ORIGINAL ARTICLE

Transcervical intrauterine levobupivacaine or lidocaine infusion for pain control during endometrial biopsy

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BACKGROUND: Endometrial biopsy is a common procedure for the investigation of many gynecological disorders including abnormal uterine bleeding, postmenopausal bleeding, abnormal cytology and infertility. Most women experience some degree of discomfort and pain during the procedure. Pain may occur during dilation of the cervix for insertion of the catheter and during endometrial biopsy, which further aggravates pain by inducing uterine contraction.

OBJECTIVES: To determine pain levels during endometrial biopsy by comparing intrauterine instillation of levobupivacaine or lidocaine with placebo in a randomized, double-blinded trial in pre- and postmenopausal women.

METHODS: Ninety patients were allocated to either control or experimental groups before endometrial biopsy. The trial medication was intrauterine anesthesia, either 5 mL 0.9% saline (control group), or 5 mL 0.5% levobupivacaine or 2% lidocaine (experimental groups). Resident doctors used the same endometrial biopsy technique to minimize the risk of technical variation. All tissue specimens were sent for cytopathological examination. The pathologists, who were blinded to the study solution, analyzed all tissue specimens. The primary outcome measure was pain experienced during the procedure. Pain was assessed using a 10 cm visual analogue pain scale. All observed adverse effects were recorded until the patients were discharged.

RESULTS: Pain scores of the intrauterine lidocaine and levobupivacaine groups were found to be significantly lower than the control group. There was no difference between the levobupivacaine and lidocaine groups with regard to pain scores. There was a moderately positive correlation between pain scores and endometrial thickness. No complications were observed due to the procedure. Most of the biopsy results were proliferative and secretory endometrium. Insufficient material causing inconclusive results was observed mostly in the control group.

CONCLUSION: Transcervical intrauterine topical instillation of levobupivacaine or lidocaine causes pain relief during endometrial biopsy. However, further studies are needed to evaluate the effectiveness of intrauterine anesthesia, to determine optimal concentration, volume and waiting time according to the type of local anesthetic agent, and to assess the applicability of the method to other intrauterine procedures.

Key Words: *Bupivacaine; Endometrial biopsy; Lidocaine; Pain*

Une perfusion intra-utérine transcervicale de lévobupivacaïne ou de lidocaïne pour contrôler la douleur pendant une biopsie de l'endomètre

HISTORIQUE : La biopsie de l'endomètre est une intervention courante pour évaluer de nombreux troubles gynécologiques, y compris des saignements utérins anormaux, des saignements postménopausiques, une cytologie anormale et l'infertilité. La plupart des femmes ressentent un certain degré d'inconfort et de douleur pendant l'intervention. Elles peuvent l'éprouver pendant la dilatation du col pour insérer le cathéter et pendant la biopsie de l'endomètre, ce qui accentue la douleur davantage en déclenchant des contractions utérines.

OBJECTIFS : Déterminer le taux de douleur pendant une biopsie de l'endomètre en comparant la perfusion intra-utérine de lévobupivacaïne ou de lidocaïne à un placebo pendant un essai aléatoire à double insu chez des femmes préménopausées et postménopausées.

MÉTHODOLOGIE : Quatre-vingt-dix patientes ont été réparties dans le groupe témoin ou le groupe expérimental avant une biopsie de l'endomètre. L'anesthésie intra-utérine était mise à l'essai, sous forme de 5 mL de solution physiologique 0,9 % (groupe témoin) ou de 5 mL de lévobupivacaïne 5 % ou de lidocaïne 2 % (groupes d'expérimentation). Les médecins résidents utilisaient la même technique de biopsie de l'endomètre pour réduire le risque de variation technique. Tous les prélèvements tissulaires ont été envoyés en vue d'un examen cytopathologique. Les pathologistes, qui ignoraient quelle solution était utilisée, ont analysé tous les prélèvements tissulaires. La mesure d'issue primaire était la douleur ressentie pendant l'intervention. Les chercheurs ont évalué la douleur au moyen d'une échelle analogique visuelle de 10 cm. Ils ont consigné tous les effets indésirables observés jusqu'au congé des patients.

