Role of Local Anesthetics on Pain Relief in Endometrial Biopsy: Randomized Clinical Trial

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Abstract
Objectives: Endometrial biopsy is necessary for diagnosing the reason of abnormal uterine bleeding in perimenopausal women. Currently outpatient endometrial biopsy is used for evaluation of abnormal uterine bleeding which is associated with moderate to severe pain. Using lidocaine is one of the procedures which is used for pain relief while biopsy. This study is aimed at comparing the effect of different local anesthesia procedures on pain relief during endometrial biopsy.

Materials and Methods: In this randomized clinical trial, 160 multiparous 40-55 years old women with AUB (Abnormal Uterine Bleeding), candidates for endometrial biopsy, were randomly assigned into four equal groups, to receive: 1-intrauterine lidocaine; 2-cervical spray lidocaine; 3-intrauterine lidocaine plus cervical spray lidocaine; or 4-intrauterine distilled water. Pain relief was measured at 3 different times: during endometrial biopsy, just after and 15 minutes after biopsy.

Results: Pain intensity was reduced significantly at different times in intrauterine lidocaine and intrauterine lidocaine with cervical spray lidocaine receivers in compare with the groups which received cervical spray lidocaine and distilled water. The mean of difference pain relief during biopsy and 15 minutes after that was reduced significantly in the group which received intrauterine lidocaine and intrauterine lidocaine with cervical spray lidocaine in comparison with the other two groups.

Conclusion: Intrauterine lidocaine was effective during endometrial biopsy, and using it with cervical spray lidocaine had no more beneficial effect.

Keywords: Anesthesia, Biopsy, Curette, Lidocaine, Pain, Suction

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Introduction:
Abnormal Uterine Bleeding (AUB) can be caused by various kinds of systemic diseases including endocrine disorders, pregnancy, medications, structural abnormalities of the uterus (such as fibroids, polyps and adenomyosis), anovulation and coagulopathies, neoplasia, trauma and infections (1, 2). Over the years, dilatation and curettage (D&C) was the standard procedure for pathological examination of endometrium in patients with AUB (3,4). D&C requires anesthesia in the operation room. Outpatient paracervical block which was done in year 1925 for the first time has been associated with adverse effects such as mortality. Recently D&C has been substituted by outpatient endometrial suction curette biopsy. All patients experience pain during the outpatient endometrial biopsy and in some cases the pain is so severe that makes it impossible to take adequate sample in biopsy. The inadequate specimen for pathological examination in these cases makes the need for D&C. Thus, a method for pain relief will be required (5,6). One of the methods for pain reduction and local anesthesia during outpatient biopsy is using intrauterine lidocaine. It is proposed to be an effective method for pain relief in the upper part of the uterus by blocking the nerve endings in the uterine corpus and fundus. Lidocaine spray is also used in some cases during pipelle biopsy (7).

Because of the necessity of using a suitable and effective method of analgesia during the intrauterine biopsy, this study was performed to evaluate the different methods of intrauterine lidocaine and cervical spray lidocaine, in order to investigate the best method of anesthesia for pain relief regarding to the results and using it in outpatient clinics as a selected method.

Material & Methods:
A randomized, double-blind, placebo controlled trial is designed. The study protocol was confirmed by Ethics Committee of Tabriz University of Medical Sciences (with the number of 89/3-8/21). According to the results of similar studies that had been estimated the mean pain intensity as 4.5, and considering 20% of pain reduction and clinical variations and statistical power = 0.8 and type I error of α=0.05, the number of patients was determined 40 in each group and 160 in total. Using Rand List software, the patients were divided into four groups randomly, each containing 40 patients enrolled (Figure 1). The inclusion criteria were abnormal uterine bleeding, lack of active uterine bleeding during the biopsy, parity of one or more and also the satisfaction of taking part in the study. Exclusion criteria were pregnancy, suspected PID, known cervical stenosis, significantly impaired respiratory or cardiac functions, active liver disease, adverse reaction to spray and solution of lidocaine, inability to determining pain score according visual analog scale (VAS), chronic pelvic pain.

After obtaining written informed consent from the patients and describing the reasons of selection and also probable side effects of medications and biopsy and training determination of pain intensity with Visual Analogue scale (VAS), the patients were placed in a lithotomy position and the cervix was exposed with a sterile speculum under aseptic techniques. Cervix and vagina were cleansed with povidone Iodine 10% (Behvazan laboratory, Rasht, Iran) and the patients were assigned in four groups according to forms grouping and check lists which were numbered with applying table of random numbers. The person who recorded pain intensity and the patient both, were not informed about grouping and anesthesia method. Also all biopsies were performed by a gynecologist. None of patients was excluded from the study after random allocation.

