*Original Article*

# Lidocaine Gel for Pain Relief during Endometrial Sampling in Women Aged over 35 Years Old with Abnormal Uterine Bleeding: A Randomized Double-Blind Controlled Trial

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**Objective**: To evaluate the effectiveness of lidocaine gel in pain relief during endometrial sampling procedure (ESP).

**Materials and Methods**: A double-blinded randomized controlled trial was conducted at the gynecology clinic of Thammasat University Hospital between January and June 2020. Women aged over 35 years old with abnormal uterine bleeding were recruited. The participants were equally randomized assigned into two groups. The study and the control group received 3 mL of 2% lidocaine gel and lubricant gel locally applied at the cervix five minutes before performing ESP, respectively. The visual analog scale (VAS) was used to evaluate pain scores. Results were collected at five timeframes, insertion of a speculum, at the first, second, and third ESP, and five minutes post-procedure.

**Results**: One hundred and ten women, with 55 in each group, were eligible for randomization. Mean age of participants was 50 years old. Half of the cases (46/110) had complaint of irregular vaginal bleeding. Demographic characters of both groups were comparable. VAS at five timeframes in the study group and the control group were 19/23, 51/51, 56/60, 60/64, and 20/18, respectively, without statistical significance. The severe pain score was highest in the third ESP for both groups. Three cases of endometrial cancer were diagnosed. Ten percent (11/110) of tissue samples were inadequate for evaluation.

**Conclusion**: Application of lidocaine gel at the cervix could not effectively reduce pain during ESP.

**Keywords**: Pain; Endometrium sampling; Lidocaine gel

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Abnormal uterine bleeding (AUB) in women aged over 35 years is a common condition presenting at gynecology clinic. Endometrial cancer is the silent malignancy in this condition[1]. Histopathology was needed for definite diagnosis. Fractional curettage (FC) was used as gold standard. However, office endometrial sampling is an alternative and acceptable procedure. Even though pain from office endometrial biopsy is lower than FC, severe pain can occur[2]. Pain relieving should be of concern for the patient's comfort.

Pain from endometrial sampling procedure (ESP) might be explained by two different mechanisms of pain perception during the biopsy. The first mechanism is during insertion of the endometrial cell sampler through the cervix and the lower part of the uterus, which is innervated by the pelvic splanchnic nerve at levels S2-S4. The second mechanism of pain happens when endometrial biopsy is performed at the upper part of the uterus, which is innervated by the inferior hypogastric plexus[3].

Lidocaine is an amino amide anesthetic agent. Its mechanism of action is blocking neuronal transmission by interfering with the flow of sodium across excitable membranes[4]. The onset and duration of action are 2 and 30 to 45 minutes, respectively[5].

Lidocaine could be applied by either local infiltration or nerve blockage namely paracervical and pudendal nerve block. However non-invasive

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technique should be applied if possible due to less invasive procedure. Topical lidocaine was available in gel or spray formula. Application of lidocaine gel at the oral mucosa or urethra has shown good result in pain reduction[6-8].

Topical lidocaine application before endometrial biopsy procedure was reported by Luangtangvarodom et al in 2019[9]. They reported the efficacy of cervical lidocaine spray application before ESP in pain reduction from the procedure. The dose of lidocaine spray might not be fully controlled because of its aerosol property during application.

In 2016, Karaca et al[10] reported the good efficacy of lidocaine gel application at both cervix and intracervical canal during ESP. Up to now, there has been no report of lidocaine gel application at the cervix before ESP.

The present study aimed to investigate the pain-reducing effect of topical lidocaine gel at the cervical epithelium during the ESP.

## Materials and Methods

The present study was a randomized controlled trial conducted at the gynecology clinic of Thammasat University Hospital, Pathum Thani, Thailand, between January and June 2020. The approval from the Ethics Committee on Clinical Research of Faculty of Medicine, Thammasat University (MTU-EC-OB-2-183/62) and Thai Clinical Trials Registry (TCTR2019 12 17 004) were obtained before starting the study.

The inclusion criteria were patients aged over 35 years presenting with AUB. Exclusion criteria included refusal to participate, pregnancy, and having the following conditions, a history of coagulopathy, anticoagulant use, allergy to lidocaine, and current pelvic infection. In cases of cervical stenosis found during the procedure, the cases will be referred to undergo manual vacuum of endometrial tissue with cervical priming by oral misoprostol on the next day.