RÉSULTATS : Les indices de douleur des groupes ayant reçu de la lidocaïne ou de la lévobupivacaïne par voie intra-utérine étaient considérablement plus faibles que ceux du groupe témoin. Il n'y avait pas de différence entre les groupes ayant reçu de la lévobupivacaïne et de la lidocaïne sur le plan des indices de douleur. La corrélation entre les indices de douleur et l'épaisseur de l'endomètre était modérément positive. Aucune complication n'a été observée en raison de l'intervention. La plupart des résultats des biopsies étaient un endomètre proliférati f et sécrétoire. Des prélèvements insuffisants responsables des résultats non concluants se sont surtout produits dans le groupe témoin.

CONCLUSION : La perfusion intra-utérine transcervicale topique de lévobupivacaïne ou de lidocaïne soulage la douleur pendant une biopsie de l'endomètre. Cependant, d'autres études s'imposent pour évaluer l'efficacité de l'anesthésie intra-utérine, pour déterminer la concentration, le volume et le temps d'attente optimaux selon le type d'anesthésique local utilisé et pour évaluer l'applicabilité de la méthode à d'autres interventions intra-utérines.

Endometrial biopsy is a common procedure for the investigation of many gynecological disorders, including abnormal uterine bleeding, postmenopausal bleeding, abnormal cytology and infertility (1,2). Most women experience some degree of discomfort and pain during the procedure. Pain may occur during dilation of the cervix for insertion of the catheter and during endometrial biopsy, which further aggravates pain by inducing uterine contraction (1,2).

The effectiveness of intrauterine anesthesia for pain relief in gynecological procedures that involve the uterine cavity has been demonstrated in many studies (3-7). Use of different local anesthetics (ie, lidocaine, mepivacaine) to lessen the pain experienced with endometrial biopsy and other intrauterine procedures, such as hysteroscopy, fractional curettage, hysterosalpingography or removal of a 'lost' intrauterine device, has been investigated in recent studies (4-7).

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Intrauterine instillation of a topical anesthetic is easy, relatively painless and promising for adequate analgesia during endometrial biopsy. This technique may be ideal for endometrial biopsies.

Bupivacaine is a long-acting local anesthetic agent. The effect of bupivacaine has a relatively delayed onset and the duration of action is longer than some other local anesthetics. Another frequently used local anesthetic agent is lidocaine. Its onset is more rapid and the duration of action is shorter.

The goal of the present study was to determine pain levels during endometrial biopsy comparing intrauterine instillation of levobupivacaine or lidocaine with placebo in a randomized, double-blinded study in pre- and postmenopausal women. Types and incidence of possible adverse events were also assessed.

METHOD

The present randomized, double-blinded, placebo-controlled trial was performed in the Department of Obstetrics and Gynecology, Faculty of Medicine, Turgut Özal University (Ankara, Turkey) between September 2009 and July 2010. The aim of the study was to compare the efficacy of intrauterine levobupivacaine versus lidocaine and placebo for pain control in patients undergoing endometrial biopsy. The study was approved by the Human Ethics Committee of the university.

The study population consisted of 101 women who were scheduled for endometrial biopsy due to abnormal uterine bleeding or for preoperative detection of endometrial pathology. Patients who had never been sexually active, with American Society of Anesthesiologists physical status class greater than II, acute cervicitis, profuse uterine bleeding, known allergy to levobupivacaine, a history of impaired liver function, pregnant, cervical stenosis or vaginismus, or who were unable to understand how to score their pain on a 10 cm visual analogue scale were excluded from the study.

