้นเนื้อโพรงมดลูก ทำการสุ่มโดยแบ่งออกเป็น 2 กลุ่ม คือ กลุ่มที่ได้รับยา 10% Lidocaine spray และกลุ่ม Placebo พ่นก่อนทำหัตถการทั้งหมด 5 puff โดย 4 puff ที่ บริเวณผิวปากมดลูก และ 1 puff ที่บริเวณปากมดลูกด้านใน ทำการวัดระดับความเจ็บปวดโดยใช้ 10 cm-visual analog scale (VAS-10) ขณะทำหัตถการเก็บดูดชิ้นเนื้อโพรงมดลูก, หลังเก็บดูดชิ้นเนื้อโพรงทันทีและคะแนนความเจ็บปวดหลังทำ 15, 30 นาที ตามลำดับ*

ผลการศึกษา: *กลุ่มที่ได้รับ 10% Lidocaine spray พบค่าเฉลี่ยความเจ็บปวดต่ำกว่ากลุ่มที่ได้รับ Placebo อย่างมีนัยสำคัญทางสถิติ ทั้งขณะทำหัตถการเก็บดูดชิ้นเนื้อโพรงมดลูก, หลังเก็บดูดชิ้นเนื้อโพรงทันทีและคะแนนความเจ็บปวดหลังทำ 15, 30 นาที โดยค่าเฉลี่ยความเจ็บปวด 3.56 ± 1.50 ในกลุ่มที่ได้รับ 10% Lidocaine spray (n=25) และ 7.28 ± 1.20 ในกลุ่ม Placebo (n = 25) (p < 0.001). ค่าเฉลี่ยความเจ็บปวดในกลุ่ม 10% Lidocaine หลังเก็บดูดชิ้นเนื้อโพรงทันทีและคะแนนความเจ็บปวดหลังทำ 15, 30 นาที คือ 3.04 ± 1.31, 0.80 ± 1.41, 0.08 ± 0.40 ตามลำดับ และค่าเฉลี่ยความเจ็บปวดในกลุ่ม Placebo คือ 7.08 ± 1.19, 3.92 ± 1.47, 1.92 ± 1.41 ตามลำดับ*

สรุป: *การพ่น 10% Lidocaine spray ที่บริเวณผิวปากมดลูก และปากมดลูกด้านใน มีประสิทธิภาพในการลดอาการปวดระหว่างการดูดชิ้นเนื้อเยื่อบุโพรงมดลูกจนถึงหลังทำหัตถการ 30 นาที*

คำสำคัญ: *เก็บชิ้นเนื้อเยื่อบุโพรงมดลูก, ลิโดเคนสเปรย์, ลดอาการเจ็บปวด, ยาระงับความเจ็บปวด*

Introduction

An endometrial biopsy (EB) is a common medical procedure for the investigation of many gynecological disorders including abnormal premenopausal and postmenopausal uterine bleeding, abnormal cytology, hormonal therapy failure, and infertility[1,2]. Over the years, office-based EB has increasingly replaced dilatation and curettage (D&C) as the standard pathological examination method of the endometrium as EB is a simple, quick, safe, and inexpensive treatment that does not require anesthesia[3]. Several disposable endometrial suction devices can be used for EB including Wallach's Endocell®, Pipelle, Vabra aspiration, Z-sampler, Accurette, Explora, and Karman systems. Wallach's Endocell® is usually used as this technique is simple, quick, less painful, and provides adequate tissue for histological examination[4]. There is no standard guideline for pain control during an EB procedure which is usually performed without any analgesia. However, recent studies found that all patients experienced pain during outpatient EB procedure, and two-thirds had moderate to severe pain that prevented collection of adequate tissue sample for biopsy[3]. Techniques proposed for pain management during EB include paracervical block, intrauterine lidocaine infusion, non-steroidal anti-inflammatory drugs (NSAIDs) and the local application of lidocaine spray as a topical anesthetic agent available in 10% form which contains 10 mg of lidocaine per puff. A long applicator is convenient for administration. Recommended dosage is 40-50 mg for an obstetrics and gynecological procedure. Onset of analgesia occurs after 1-2 minutes with duration of action at 15-30 minutes which is adequate for the EB procedure[5,6]. However, previous studies concerning the efficacy of lidocaine for pain control during office-based EB are inconclusive[7-12].

Hence, this randomized, double-blinded, placebo-controlled trial evaluated the effectiveness of 10% lidocaine spray on reducing pain perception during office-based EB.