Demographic data included age, body mass index (BMI), education level, occupation, income, underlying diseases, history of curettage, menopausal status, and indication for endometrial biopsy. After counseling, all participants signed the informed consents. Participants were randomly assigned into two groups, the study and the control group, using block of four randomization method. A research nurse assistant performed this process. Group allocations, as shown in Figure 1, were concealed in metal file cabinets.

Participants were then placed on a lithotomy position and underwent pelvic examination before starting the procedure. Only one obstetrics and gynecologic chief resident did ESP. The bivalve speculum was inserted into the vaginal canal. Vagina and cervix were irrigated by 0.9% normal saline solution to remove any vaginal discharge. After vaginal irrigation and removing the excess fluid, either 3 mL of 20 mg/mL and 60 mg of 2% lidocaine, or 3 mL of lubricant gel were applied via Dacron swab to the study and the control group, respectively, at the cervical surface. Both types of gel were clear in color, odorless, and were prepared in the same type of containers by one research assistant. The tenaculum application at the cervix was conducted under operator consideration. After the application of lidocaine, the physician waited for five minutes before inserting the endometrial cell sampler (Wallach Endocell®, W&H surgical, CA, USA) into the uterine cavity.

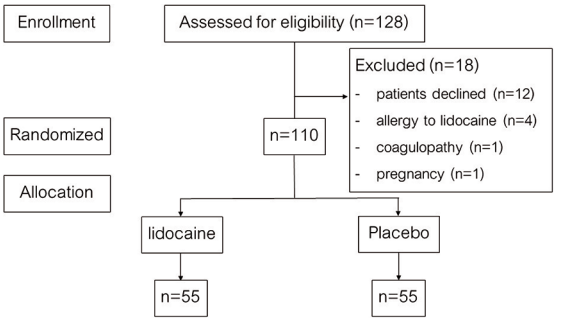


**Figure 1.** CONSORT flow diagram.

Endometrial aspiration was performed and repeated three times to ensure sample adequacy. Pain severity was assessed with a 100-mm visual analog scale (VAS), rating from 0 (no pain) to 100 (worst pain in life), after each step, T0, which was the insertion of bivalve speculum, T1 to T3 during each ESP, and T5 at five minutes after the procedure. Pain assessment was performed by asking the subject after finishing each time of endometrial aspiration by research nurse assistant.

The possible side effects such as nausea, vomiting, vasovagal syncope, and hypotension were also recorded. All endometrial specimens were submerged in 10% formaldehyde solution and sent for pathologic study. Acetaminophen 500 mg was orally prescribed for pain relived after the procedure.

The sample size was calculated from the pilot study. The alpha and beta errors were set at 0.05 and 0.2. The sample size should be at least 44 cases for each group to verify null hypothesis ($P_0$=0.6) compared to the alternative hypothesis ($P_1$=0.3).

Given a 20% dropout rate, the number of participants was 55 cases for each group. The sample size formula was as follows.

$$N = \frac{2(Z\alpha/2 + Z\beta)^2 PQ}{(P_0 - P_1)^2}$$

All data were then analyzed using the IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Continuous data were analyzed using the t-test and the Mann-Whitney U test for normal distributed and non-normal distributed data, respectively. Categorical data were computed by the chi-square test. A p-value of less than 0.05 was used to express statistical significance.

## Results

One hundred twenty-eight participants were recruited. One hundred ten participants were randomized into the study as presented in Figure 1. Subjects were divided equally at 55 participants each, into study and control group.

Mean age of participants was 50 years old. Half of cases (46/110) had a complaint of irregular vaginal bleeding. Two-third of cases (76/110) were in pre-menopause state. Education level less than primary school was found in one-third of participants (36/110). Tenaculum was used in more than half of the cases (73/110). Both groups had comparable demographic characters as shown in Table 1.

ESP were performed three times in each case. After insertion of vaginal speculum before procedure (T0), median pain of the study and the control groups were 23 and 19, respectively. After the first round of endometrial aspiration (T1), both groups reported significant increase in pain score. Median pain score of the study and the control group were 51 and 51, respectively. At the second and third round of endometrial aspiration (T2 and T3), the pain score of both groups appeared to be comparable to T1. Five minutes after removal of the vaginal speculum (T5), the pain score was much less than T1 through T3 but was not decreased down to 0/100 on the VAS as shown in Figure 2.

Histopathological reports of both groups were comparable. One-third of the reports revealed atrophic endometrium. There were three cases of endometrial cancer in the present study. All of them underwent surgical staging surgery within one month after diagnosis. Only one case of endometrial intraepithelial neoplasia was diagnosed and later underwent type 1 hysterectomy. Ten percent (11/110) of tissue samples were inadequate for evaluation. All of them were re-appointed for additional endometrial tissue collection by FC. Six of these patients were lost to follow up. Four of them had inactive endometrium and the other had a secretory phase endometrium.