Of the 101 patients, 95 were deemed to be eligible and were informed about the study protocol; a signed informed consent was obtained from all patients. Before the procedure, patient demographic data, such as age, gravidity, parity, menopausal status and indication for the biopsy, were recorded. Endometrial thickness was measured using transvaginal sonography before the procedure. Patients were allocated to either control or experimental groups by simple randomization before endometrial biopsy. An assistant who was not involved in the study produced experiment codes using a computer-generated list of random numbers. The codes were individually contained in envelopes that were numbered sequentially. A nurse who had no contact with the participants opened the envelopes and prepared the trial medications accordingly. The trial medications were 5 mL of 0.9% saline for the control group, or 5 mL of 0.5% levobupivacaine (Chirocaine ampule; Abbott, Republic of Ireland) or 2% lidocaine (Aritmal ampule; Biosel, Turkey) for the experimental groups. Trial solutions were contained in identical, colourless, unlabelled 10 mL disposable syringes. All resident physicians and nurses caring for study subjects were blinded to the type of solution.

Biopsies were taken with the Pipelle (Unimar, USA), a flexible plastic catheter with a diameter of 3.1 mm. The same technique was used to sample the endometrium by resident doctors to minimize the risk of technical variation.

The procedures were performed under aseptic technique according to the following protocol: the patient was placed in a modified lithotomy position. A sterile bivalve speculum was introduced into the vagina for visualization of the cervix. The cervix and vagina were then cleansed with 10% povidone iodine solution. To obtain standardization in all cases, a tenaculum was used to grasp the upper limb of the cervix and it was pulled slightly. Unlabelled test solution (5 mL) was instilled through the endocervix into the uterine cavity using an 18 gauge angiocatheter. Each patient received 5 mL of intrauterine 0.5% levobupivacaine, 5 mL of 2% lidocaine (experimental groups) or 5 mL saline (control group) before endometrial sampling. The speculum was removed after instillation, but the angiocatheter was left in place for 15 min before it was withdrawn to decrease backflow and allow the anesthetic to take effect. After 15 min, the speculum was again inserted, the angiocatheter was withdrawn and Pipelle was then pushed into the uterine cavity for three passes to ensure complete sampling. The patients were observed for 60 min in a recovery room and assessed for side effects and complications. None of the patients had received any oral or parenteral analgesic drugs. All tissue specimens were sent for cytopathological examination. The pathologists, who were blinded to the test solution, analyzed all tissue specimens.

The primary outcome measure was pain experienced during the procedure. Pain was assessed using a 10 cm visual analogue pain scale just after the procedure. Patients were asked to rate their pain levels on the visual analogue scale by marking an 'X' on a 10 cm line (0 cm: no pain; 10 cm: unbearable pain). Only the pain scores during endometrial sampling were measured using the scale and recorded. To control for possible confounding as a result of a nonequal distribution of women with pain during insertion, women with speculum insertion pain as well as severe cervical stenosis not allowing entry through the cervical canal were excluded. In cases of intolerable pain, the procedure was terminated immediately, and the pain score was not recorded. Pain experienced during application of the tenaculum was not rated. All observed adverse effects were recorded until the patients were discharged.

Group allocation was unblinded after the statistics were completed. Statistical analyses were performed using SPSS version 15.0 (IBM Corporation, USA). After patient data were entered into the computer, all necessary diagnostic checks and corrections were performed. Conformity of the measured values to normal distribution was examined graphically and using the Shapiro-Wilk test. To present descriptive statistics, numbers and percentages were used for categorical variables, and median (interquartile range) values were used for the data that were not distributed normally; mean ± SD values were used for normally distributed data. For comparison of normally distributed data, ANOVA and post hoc Bonferroni tests were used. The Kruskal-Wallis test and Bonferroni-corrected Mann-Whitney tests were used in comparing data that did not show a normal distribution. Spearman correlation analysis was used for parameters that could affect pain scores. Two-tailed $P<0.05$ was considered to be statistically significant.