In the group of patients who received intrauterine lidocaine, 5cc of 2% lidocaine solution was instilled into uterine cavity through the endocervix with an 18-gauge angiocatheter. The angiocatheter was left in place for 3 minutes before it was withdrawn in order to limit backflow and to allow the anesthetic to take effect. Then, endometrial biopsy was performed using a 3mm suction curette pipelle (Trumbull, CT, USA). The second group received 3 puffs of cervical
lidocaine spray 3 minutes before biopsy. In third group, who received intrauterine 2% lidocaine solution in combination with cervical lidocaine spray, 5 cc of 2% lidocaine was instilled into uterine cavity by 18-gauge angiocatheter followed by 3 puff of cervical lidocaine spray, and biopsy was performed after 3 minutes. In the fourth group who received intrauterine distilled water, 5cc of distilled water was injected into the uterus as a placebo by angiocatheter and biopsy was performed after 3 minutes.

Pain intensity scoring was performed by visual analogue scale. This scale is a kind of colored scale which each color is the indicator of pain level, which was calibrated from zero to 10. Zero indicates “Null pain” zone and 10 has been allocated to highest pain intensity. Pain scoring was performed at 3 different time points: During biopsy, immediately and 15 minutes after biopsy (VASt1-VASt3) by a trained nurse. Blood pressure and pulse rate of patients were measured before and after biopsy and vasovagal symptoms such as bradycardia (HR < 60), hypotension (>20% decrease in BP), nausea and vomiting were recorded in check lists. The collected data was analyzed by SPSS Ver. 13 software with descriptive statistics (percentage and mean or median ± standard deviations), Repeated Measures ANOVA (RMA) test and chi-square relationship test to compare the secondary outcomes in four study groups. Also, data with few numbers was evaluated by Kolmogorov-Simonov test to determine normality of distribution. The amounts of P-value less than 0.05 were considered to be statistically significant.

Results:
A total of 160 multiparous women with AUB and age of 40-55 years were divided into four equal groups randomly. Demographic and clinical characteristic were compared using ANOVA and chi square tests, as shown in table 1. The mean pain intensity during endometrial biopsy in the group who received intrauterine lidocaine and intrauterine lidocaine with cervical lidocaine spray was significantly less than the groups who received cervical lidocaine spray and intrauterine distilled water (P<0.001) (Table2). Mean of pain intensity during biopsy was not significantly different between groups who received intrauterine lidocaine and intrauterine lidocaine plus cervical lidocaine spray and also groups who received cervical lidocaine spray and intrauterine distilled water (Figure 2). Table 2 shows the comparison of pain intensity in three times (VASt1-VASt3). According to the table 2, the pain intensity was relieved more considerably immediate and 15 minutes after biopsy in groups that received intrauterine lidocaine and intrauterine lidocaine with cervical lidocaine spray than whom received lidocaine spray and intrauterine distilled water. Although pain relieving in groups who received cervical lidocaine spray and intrauterine distilled water was reduced in immediate stage just after biopsy comparing to biopsy stage, it was not seen any considerable difference in pain intensity 15 minutes after biopsy.

Mean difference in pain intensity during biopsy and 15 minutes after biopsy termination was reduced in groups who received intrauterine lidocaine and intrauterine lidocaine in combination with cervical lidocaine spray compared with the groups who received cervical lidocaine spray or intrauterine distilled water (p<0.001) (Figure 3, Table 3). There was no significant difference between the study groups about adverse effects. The only reported side effect was hypotension which reported in one case in the group who received cervical lidocaine spray and two cases in group who received intrauterine distilled water, which was resolved by trendelenburg position. Endometrial samples were enough for pathological investigations in 100% of cases who received intrauterine lidocaine, 95% for groups who received cervical lidocaine spray and two cases in group who received intrauterine distilled water, which was resolved by trendelenburg position. Endometrial samples were enough for pathological investigations in 100% of cases who received intrauterine lidocaine, 95% for groups who received cervical lidocaine spray with intrauterine lidocaine or just cervical lidocaine spray and 80% for cases who received distilled water.