Materials and Methods

This study was performed at the Department of Obstetrics and Gynecology, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand from July 2016 to April 2017. This study was approved by the Vajira Institutional Review Board (VIRB), Faculty of Medicine, Vajira Hospital, Bangkok, Thailand and registered at http://www.thaiclinicaltrials.gov (TCTR20170714001) according to the standards set by the International Committee of Medical Journal Editors and the World Health Organization. Sample size was calculated using the estimated difference in pain score between lidocaine and placebo groups determined by Aksoy H et al[8]. With power of 80%, a type I error of 0.05 and a two-sided test sample gave the size of each group as 22. Adding 10% drop out, this was increased to 25. Inclusion criteria were age ≥ 18 years, showing indication for office-based EB, no previous allergic reaction or sensitivity to lidocaine and a written consent form. Exclusion criteria were currently pregnant, had cervical pathology, uterine anomaly, untreated acute cervicitis or pelvic inflammatory disease, inability to determine 10-cm visual analog scale (VAS-10) pain score, received medication such as analgesics and misoprostol prior to operation, had respiratory tract problems, cardiovascular system failure, acute liver disease, or active bleeding from the vagina on the date of operation[15]. A total of 50 women met the eligibility criteria. After receiving adequate study information, written informed consent was obtained from all participants prior to enrollment.

Randomization was performed using a computer-generated random number chart. The randomization order was blinded to the physician who performed the EB, participants, and research assistants who assessed the pain score. Ten percent lidocaine (10% Xylocaine spray®, 10 mg/ 1 ml/ 1 puff, AstraZeneca) and placebo (isotonic saline solution) were prepared by the pharmacist with identical appearance. The suction device used was a Wallach Endocell®, a flexible plastic catheter with

manual suction of diameter 3.1 mm. A pain measurement scale calibrated from zero to ten was used to assess pain score with "0" indicating "Null pain" and "10" indicating highest pain intensity. Participants were randomly assigned to 2 groups (lidocaine and placebo). The lidocaine group A received 5 puffs of 10% lidocaine solution spray, 4 puffs to the cervical surface and 1 puff toward the internal cervical os for 2 cm. A long applicator was convenient for administration. Group B received 5 ml placebo solution spray administered in the same manner. The EB was performed by the same gynecologist to maintain consistency as per the following steps: the participant was placed in the lithotomy position and a sterile bivalve speculum was introduced into the vagina to visualize the cervix, the cervix and vagina were cleaned with 10% povidone-iodine solution, each participant received 5 puffs of either 10% lidocaine solution spray or placebo and waited for 2 minutes for the analgesic to take effect. The EB was performed by passing a Wallach Endocell® into the uterine cavity. Once in position, the plunger was drawn back to create suction and the device was moved gently from the fundus down to the internal os until it was filled with tissue. If required, a tenaculum was used to grasp the anterior cervix and straighten the uterine axis, and EB was performed as standard manner. Bleeding was checked and the speculum was withdrawn. Participants were observed for 30 minutes after the procedure. Pain intensity was assessed by a research assistant at 5 different time points: speculum introduction which was considered as baseline pain, during biopsy and then immediately, 15 minutes, and 30 minutes after the biopsy. Participants' demographics and medical data including age, body mass index, gravidity, parity, previous vaginal delivery, menopause status, medical history, indication for biopsy, uterine size, length, position and uterine pathology, pain score at each time point, complications from the procedure such as vasovagal reactions, and adverse reaction from the lidocaine were collected.

Data were analyzed using Stata/SE 13 statistical software. Continuous variables were presented as descriptive statistics (mean ± standard deviation) and analyzed by Student's t-tests. Multilevel linear regression was used to compare the difference of overall pain score between the lidocaine and placebo groups. A p value < 0.05 was considered to be statistically significant.

Results

A total of 50 women who met the eligibility criteria were enrolled from 58 candidates (86.21%, Fig. 1). Eight patients refused to participate and were excluded. All procedures were successfully completed without any complications, and no serious adverse reactions associated with Lidocaine were noted. Participants were equally randomized into Lidocaine and placebo groups. Demographic and clinical characteristics of the patients were similar in each group (Table 1), regression was used to compare the difference of overall pain score between the Lidocaine and placebo groups. A $p<0.05$ was considered to be statistically significant.