RESULTS

Ninety-five women were enrolled in the study and randomly allocated into three groups. Five patients were excluded from the study: three due to pain during speculum insertion and two due to cervical stenosis. Mean age, gravidity, parity, mode of delivery and menopausal status of the women in the three groups were similar. Endometrial thickness was measured by transvaginal sonography before the procedure, and was ≥5 mm in 70% of the patients. There was no difference among groups in terms of endometrial thickness. Because there were only two patients in the postmenopausal group using hormone replacement therapy (one in the levobupivacaine group and one in the control group), this characteristic was not taken into the consideration. Demographic and clinical characteristics of groups are summarized in Table 1.

When the biopsy indications were investigated, of the 90 subjects, biopsies were performed in 67 (74.4%) for abnormal uterine bleeding, in six (6.7%) for postmenopausal bleeding and in 17 (18.9%) for preoperative evaluation of the endometrium.

When pain scores of the groups were compared, scores in the intrauterine lidocaine and levobupivacaine groups were found to be significantly lower than the control group ($Z=3.310$, $P=0.001$; and $Z=3.512$, $P<0.001$, respectively). There was no difference between the levobupivacaine and lidocaine groups in terms of pain scores ($Z=0.467$; $P=0.641$). Distribution of pain scores and median pain scores according to groups are shown in Table 2, Figure 1 and Figure 2.

There was a moderately positive correlation between pain scores and endometrial thickness (<5 mm or ≥5 mm) and a mild positive

TABLE 1
Demographic and clinical characteristics of group

Characteristic	Group			P
	Levobupivacaine	Lidocaine	Control	
Age, years, mean ± SD	44.6±7.9	44.8±8.8	47.8±9.2	0.122
Gravida, median (interquartile range)	3 (2)	2 (2)	3 (2)	0.632
Parity, median (interquartile range)	2 (1)	1 (1)	2 (1)	0.458
Menopausal status, n (%)				
Premenopause	24 (80.0)	23 (76.7)	23 (76.7)	0.938
Postmenopause	6 (20.0)	7 (23.3)	7 (23.3)	
Endometrial thickness, n (%)				
<5 mm	8 (26.7)	10 (33.3)	9 (30.0)	0.853
≥5 mm	22 (73.3)	20 (66.7)	21 (70.0)	

TABLE 2
Distribution of pain scores according to group

Pain score	Group			P
	Levobupivacaine	Lidocaine	Control	
0	9 (30.0)	13 (43.3)	2 (6.7)	0.002*
1	9 (30.0)	5 (16.7)	4 (13.3)	0.233
2	5 (16.7)	3 (10.0)	5 (16.7)	0.684
3	3 (10.0)	5 (16.7)	6 (20.0)	0.539
4	1 (3.3)	3 (10.0)	5 (16.7)	0.201
5	1 (3.3)	0 (0.0)	2 (6.7)	0.242
6	0 (0.0)	0 (0.0)	2 (6.7)	0.106
7	0 (0.0)	0 (0.0)	2 (6.7)	0.106
8	2 (6.7)	0 (0.0)	1 (3.3)	0.242
9	0 (0.0)	1 (3.3)	0 (0.0)	0.330
10	0 (0.0)	0 (0.0)	1 (3.3)	0.330
Median (IQR)	1 (2.25)	1 (3)	3 (3)	<0.001*

*Data presented as n (%) unless otherwise specified. *Significant difference between control versus levobupivacaine and control versus lidocaine. IQR Interquartile range*