Discussion:
This study evaluated the different methods of intrauterine lidocaine and cervical spray lidocaine and showed that intrauterine
lidocaine reduced pain considerably during endometrial biopsy with pipelle catheter. Combination of this with cervical lidocaine spray will not tend to more pain relieving. Injecting 5cc of 2% intrauterine lidocaine, 3 minutes before pipelle biopsy decreased pain score comparing to distilled water (placebo) considerably in premenopausal women. Blocking nerve endings within endometrial mucosa was proposed mechanism for pain relieving. Trolice et al. achieved similar results with applying intrauterine 2% lidocaine, but this samples volume was low (8). In a double-blind randomized controlled trial, Chanrachakul et al. (2001) compared the effects of lidocaine and normal saline in pain reduction of outpatient curettage in 140 women of which 70 received normal saline and the other 70 received intrauterine lidocaine. They reported that the intensity of pain was significantly lower in the lidocaine group than in the normal saline group (9). On the other hand Davies et al. suggested that application of lidocaine spray during hysteroscopy, relieved pain significantly only during grasping of the cervix but not during the endometrial biopsy. Since, the cervix did not be grasped with mezzo forceps during pipelle biopsy so it seems that its governing pain did not any role in the study, thus cervical spray of lidocaine in combination with intrauterine lidocaine could not relief pain in more extents. Injection of anesthesia agent into the cervix (paracervical block) not only did not have positive impact on pain relieving but also led to complications such as bradycardia, hypotension and even death (10). In a double blind placebo controlled trial, Api et al suggested that both oral dexketoprofen and intrauterine lidocaine have the same pain relieving effect during fractional curettage but combination of them does not tent to more pain relieving (11). Zupi et al. applied topical anesthesia to relief pain in diagnostic hysteroscopy and endometrial biopsy; they applied 5cc of 2% intrauterine mepivacaine and evaluation of pain reduction on a VAS. Pain intensity was reduced effectively in those who used agent during and after the procedures (12). Guney et al. studied the effect of intrauterine lidocaine with 200 mg of buccal misoprostol in pain decreasing during outpatient endometrial biopsy and suggested that use of 200 mg of misoprostol with 5cc of intrauterine lidocaine relieved pain in premenopausal women but had no effect on menopausal women (5). Dogan et al. conducted a study in which 120 women became candidate of outpatient endometrial biopsy and assigned to four Local Anesthesia Methods in Outpatient Endometrial Biopsy groups; a group received 5cc of intrauterine 2% lidocaine, and the other three received 550mg oral naproxen, 5cc of intrauterine lidocaine and 550 mg oral naproxen plus intrauterine normal saline. They concluded that intrauterine lidocaine instillation significantly decreases pain of pipelle endometrial when used in combination with oral naproxen sodium; while there was not seen considerable difference in two groups which received lidocaine and naproxen with controlling group (13). As it is declared, the results of different researches in this field were not aligned necessarily. Numerous reasons may be involved in the diversity of results of various studies including sample size, applied medicine type, method of its application, age of patients, inclusion and exclusion criteria, pain intensity determination method and times of pain evaluations and statistical methods. In most of studies and also in this study, pain score was more than 6 during endometrial biopsy with using placebo, which indicate the necessity of application of an analgesic agent. The strength of this study was that it was a randomized placebo controlled trial with minimum of 80% and was double-blind and also the procedure was performed by a gynecologist. The weakness of the study was absence of postmenopausal women in the study and so, the results cannot be generalized for the women in this range of ages. It is proposed to apply a similar study on two age groups of pre and postmenopausal women. This study presents that intrauterine lidocaine is a useful and harmless method reducing pain and ailment during outpatient endometrial
biopsy on premenopausal women.

**Conclusion:**
Intrauterine lidocaine was effective during endometrial biopsy, and using it with cervical spray lidocaine had no more beneficial effect.