No statistically significant differences were recorded in mean pain score at the time of speculum insertion, considered as baseline pain, between Lidocaine (3.24 ± 1.58) and the placebo group (2.58 ± 1.79) ($p = 0.21$, Table 2). Lidocaine spray application significantly lowered overall pain score of the EB procedure compared with placebo (coefficient -3.27, $p < 0.001$, multilevel linear regression). Mean pain score during the procedure was 3.56 ± 1.50 in the Lidocaine group ($n = 25$) and 7.25 ± 1.03 in the placebo group ($n = 24$) ($p < 0.001$). Mean pain scores immediately after and at 15 and 30 minutes after the procedure were 3.04 ± 1.30, 0.80 ± 1.41 and 0.08 ± 0.40 in the Lidocaine spray group and 7.04 ± 1.03, 3.88 ± 1.48 and 1.92 ± 1.44 in the placebo group, respectively ($p < 0.001$). Significant differences between the two groups regarding pain intensity are shown in Table 1. Fig. 2. elucidates the subgroup analyses performed for groups where a tenaculum was or was not used. Results indicated that Lidocaine was significantly effective in

reducing pain whether or not a tenaculum was used (Fig. 2. and 3.).

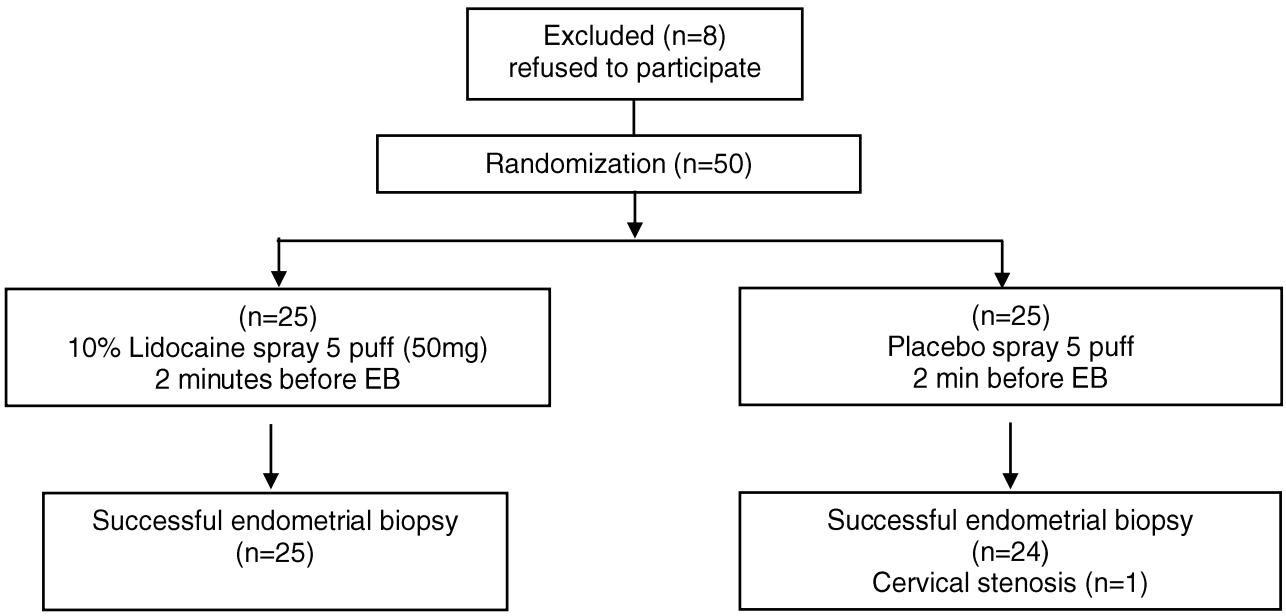
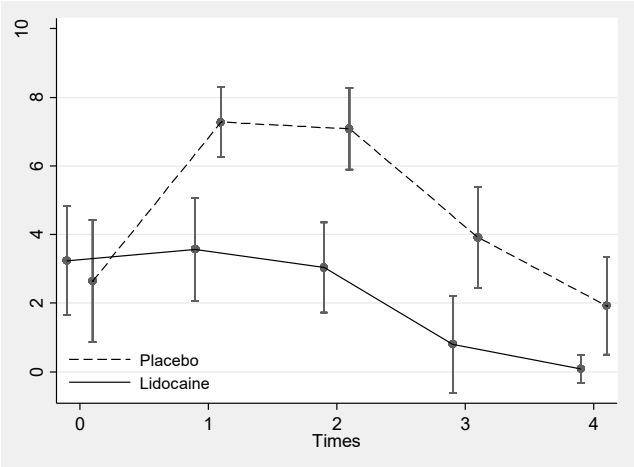


Fig. 1. Flow chart showing progression of participants through trial.

Table 1. Demographic and clinical characteristics of the study groups.