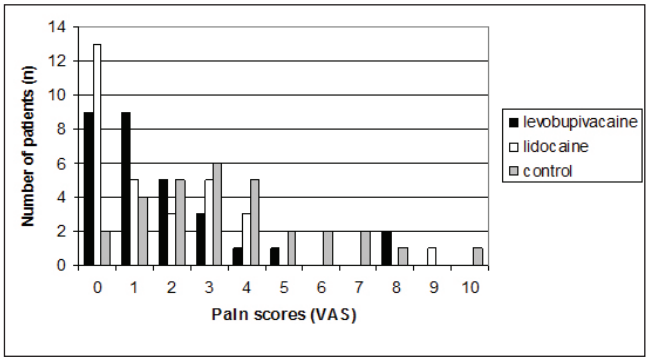

Figure 1) *Distribution of pain scores among groups. VAS Visual analogue scale*

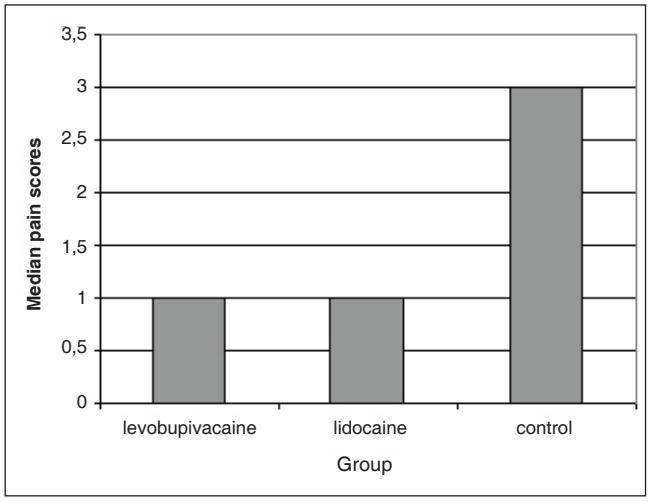

Figure 2) *Median pain scores according to group*

correlation between pain scores and type of anesthesia used (Rho=0.406, P<0.001; and Rho=0.256, P=0.005, respectively). No complications were observed due to the procedure.

Most of the biopsy results showed proliferative (29 [2.2%]) and secretory (18 [20%]) endometrium. Simple hyperplasia was reported in only three cases (3.3%). Insufficient material resulting in inconclusive pathological examination results was mostly seen in the control cases (6 [6.6%]) (Table 3).

DISCUSSION

In the present study, the goal of transcervical anesthetic agent applications was to reduce pain experienced during endometrial biopsies, with an optimum end point of complete pain elimination. In accordance with our goal, within the study groups, 36.7% of patients did not experience any pain (pain score 0) during the procedure, while this rate was only 6.7% in the control group; this difference was statistically significant. A pain score of 1 was observed more frequently in the levobupivacaine group than the other groups; however, this difference was not significant (Table 2). Because the optimal end point was to completely eliminate pain during the procedure, and a pain score of 0 was the only significant difference among groups, obtaining a pain score of 0 may be considered to be clinically significant. However, we speculate that, in addition to measuring pain, patient satisfaction with the overall procedure should also be evaluated before concluding that the reduction in discomfort was clinically significant. This may be considered to be one of the limitations of the present study.

Endometrial biopsy is an essential but painful gynecological outpatient procedure. Procedural pain appears to arise from two separate anatomical structures: the cervix and the uterus. The cervix and uterus are richly innervated and pain perception from the cervix and the corpus of the uterus appears to pass through two distinct neural pathways: the Frankenhäuser plexus (parasympathetic nerves S2, S3 and S4) supplying the cervix and lower uterus, and the sympathetic nerves via the infundibulopelvic ligament from the ovarian plexus supplying the uterine fundus (8,9).

Procedural pain may occur during tenaculum placement, dilation of the cervix for insertion of the catheter and during endometrial biopsy, which further aggravates pain by inducing uterine contraction. The paracervical block aids in decreasing pain of cervical origin (10-12). However, it was found to be ineffective in reducing pain arising from the uterine corpus and was associated with risk of inducing bradycardia, hypotension, convulsion, respiratory arrest and death (13,14). On the other hand, a local or topical anesthetic injected into the