There were no serious side effects in the present study. Throughout the process, no additional analgesia was requested from the subjects.

**Table 1.** Demographic data of participants (55 cases each)

| | Lidocaine | Placebo | p-value |
|---|---|---|---|
| Age (years); mean±SD | 51.4±11.2 | 48.6±7.0 | 0.13 |
| BMI (kg/m$^2$); mean±SD | 24.8±4.8 | 26.3±5.1 | 0.13 |
| Education level; n (%) | | | 1 |
| Primary school | 18 (32.7) | 18 (32.7) | |
| High school or higher | 37 (67.3) | 37 (67.3) | |
| Occupation; n (%) | | | 0.85 |
| Employee | 25 (45.5) | 25 (45.5) | |
| Housewife | 16 (29.1) | 13 (23.6) | |
| SME | 13 (23.6) | 15 (27.3) | |
| Agriculture | 1 (1.8) | 2 (3.6) | |
| Low income#; n (%) | 5 (9.1) | 4 (7.3) | 0.99 |
| No UD; n (%) | 29 (52.7) | 26 (47.3) | 0.57 |
| History of curettage; n (%) | 7 (12.7) | 5 (9.1) | 0.54 |
| Pre-menopause; n (%) | 36 (65.5) | 40 (72.7) | 0.41 |
| Tenaculum usage; n (%) | 35 (63.6) | 38 (69.1) | 0.55 |
| Multiparity; n (%) | 48 (87.3) | 50 (90.9) | 0.54 |
| Bleeding type; n (%) | | | 0.61 |
| Heavy menstrual | 13 (23.6) | 17 (30.9) | |
| Postmenopausal | 19 (34.5) | 15 (27.3) | |
| Irregular@ | 23 (41.8) | 23 (41.8) | |

SD=standard deviation; BMI=body mass index; SME=small to medium enterprise; UD=underlying disease

# Income less than 10,000 Baht/month, @ Refers to any other etiologies such as intermenstrual bleeding, prolonged bleeding, post-coital bleeding

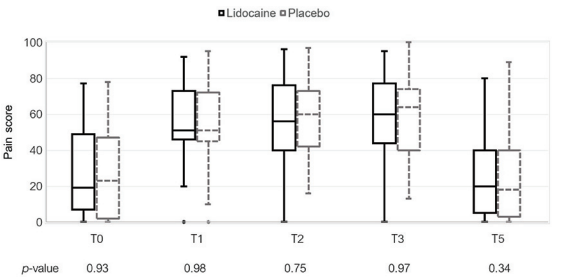


**Figure 2.** Comparison of median pain scores during endometrial sampling.

Lidocaine=2% lidocaine 60 mg applied at the cervix; Placebo=lubricant gel applied at the cervix; T0=speculum insertion pain score; T1=first ESP; T2=second ESP; T3=third ESP; T5=pain score after 5 minutes

## Discussion

Endometrial cell sampling done in an office is the preferred choice for outpatients with AUB. It

**Table 2.** Summary data of topical lidocaine in office endometrial aspiration

| | Olad-Saheb-Madarek | Aksoy | Karaca | Benchahong | Luangtangva-rodom | Korsuwan | Piyawetchakarn | Present |
|---|---|---|---|---|---|---|---|---|
| Year | 2013 | 2016 | 2016 | 2018 | 2018 | 2018 | 2019 | 2021 |
| Country | Iran | Turkey | Turkey | Thailand | Thailand | Thailand | Thailand | Thailand |
| Age (year) | 47.6 | 45.1 | 44 | 47.9 | 47.8 | 50.6 | 46 | 50 |
| Case (n) | 160 | 119 | 137 | 250 | 140 | 50 | 160 | 110 |
| Tools | Pipelle | Karman | Pipelle | Novak | Novak | Endocell | Pipelle | Endocell |
| Preparation | Spray | Spray | Gel | Spray | Spray | Spray | Spray | Gel |
| Dose (mg) | 100/60/160 | 40 | 20/40 | 70 | 40 | 50 | 40 | 60 |
| Site | Ut/Cx/Ut+Cx | Cx, Ic | Cx, Ic | Ut | Cx | Cx, Ic | Cx, Ic | Cx |
| Time (minutes) | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 5 |
| Effect | Ut&Ut+Cx Sig | Sig | Sig | Sig | Sig | Sig | Ns | Ns |