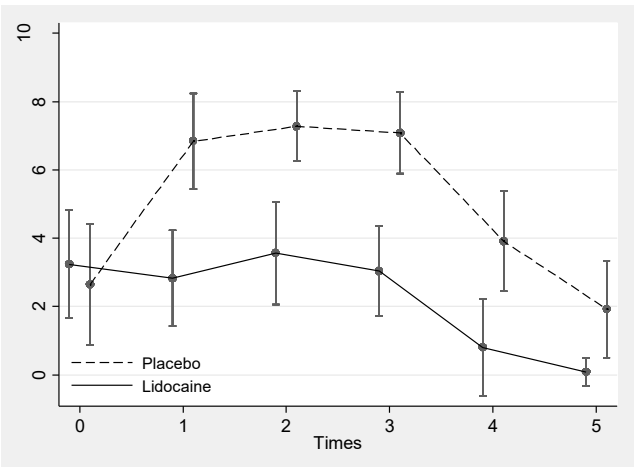
	Lidocaine group (n=25)	**Placebo (n=25)**
Age (year)* (mean ± SD)	51.5 ± 10.6	49.6 ± 11.3
BMI (mean ± SD)	25.6 ± 3.1	26.1 ± 6.2
Previous vg delivery n (%)	19 (76)	17 (68)
Menopausal status' n (%)		
Premenopausal	18 (72)	17 (68)
Post-menopausal	7 (28)	8 (32)
Indication n (%)		
abnormal uterine bleeding	18 (72)	14 (56)
postmenopausal bleeding	7 (28)	8 (32)
endometrial dating	0 (0)	3 (12)
Tenaculum used	11 (44)	12 (48)

Values are expressed as n (%) unless otherwise specified.



Time
0 = At the time of introduce speculum
1 = During endometrial biopsy
2 = Immediately after endometrial biopsy
3 = 15 min after endometrial biopsy
4 = 30 min after endometrial biopsy

Fig. 2. Mean pain score in each group within the course of study.



Time
0 = At the time of introduce speculum
1 = During endometrial biopsy
2 = Immediately after endometrial biopsy
3 = 15 min after endometrial biopsy
4 = 30 min after endometrial biopsy

Fig. 3. Mean pain score in each group when Tenaculum were used.

Table 2. Mean pain score at five time point of study groups.

	Lidocaine group (n=25)	Placebo (n=25)	p value
VAS speculum (cm)	3.24 ± 1.58	2.58 ± 1.79	0.21
VAS intra-op (cm)	3.56 ± 1.50	7.28 ± 1.02	< 0.001
VAS immediate post-op (cm)	3.04 ± 1.31	7.08 ± 1.19	< 0.001
VAS postop 15 min (cm)	0.8 ± 1.41	3.92 ± 1.47	< 0.001
VAS post op 30 min (cm)	0.08 ± 0.4	1.92 ± 1.46	< 0.001

Values are expressed as n (%) unless otherwise specified.

Discussion

Assessment of the endometrium is required in many gynecological examinations and an endometrial biopsy is a common outpatient procedure for detection of endometrial pathology. Screening for cancer or precancerous conditions can determine the cause of abnormal uterine bleeding, fertility problems and response to hormonal treatment[2,3]. An endometrial biopsy allows the collection of tissue from the cervix and the uterus for histological evaluation but the procedure may be painful. The cervix and uterus are richly innervated and pain perception results from two distinct neural pathways as the Frankenhäuser plexus (parasympathetic nerves S2-4) supplying the cervix and lower uterus, and sympathetic nerves passing via the infundibulopelvic ligament from the ovarian plexus supplying the uterine fundus[13,14]. Pain and discomfort are associated with the transcervical insertion of an endometrium suction device and a tenaculum used for uterine traction. Currently, there are many treatment options but pain management for the successful completion of procedures is inconclusive. Previous studies indicated pain scores ranging from 5-7 on the 10-cm VAS scale12 while Paphada et al., 2013 reported that 60% of patients experienced moderate to severe pain during the procedure[4].

Lidocaine spray is a simple and convenient topical anesthetic agent with no pain related to application and rapid onset of action at 1-2 minutes with 15-30 minute duration. The mechanism of local lidocaine can block pain at the Frankenhäuser plexus[12]. Previous authors showed that lidocaine spray is effective in reducing pain during minor gynecological procedures[16,17], with positive effects during Pipelle endometrial aspiration; however, these results were inconsistent with other studies which examined the potential role of topical anesthetics for pain control during endometrial biopsy. Results in Table 1. and Fig. 1. showed that lidocaine spray can reduce pain during and immediately after the procedure, and was effective for up to 30 minutes.

Our study was a randomized, double-blinded, placebo-controlled trial. One limitation was the use of a Wallach Endocell® diameter 3.1 mm; other types of suction devices with larger diameters may require different dosages of analgesia.

Conclusion

Ten percent lidocaine spray was an effective option for pain management during office-based EB. Gynecologists should, therefore, consider using this spray in routine practice.

Potential conflicts of interest

The authors declare no conflict of interest.

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