TABLE 3
Histopathological results of patients according to group

	Group			
Endometrial biopsy results	**Levobupivacaine**	**Lidocaine**	**Control**	**Total**
Simple hyperplasia	1 (3.3)	1 (3.3)	1 (3.3)	3 (3.3)
Proliferative endometrium	12 (40.0)	6 (20.0)	11 (36.6)	29 (32.2)
Secretory endometrium	6 (20.0)	5 (16.6)	7 (23.3)	18 (20.0)
Endometrial polyp	2 (6.7)	0 (0.0)	0 (0.0)	2 (2.2)
Stromal glandular destruction	3 (10.0)	0 (0.0)	0 (0.0)	3 (3.3)
Chronic endometritis	1 (3.3)	4 (13.4)	2 (6.7)	7 (7.8)
Menstrual endometrium	3 (10.0)	0 (0.0)	0 (0.0)	3 (3.3)
Endometrial tissue fragments	2 (6.7)	3 (10.0)	1 (3.3)	6 (6.7)
Endometrium under drug effect	0 (0.0)	1 (3.3)	2 (6.7)	3 (3.3)
Atrophic endometrium	0 (0.0)	4 (13.4)	0 (0.0)	4 (4.5)
Blood, fibrin and mucous	0 (0.0)	3 (10.0)	0 (0.0)	3 (3.3)
Insufficient material	0 (0.0)	3 (10.0)	6 (20.0)	9 (10.0)
Total	30 (100.0)	30 (100.0)	30 (100.0)	90 (100.0)

Data presented as n (%)

uterine cavity may inhibit nerve responses and decrease pain primarily arising from the body of the uterus.

Intrauterine instillation of local anesthetic has been variably reported to be ineffective or effective in reducing pain associated with an intrauterine procedure when compared with saline in randomized trials (4,5,15,16); however, in most of the studies, it has been demonstrated to be effective.

In a recent study by Guler et al (17), the efficiency of paracervical block and intrauterine lidocaine in decreasing the pain caused by endometrial sampling was evaluated. They found that intrauterine lidocaine anesthesia decreases pain in endometrial sampling with Pipelle more efficiently than paracervical block. In contrast, a study investigating administration of a 2 mL infusion of 2% lidocaine, in addition to oral naproxen sodium, before hysterosalpingography demonstrated no reduction of pain and the possibility of increased postprocedural pain (18). Zupi et al (4) also found no statistically significant reduction in pain in their study involving 45 women.

Guney et al (19) compared the effects of a local anesthetic and placebo for removal of 'lost' intrauterine devices. A significant difference was found in terms of pain reduction with the use of intrauterine topical local anesthetic either during or immediately after the procedure. Cicinelli et al (5) randomly assigned 80 women to receive 2 mL of 2% mepivacaine or normal saline with a 5 min delay before an office hysteroscopy and/or endometrial biopsy. Results also showed a statistically significant reduction in pain in women receiving the mepivacaine infusion. They reported a considerably higher (32.5%) incidence of vasovagal reaction in their placebo group. Similar results were observed by Dogan et al (7). They found that the combination of local lidocaine and oral naproxen sodium significantly reduced patient discomfort during an endometrial biopsy.

The time interval allowed for the local anesthetic to become effective is also important. The peak anesthetic effect after topical application of 1% lidocaine occurs within 10 min (20). Edelman et al (20) randomly assigned 80 women to receive 10 mL of 1% lidocaine or saline with a 3 min delay during first-trimester abortions and did not observe a reduction of pain during or after suction aspiration. The 3 min waiting period may have been too short. It is also possible that tubal extravasation of high-dose lidocaine may have caused peritoneal irritation. In our study, we waited 15 min after instillation of local anesthetic agents before removing the catheter due to the need for a longer period to attain an anesthetic effect for levobupivacaine. The volume of anesthetic used in our study was 5 mL. The volume of 5 mL of anesthetic is sufficient to fill the uterine cavity. At this volume, tubal extravasation of the drug was also prevented.

Rattanachaiyanont et al (21) found a statistically significant reduction in pain when a combination of paracervical block and intrauterine anesthesia was used before fractional curettage. We did not apply paracervical block because no cervical dilation was necessary in our patients. Patients with cervical stenosis who needed cervical dilation were excluded from the study.

Because pain is a subjective symptom, it is difficult to evaluate, and anxiety may be a potential confounder. Ethnic and cultural differences among patients may affect pain perception and tolerance. Measurement of anticipatory pain may be of value in studies on pain for determination of true pain. It is likely that the speculum insertion measurement is a surrogate for a patient's overall tolerance of pain and/or anxiety. Pain with speculum insertion occurs in many conditions, such as dyspareunia, vulvar vestibular syndrome and vaginismus. To control for possible confounding as a result of a nonequal distribution of women with pain during insertion, we excluded those subjects with speculum insertion pain.

Endometrial biopsy is an essential office procedure to collect tissue for histological evaluation of the endometrium. Patient acceptability and compliance with the procedure may be difficult because of associated pain. According to our MEDLINE search, the present study was the first to evaluate efficacy of intrauterine topical levobupivacaine instillation for endometrial biopsy. We could find only one study (22) investigating the application of transcervical intrauterine bupivacaine for the management of postoperative pain following endometrial balloon ablation. They used dilute bupivacaine solution for prevention of severe postoperative pain after balloon ablation in 10 consecutive women; it was found to be effective with no side effects (22).

In our study, pain scores of the levobupivacaine and lidocaine groups were significantly lower than in the control group. Although not significant, the pain score of the lidocaine group was lower than the levobupivacaine group. This can be explained by the rapid effect of lidocaine and its peak analgesic effect at 10 min.

Another important point is the positive correlations that were found between pain scores and endometrial thickness or type of anesthesia. This means that it is possible to lessen pain in cases with endometrial thickness >5 mm and by appropriate anesthesia.

The effect of endometrial thickness on the pain score may be that the physicians who performed endometrial sampling or biopsy in the cases with a thick endometrium may have performed the procedure more aggressively to obtain more endometrial tissue, thereby causing more pain.

Another important point is the effect of intrauterine anesthesia on pathology results. Intrauterine topical instillation of anesthetic also did not affect pathology results. A result of insufficient material was lower in both groups using a local anesthetic agent compared with control. This can be explained, in contrast to the aforementioned comment, by a lack of sufficient manipulation by the physician due to fear of causing further pain and discomfort of patients during the procedure.

A limitation to our study was the small sample size; however, analysis of our data showed a statistically significant reduction in pain

during endometrial biopsy with intrauterine levobupivacaine and lidocaine in pre- and postmenopausal women, regardless of parity. Although instillation may lengthen the procedure time, the reduction in patient discomfort outweighs the time factor; however, we did not assess satisfaction with the entire procedure. In addition, the cost of occupying a room and of staff should be taken into account; in the present study, these costs were not calculated. These two items may be accepted as major limitations of the present study. Among local anesthetic agents, lidocaine may have an advantage over levobupivacaine because of the shorter time needed for initiation of its effect. We used the same 15 min interval between instillation and the procedure to be able to provide standardization among the groups. The length of this interval may be perceived as too long and is accepted as a drawback of the study. Nevertheless, further studies with larger series are needed to evaluate the effectiveness of intrauterine anesthesia, for determination of optimal concentration, volume and waiting time according to type of local anesthetic agent and also for applicability of the method to other intrauterine procedures.

Because the application of transcervical anesthetic agents into the uterus takes time and may be costly related to occupying a room, it is difficult to recommend the protocol without a recording of patient satisfaction and a cost calculation. However, transcervical intrauterine topical instillation of levobupivacaine or lidocaine leads to pain relief during endometrial biopsy and appears to be a useful and practical method for physicians who consider medication for patients who would have required a paracervical block or are at risk for vasovagal phenomena, or for those who are more concerned about pain.

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