Ut=uterine cavity; Cx=cervix; Ic=intracervical canal; Time=waiting time after lidocaine application; Sig=significant pain relief; Ns=non-significant pain relief

is a convenient and minimally invasive procedure. Analgesic should be used to increase the patient's comfort. Korsuwan[11] and Piyawetchakarn[12] used small disposable plastic canula same as the present study (Endocell® and Pipelle®, respectively). Both studies used lidocaine spray at the cervical epithelium and intracervical canal before ESP. Korsuwan's results showed lidocaine spray effective for pain relief while Piyawetchakarn's study revealed ineffective results. However, dose of lidocaine in Korsuwan's and Piyawetchakarn's studies were 50 mg and 40 mg, respectively, which might be the possible factor for different results.

Karaca et al's study[10] revealed significant result in pain relief when applying 20 and 40 mg of lidocaine gel at the cervical epithelium and in intracervical canal, respectively. Their works used the small diameter of endometrial tissue collector as in Piyawetchakarn's and Korsuwan's studies. Aksoy et al[13] reported that lidocaine spray being applied at the cervix and in intracervical canal could reduce pain from ESP, but Aksoy et al's study was using Karman canula, known to be a large plastic bore. In the present study, the total dose of 60-mg lidocaine gel was applied solely at the cervix. The present study result showed an insignificant pain relief despite using the equivalent dose of lidocaine gel as demonstrated in Karaca et al's study.

The difference of the present study from Karaca's, Piyawetchakarn's, and Korsuwan's studies was the site of lidocaine application, which were at both the cervix and intracervical canal, while in the present study, application of lidocaine was solely at the cervical surface. Therefore, the different site of application could have been the factor affecting the pain score in ESP.

Two other studies by Benchahong et al[14] and Olad-Saheb-Madarek et al[15] reported the significant pain reduction using topical lidocaine in the intrauterine cavity, and both intrauterine cavity and cervical epithelium, respectively, before ESP. Even with the different sizes of the endometrial tissue collector in these studies, both still produced effective result. Therefore, an application of lidocaine in intrauterine cavity may be a factor to reduce pain scores during the procedure. The summary of these previous studies is presented in Table 2.

As previously mentioned, non-significant results can be explained by two different mechanisms of pain reception during ESP. The intrauterine cavity would be the main site where pain is inflicted. Pain from insertion of the instrument was less painful. Therefore, the application of lidocaine gel at only the cervix would not be as effective. The prevalence of endometrial cancer in the present study was 2.7%. Therefore, intrauterine cavity application of topical lidocaine should be of concern because it is not a closed space and connected to the intraperitoneal cavity. Such procedure may induce spillage of cancerous cells into the intraperitoneal cavity via the fallopian tubes. No evidence was reported to support that the insertion of topical lidocaine in intrauterine cavity did not interfere with the pathological results.

In most previous studies, ESP was performed three to four times[16-18] as corresponding to the present study, to ensure the adequacy of endometrial tissue retrieval. In the current study, the third round of endometrial sampling generated more pain than the first and second round. For future studies, histopathology for each round of aspiration is suggested. This should validate if up to three aspirations were necessary for ESP procedures.

The strength of the present study was implementing a 100-mm VAS for higher specificity

and accuracy compared to the commonly used 10-cm VAS rating. It is also the first study to distinctively record pain scores on three separate attempts. All cases provided complete data for final analyses. The study was performed in a prospective double-blinded randomized control pattern. The limitation of the present study was that pain was individually perceptualized. ESP produced mild pain and thus comparing the pain with the intervention, the difference would be insignificant.

In conclusion, all pain scores recorded at five precise timepoints in the present clinical study demonstrated no statistical significance between the study and the control group. An application of topical lidocaine solely at the cervix did not relieve the pain during ESP. Pain reduction may be most effective when topical lidocaine is applied in endocervical canal. This topic is suggested for further studies.

## What is already known on this topic?

AUB in women aged over 35 years is a common condition presenting at gynecology clinic. Endometrial tissue for histopathology study is needed for diagnosis. Office endometrial biopsy is preferred because of its minimal pain and adequacy procedure for specimen collection. Aggravating pain during and after the procedure can occur. Lidocaine is an amino-amide anesthetic agent effective for pain relief for either regional or topical application.

## What this study adds?

Inadequacy of endometrial tissue for diagnosis by endometrial aspiration was 10%. The highest pain from ESP was the third attempt of endometrial aspiration. Lidocaine gel solely applied at the cervix did not relieve the pain during ESP.


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## Conflicts of interest

The authors declare no conflict of interest.

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