**Conflicts of interest:**
The authors declare no conflict of interest in this study.

**Acknowledgments:**
We would like to thank authorities of Tabriz University of Medical Sciences for the scientific and ethical approval and financial support of this research. This study has been done as a thesis for specialty degree of Fahimeh Behjati in Women’s Reproductive Health Research Center Tabriz University of Medical Sciences. (proposal ID: 897, IRCT No: IRCT201101135563N2 ).
**Table 1:** Diagnostic and clinical characteristics of the study groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group</th>
<th>Intrauterine lidocaine (n=40)</th>
<th>Cervical lidocaine spray (n=40)</th>
<th>Intrauterine lidocaine+ Cervical lidocaine spray (n=40)</th>
<th>Distilled water (n=40)</th>
<th>Statistical Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>46.85(4.51)</td>
<td>48.02(3.06)</td>
<td>48.02(4.14)</td>
<td>47.62(3.65)</td>
<td>F(3,156)=0.81, P=0.53</td>
<td></td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>72.78(9.61)</td>
<td>71.85(10.32)</td>
<td>72.80(9.36)</td>
<td>74.70(10.43)</td>
<td>F(3,156)=0.63, P=0.59</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.98(5.20)</td>
<td>162.72(4.99)</td>
<td>162.38(6.007)</td>
<td>162.98(4.38)</td>
<td>F(3,156)=0.70, P=0.55</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>3.12(1.28)</td>
<td>3.32(4.43)</td>
<td>3.35(1.52)</td>
<td>3.52(3.52)</td>
<td>F(3,156)=0.58, P=0.62</td>
<td></td>
</tr>
<tr>
<td>Gravidity</td>
<td>3.32(1.43)</td>
<td>3.72(1.64)</td>
<td>3.70(1.55)</td>
<td>4.20(1.24)</td>
<td>F(3,156)=2.28, P=0.08</td>
<td></td>
</tr>
<tr>
<td>Endometrial thickness (mm)</td>
<td>10.92(4.13)</td>
<td>9.90(3.91)</td>
<td>11.35(4.57)</td>
<td>10.60(3.41)</td>
<td>F(3,156)=0.92, P=0.43</td>
<td></td>
</tr>
<tr>
<td>Large size of Uterus</td>
<td>10(25)*</td>
<td>9(22.5)*</td>
<td>9(22.5)*</td>
<td>12(30)*</td>
<td>X²=0.80, df=3, P=0.84</td>
<td></td>
</tr>
<tr>
<td>Fibroma</td>
<td>15(37.5)*</td>
<td>15(22.5)*</td>
<td>13(32.5)*</td>
<td>11(27.5)*</td>
<td>X²=2.38, df=3, P=0.49</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as Mean (SD) unless otherwise is specified; P<0.005
*The data are given as N (%).

**Table 2:** Pain score immediately after biopsy

<table>
<thead>
<tr>
<th>Group</th>
<th>Intrauterine lidocaine (n=40)</th>
<th>Cervical lidocaine spray (n=40)</th>
<th>Intrauterine lidocaine+ Cervical lidocaine spray (n=40)</th>
<th>Distilled water (n=40)</th>
<th>Inter groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS₃₀</td>
<td>3.82(1.21)</td>
<td>6.05(1.39)</td>
<td>3.58(1.10)</td>
<td>7.18(1.97)</td>
<td>F(3,156)=21.08</td>
</tr>
<tr>
<td>VAS₃₅</td>
<td>0.98(0.83)</td>
<td>3.08(1.42)</td>
<td>0.88(0.91)</td>
<td>3.40(1.91)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>VAS₅₀</td>
<td>0.37(0.54)</td>
<td>1.38(1.07)</td>
<td>0.25(0.43)</td>
<td>1.57(1.31)</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as Mean (SD). VAS₃₀: mean pain score during biopsy.
VAS₃₅: mean pain score immediately after biopsy. VAS₅₀: mean pain score 15 minutes after biopsy.
**Figure 1:** Follow the diagram of the progress through the phases of the trial.

Assessed for eligibility 
(n=200)

Excluded 
(n=40)
CVD (n=3)
Pregnant (n=15)
PID (n=3)
Cervical stenosis (n=5)
refused to participate (n=12)

Randomization 
(n=160)

(n=40) 
Received 5ml
intrauterine 2% lidocaine 3 min
before endometrial biopsy. 
Lost to follow up 
(n=0)

(n=40) 
Received cervical
lidocaine spray
3 min before
endometrial biopsy. 
Lost to follow up 
(n=0)

(n=40) 
Received 5ml
intrauterine 2%
lidocaine+Received
cervical lidocaine
spray 3 min before
endometrial biopsy. 
Lost to follow up 
(n=0)

(n=40) 
Received 5ml
intrauterine
distilled water 3 min
before endometrial biopsy. 
Lost to follow up 
(n=0)

**Figure 2:** Mean pain intensity in four groups at three time intervals.
**Figure 3:** Mean differences in pain intensity between four study groups.

References:


