ORIGINAL ARTICLE

Lidocaine and tenoxicam effectiveness for pain relief during Pipelle: Non-randomised double-blind placebo-controlled trial

Mehmet Akif Sargin, Murat Yassa, Ayhan Celik, Emrah Ergun, Niyazi Tug

Abstract

Objective: To compare the effectiveness of intrauterine lidocaine infusion with lidocaine and intravenous tenoxicam for decreasing the pain levels associated with endometrial biopsy.

Methods: This double-blind, placebo-controlled trial was conducted at Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey, from May to November 2015, and comprised patients undergoing endometrial biopsy with Pipelle. Intrauterine lidocaine infusion, paracervical block with lidocaine, intravenous tenoxicam or 4ml intravenous normal saline administered prior to biopsy. The main outcome measure was pain intensity immediately afterwards and 30minutes after biopsy, determined by a visual analogue scale score. Number Cruncher Statistical System 2007 was used for statistical analyses.

Results: Of the 232 participants, intrauterine lidocaine infusion group had 59(25.4%) patients, 57(24.6%) were controls while paracervical block group and intravenous tenoxicam group each had 58(25%) patients. Both visual analogue scale 0 and 30 scores of the control group were significantly higher than the other three groups ($p<0.05$). Also, the scores of intravenous tenoxicam group were significantly higher than both intrauterine lidocaine infusion and paracervical block with lidocaine groups ($p<0.05$ each).

Conclusion: Intravenous tenoxicam had a significantly lower effect than intrauterine lidocaine infusion and paracervical block with lidocaine during the early period after the procedure.

Keywords: Biopsy, Lidocaine, Suction curettage, Tenoxicam, Visual analogue scale. (JPMA 67: 527; 2017)

Introduction

The endometrial sampling procedure (ESP) is a diagnostic tool that is widely performed in outpatient clinics for the evaluation of abnormal uterine bleeding in perimenopausal women and for postmenopausal bleeding.[1] Other indications for an ESP are abnormal cytology, hormone replacement therapy monitoring, and infertility. ESPs can be performed under both local and general anaesthesia. Today, minor surgical procedures are frequently performed in office settings rather than operating rooms.[2] The Pipelle de Cornier is the most popular disposable suction curettage tool for ESPs and is the most studied device in the literature. It features a 23.5cm long, flexible, polypropylene sheath with a 3.1mm outer diameter and a single 2.4-mm opening at its distal end. Withdrawal of an inner plunger creates suction by a negative pressure gradient.[3] The Pipelle is easier, faster, more reliable and more economical than the conventional cervical dilatation and curettage (D&C).[4,5]

The uterus has a complex innervation. The afferent pain fibres of the cervix and lower uterine segment are carried along with the utero-vaginal plexus to the inferior hypogastric plexus. The afferent pain fibres of the uterine corpus continue to the superior hypogastric plexus and ovarian plexus.[6] Different pain control regimens are used for office-based procedures for the safe and successful performance of endometrial sampling to ensure the patient's comfort. These pain control regimens include the paracervical block, injection of local anaesthetics into the uterine cavity, paracetamol administration, non-steroidal anti-inflammatory drugs (NSAIDs), intravenous (IV) morphine, and avoiding the use of a tenaculum for endometrial sampling. Each of these various pain-control regimens are effective in relieving pain that originates from different points of the complexly innervated uterus. Pain reduction by a paracervical block during fractional curettage is an effective method, but this reduction in pain is only moderate.[7,8] The injection of local anaesthetics into the uterine cavity is a simple and effective method to reduce the pain during endometrial biopsy at low cost. The patient acceptability and compliance is also very good.[9] IV paracetamol, IV or oral NSAIDs (e.g. dexketoprofentrometamol, naproxen sodium, etodolac, diclofenac sodium), and IV morphine are demonstrated as effective for treatment of ESP-associated pain.[4,7,10-12]

The current study was planned to compare the

Department of Obstetrics and Gynecology, Fatih Sultan Mehmet Research and Training Hospital, Istanbul, Turkey.

Correspondence: Mehmet Akif Sargin. Email: drmehmetakifsargin@yahoo.com

effectiveness of intrauterine lidocaine infusion (IUL), a paracervical block with lidocaine (PBL), and IV administration of an NSAID (tenoxicam) for decreasing the pain levels associated with endometrial sampling with a Pipelle suction curettage device.

Patients and Methods

This non-randomised, double-blind, placebo-controlled trial was conducted at the Department of Obstetrics and Gynaecology of Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey, between May and November 2015. The efficacy of IUL infusion (Jetokain™ 2ml flacon; Adeka Pharmaceutical Company, Istanbul, Turkey), a PBL, and IV tenoxicam (IVT) (Oksamen™, 20 mg/ml flacon; Mustafa Nevzat, Istanbul, Turkey) was compared with a placebo (normal saline) for pain control in women undergoing endometrial sampling with a Pipelle.

The study was approved by institutional ethics committee. After the participants submitted written informed consent, pelvic examinations were performed by speculum to evaluate abnormal uterine bleeding, vaginal discharge, and to screen for any cervical pathology. Endometrial thickness, uterus, and ovaries were evaluated by transvaginal sonography. Post-power analysis was performed using G Power programme in order to evaluate the sufficiency of the sample size. Post-power effect size value was found to be 0.278 which was calculated considering visual analogue scale (VAS) as the main variable for the 4 groups of patients. Analysis indicated a power of 95.44% at α=0.05 significance level. It was determined that sample size of the study was sufficient and exhibited adequate power level.

The study included women who required further evaluation for abnormal uterine bleeding (e.g. menorrhagia, intermenstrual bleeding, heavy or prolonged uterine bleeding, postmenopausal bleeding, unscheduled bleeding on tamoxifen, or hormone replacement therapy), the presence of atypical glandular cells (AGC) or endometrial cells in cervical cytology, and a requirement for an endometrial biopsy before surgery for other conditions. Exclusion criteria comprised virginity, pregnancy or suspicion of pregnancy, cervical stenosis, vaginismus, any pathology that distorted the cervical canal or uterine cavity, active pelvic inflammatory disease or sexually transmitted infection and purulent cervicitis. Patients with known sensitivity to NSAIDs or lidocaine, epilepsy, peptic ulcer disease, history of impaired respiratory or cardiac conduction functions, history of cerebrovascular or psychiatric disorders, and active liver disease were also excluded. The patients who were illiterate or unable to successfully complete the 10cm VAS pain score were also excluded.

The initial blood pressures and pulse rates of patients were measured. All participants had an 18-20-gauge venous catheter inserted into a superficial vein of the non-dominant hand for patient safety. None of the patients enrolled in the study had taken any oral analgesic drugs prior to the procedure. The IUL group treatment consisted of instillation of 5ml of 2% lidocaine slowly applied into the uterine cavity through a blue feeding catheter (2.70mm in diameter). Endometrial biopsy was started after a 3-minute wait. The PBL group underwent a paracervical block with a total of 5ml of 2% lidocaine solution. The local anaesthetic was injected through a 22-gauge hypodermic needle at the 4 and 8 o'clock positions of the cervicovaginal junction, at approximately 0.5-1cm depth after intermittent aspiration to avoid intravenous injection. The endometrial biopsy was started after a 3-minute wait. The IVT group was administered 4ml tenoxicam intravenously and endometrial biopsy was started after a 30-minute wait. All groups were also administered 4ml saline intravenously as placebo. The IVT and the control group were also submitted to a sham procedure comprising drying of the cervix with gauze for 30 seconds.

All endometrial biopsies were performed by the same operator. Prior to the ESP, another operator explained VAS to the patients and how to score their pain(with 0 indicating 'no pain' or "null pain" zone and 10 indicating the highest pain intensity or worst possible pain).

As the study design was double-blind, the patients, the operator performing VAS, and the gynaecologist performing the procedure were blinded to the assignments and the contents of the intrauterine lidocaine, paracervical block, IVT medications, and control groups. Pain scoring was performed and scheduled at 2 different time points: immediately afterwards and 30minutes after the ESP (VAS 0 and VAS 30).

After completion of the ESP and removal of the speculum, the pain scores (VAS 0) were obtained immediately from the patients; the pain score measurement was repeated 30minutes after the procedure. The patients' data were recorded, including age, gravidity, parity, previous type of delivery, previous curettage history, menopausal status and indications for biopsy. Primary outcome was the pain score in between the groups while secondary outcome was the menopausal status and history of vaginal delivery. All patients were observed for 30minutes in the recovery room. We completed the present study without any complications. No further follow-up was scheduled.

Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, United States) software was used for statistical analyses. In addition to descriptive statistics (mean, standard deviation, median, frequency and ratio), one-way analysis of variance (ANOVA) test was used for group comparisons of normally distributed variables. Kruskal-Wallis test was used for group comparisons, Wilcoxon signed-rank test was used for intergroup comparisons of non-normally distributed variables. Pearson's chi-squared test and Mann-Whitney U test was used to determine the group that caused significant difference. P<0.05 was considered statistically significant.

Results

Of the 240 patients enrolled, 8(3.33%) were excluded, including 1(0.42%) participant in the IUL group, 2(0.83%) in PBL, 2(0.83%) in IVT and 3(1.25%) in the control group, because of cervical stenosis or need of cervical dilatation during the endometrial sampling. Finally, 232(96.7%) participants were included. Of them, the IUL group had

Table-1: Demographic and clinical data of the patients.

	IUL (n= 59)	PBL (n= 58)	IVT (n= 58)	Control (n= 57)	p-value
Age (years)	46.2±7.5	47.1±7.9	46.7±9.5	46.8±6.3	[a]0.94
Gravida	3.9±1.7	3.3±2.1	4.3±1.9	3.8±2.0	[b]0.05
	3 (0-9)	3 (0-9)	4 (0-9)	3 (0-11)	
Parity	2.8±1.1	2.5±1.5	3.1±1.2	2.6±1.2	[b]0.02*
	3 (0-5)	2 (0-6)	3 (0-6)	2 (0-6)	
Abortus	0.8±1.0	0.7±1.0	0.9±1.1	1.0±1.4	[b]0.57
	0 (0-4)	0 (0-3)	1 (0-5)	1 (0-9)	
Curettage	0.3±0.6	0.05±0.2	0.1±0.3	0.1±0.5	[b]0.001**
	0 (0-3)	0 (0-2)	0 (0-1)	0 (0-4)	
Endometrial thickness (mm)	7.9±2,8	8.3±3	8.0±2,5	8.7±3,7	[b]0.81
	8 (3-16)	8 (2-15)	8 (4-15)	8 (2-20)	

[a]One-WayAnova Test [b]Kruskal-Wallis H Test *p<0.05 **p<0.01
Data given as mean± Standard Deviation and Median (Min - Max)
IUL: Intrauterine lidocaine infusion anaesthesia
PBL: Paracervical block with lidocaine,
IVT: Intravenous tenoxicam

Table-2: Comparison of VAS 0 and VAS 30 scores according to the anaesthesia type.

	IUL (n= 59)	PBL (n= 58)	IVT (n= 58)	Control (n= 57)	p-value
VAS 0	3.3±1.6	3.7±1.4	5.2±1.7	6.1±1.3	[a]0.001**
	3 (1-7)	4 (1-7)	5 (2-9)	6 (4-9)	
VAS 30	1.3±0.9	1.6±1.1	2.5±1.3	3.5±1.3	[a]0.001**
	1 (0-4)	1 (0-5)	3 (0-6)	3 (1-8)	
Intergroup comparisons (p)	[b]0.001**	[b]0.001**	[b]0.001**	[b]0.001**	
Decrement VAS 0 and 30	2.0±1.2	2.1±1.1	2.6±1.2	2.6±1.2	0.003**
Intergroup analysis of VAS 0 scores	IVT&IUL				[c]0.001**
	IVT&PBL				[c]0.001**
	IVT & Control				[c]0.003**
	Control & IUL				[c]0.001**
	Control & PBL				[c]0.001**
Intergroup analysis of VAS 30 scores	IVT & IUL				[c]0.001**
	IVT & PBL				[c]0.001**
	IVT & Control				[c]0.001**
	Control & IUL				[c]0.001**
	Control & PBL				[c]0.001**

[a]Kruskal-Wallis H Test [b]Wilcoxon Signed Ranks Test [c]Mann Whitney U Test *p<0.05 **p<0.01.
Data given as mean± Standard Deviation and Median (Min - Max).
IUL: Intrauterine lidocaine infusion anaesthesia. PBL: Paracervical block with lidocaine. IVT: Intravenous tenoxicam. VAS: Visual analogue scale.

Table-3: Comparison of VAS 0 and VAS 30 scores according to the menopausal state and history of vaginal delivery of the patients.

		Total (n=232)	IUL (n=59)	PBL (n=58)	IVT (n= 58)	Control (n= 57)	VAS 0	VAS 30
Menopausal State	Pre-Menopause	81	22 (37%)	19 (33%)	21 (36%)	19 (33%)	4.6±1.94 4 (1-9)	2.33±1.43 2 (0-8)
	Peri-Menopause	82	20 (34%)	22 (38%)	19 (33%)	21 (37%)	4.54±1.99 4 (1-8)	2.21±1.49 2 (0-6)
	Post-Menopause	69	17 (29%)	17 (29%)	18 (31%)	17 (30%)	4.79±1.75 5 (1-8)	2.24±1.4 2 (0-5)
Individually comparisons of VAS 0 and 30 scores according to menopausal state (p)							p^a=0.58	p^a=0.84
Vaginal Delivery	Presence Vaginal Delivery	174	45 (76%)	43 (74%)	44 (76%)	42 (74%)	4.73 ± 1.44 5 (1-8)	2.31 ±1.34 2 (0-6)
	Absence Vaginal Delivery	58	14 (24%)	15 (26%)	14 (24%)	15 (26%)	4.94 ± 1.80 4 (1-9)	2.46 ± 1.42 2 (0-8)
Individually comparisons of VAS 0 and 30 scores according to history of vaginal delivery (p)							p^b=0.48	p^b=0.63

[a]Pearson'schi-squared test, [b]Mann-Whitney U test, p>0.05.
Data given as mean±Standard Deviation and Median (Min - Max)
IUL: Intrauterine lidocaine. PBL: Paracervical block with lidocaine. IVT: Intravenous tenoxicam. VAS: Visual analogue scale.

59(25.4%) patients, 57(24.6%) were controls while PBL and IVT groups each had 58(25%) patients. The mean age was 46.2±7.5 years in the IUL group, 47.1±7.9 years in PBL, 46.7±9.5 in IVT and 46.8±6.3 among controls (p=0.94). The mean endometrial thickness was 7.9±2.88mm (range: 3-16), 8.3±3.8mm (2-15), 8.0±2.58mm (4-15) and 8.7±3.78mm (2-20) among the four groups, respectively (p=0.81). Mean age, gravidity, abortus and endometrial thickness in the four groups were similar except parity. Although parity showed a statistically significant difference (p=0.02) between the study arms, it was not a source of bias since vaginal delivery rates did not exhibit statistically significant difference (p>0.05) (Table-1).

Abnormal uterine bleeding was observed in 133(57.3%) patients, postmenopausal bleeding in 40(17.3%), unscheduled bleeding on tamoxifen or hormone replacement therapy in 3(1.2%), presence of AGC-endometrial cells in cervical cytology in 1(0.04%), requirement of an endometrial biopsy prior to the surgery for other conditions in 32(13.7%) and incidental finding of thickened endometrium 17(7.3%) or fluid in 6(2.6%) postmenopausal women.

VAS 0 and VAS 30 scores were significantly different between the four groups (p=0.001). VAS 0 scores of IVT group were significantly higher than the IUL and PBL groups (p=0.001). VAS 0 scores of the control group were significantly higher than the IUL (p=0.001), PBL (p=0.001) and IVT (p=0.003) groups.

A statistically significant difference was found between all the groups for the VAS 30 scores (p=0.001). VAS 30 scores of IVT group were significantly higher than the IUL and PBL groups (p=0.001). VAS 30 scores of the control group were significantly higher than the IUL, PBL and IVT groups (p=0.001) (Table-2).

Menopausal status and history of vaginal delivery of the patients were found similar among the four groups. VAS 0 scores of the 174(75%) patients with history of at least one vaginal delivery and the 58(25%) patients with no history of vaginal delivery were 4.73±1.44 and 4.94±1.80 (p=0.48), respectively. Their VAS 30 scores were 2.31±1.34 and 2.46±1.42 (p=0.63), respectively (Table-3).

Discussion

The present study demonstrated that IUL and PBL are prominently effective methods in pain management during endometrial biopsy with Pipelle. IVT administration was also statistically effective when compared to control group, however, it did not decrease pain scores as much as IUL and PBL.

The Pipelle de Cornier is the most popular disposable biopsy device for ESP, and provides a relatively painless method that frequently does not require cervical dilatation and shows low morbidity.[13] A small pilot study to compare the use of infant feeding tubes (IFT) and a Pipelle for endometrial biopsy showed that the IFT had lower pain scores.[5] However, no statistical analysis was performed in that study due to the small numbers and IFTs are not widely used in daily gynaecology practice. Currently, the Pipelle is the most common endometrial sampling device used in gynaecology and obstetrics clinics, including our own.

Although endometrial sampling with a Pipelle is considered to be painless, a moderate degree of pain was expressed by the patients when anaesthesia was not

applied during the procedure.[14] Different anaesthesia and analgesia techniques have been described in the literature, with the most frequently used main techniques being intrauterine local anaesthesia, paracervical blocks, NSAIDs (oral, intravenous or intramuscular), and paracetamol (intravenous). The current study was conducted to compare effect of the IUL, PBL and IVT. Evaluation was made using VAS 0 and VAS 30 scores, following the guidance of the literature. In contrast to some articles that have compared the pain scores before and during the biopsy process, in our opinion the preparation phase of the biopsy, consisting of inserting the vaginal speculum and holding the cervix by the tenaculum, may cause inaccuracies in pain assessment. We believe that the pain scoring should only start immediately after the biopsy. The VAS 0 and VAS 30 scores showed that IUL was more effective than PBL and IVT in reducing pain in patients who did not undergo cervical dilatation.

The most commonly used local anaesthetic in studies is lidocaine, although lignocaine, mepivacaine, and levobupivacaine are also widely used. The main successful usage for pain reduction are in endometrial sampling with a Pipelle,[8,15] first-trimester suction termination,[16] hysteroscopy,[17] saline solution infusion sonohysterography,[18] and removal of a lost intrauterine device (IUD).[19] On the other hand, IUL is found ineffective and does not reduce pain scores, according to some articles, during IUD insertion,[20] laminaria insertion,[21] and outpatient transcervical tubal sterilisation.[22]

The comparison between IUL and intrauterine saline infusion in several articles, using the pain VAS to determine the efficacy, indicated that administered lidocaine concentrations vary from 1-2% up to 4% and the volume ranges from 2-10 ml. The waiting period after lidocaine application is generally 3-5 minutes. The administration of higher volumes of lidocaine can lead to tubal extravasation and subsequent peritoneal irritation and abdominal pain.[16] Thus, we applied 5ml of 2% lidocaine in our study and used a 3-minute wait time after the biopsy to achieve successful pain management. IUL is effective for surgical intervention of the corpus uteri. Topical anaesthetic spray is also found insufficiently effective at inhibiting nerve responses and decreasing the pain that originates from the corpus uteri. Cervical dilatation is one of the major causes of pain associated with endometrial sampling procedures.[23] In the present study, we included patients who had no necessity for cervical dilatation and this is the one reason or explanation for our lower pain scores.

Paracervical block has been reported as an effective pain-reducing anaesthetic technique for endometrial sampling in most studies.[8,24] The paracervical block aids in reducing pain from cervical dilatation and surgical intervention in the cervix, lower uterine segment, and upper vagina. However, it is ineffective at reducing pain originating from the uterine corpus. Nerves enter the uterus through the cardinal ligaments (at the 3 and 9 o'clock positions) and the uterosacral ligaments (at the 5 and 7 o'clock positions). Performing a paracervical block at the 4and 8 o'clock positions has a better impact on the pain score rather than one performed at the 3 and 9 o'clock or 5 and 7 o'clock positions.[24] The possible complications of the paracervical block are bradycardia, hypotension, convulsion, and respiratory arrest (vasovagal syncope or cervical shock). Respiratory arrest may also result in death.[25]

In the present study, we found significant difference in pain scores between the application of intrauterine lidocaine or performing a paracervical block immediately after and 30minutes after the ESP. A marked reduction in the pain scores has been reported in a previous study in which both IUL and PBL were applied together.[16] In fact, combined anaesthesia methods are naturally more effective. However, in our study, the aim was to be minimally invasive. We believe that intrauterine injection of local anaesthetic is sufficient for patients who do not require cervical dilatation.

The use of NSAIDs, paracetamol, and opioids has been commonly studied for pain relief during different minor gynaecologic surgical procedures. To our knowledge, ours is the first study to evaluate the efficacy of IVT and compare it with intrauterine local anaesthesia and paracervical block for pain relief during endometrial biopsy with a Pipelle.

Tenoxicam belongs to the class of NSAIDs known as oxicams, which exert potent anti-inflammatory and analgesic actions by inhibiting prostaglandin synthesis. Compared with many other NSAIDs, tenoxicam offers some advantages as it can conveniently be administered once daily and dosage adjustment is not required in the elderly or in patients with renal or hepatic impairment.[25] It is superior to naproxen sodium and diclofenac sodium in terms of upper gastrointestinal complications, such as gastrointestinal perforation, bleeding, and obstruction.[26] We found statistically significant difference between the tenoxicam group and control group in terms of VAS 0 and VAS 30 scores. Api et al. reported an equal effect in decreasing pain among premenopausal women during fractional curettage between administration of oral 25mg dexketoprofentrometamol 30 minutes before the

procedure and intrauterine lidocaine.[5] Buppasiriet al. reported a pain relief study with oral 500mg mefenamic acid 2 hours before the procedure and also with a paracervical block. They reported no statistically significant difference between mefenamic acid administration and a paracervical block; however, fewer side effects occurred in the paracervical block group.[27]

Manyou and Phupong found that administration of 120mg oral etoricoxib 30 minutes before the procedure slightly reduced pain during fractional curettage under a paracervical block.[28] However, in another trial by Poomtavorn et al., the administration of 50mg rofecoxib 60minutes before procedure was ineffective at reducing pain during uterine curettage.[29] Dogan et al. found that the administration of 550mg naproxen sodium 60 minutes before procedure was equally effective as intrauterine lidocaine injection. They concluded that a more significant decrease in pain perception could only be obtained by the combined use of these drugs.[4] IVT may be as effective as IUL and PBL in the case of questioning the pain scores after the first 30minutes following the procedure.

In some of the previous studies,[10,15] menopausal status has been suggested to influence the pain scores during minor gynaecologic procedures. In particular, postmenopausal genital atrophic changes might be the responsible factor for this pain. We also found no significant differences in pain scores between the intervention and control groups according to the menopausal status (premenopausal, perimenopausal, and postmenopausal). We think that the use of the Pipelle endometrial sampling device, which has such thin features (a 3mm diameter) is the main reason for not finding any statistically significant difference between the groups according to their menopausal status.

The strengths of this study include its double-blind and placebo-controlled trial design, the evaluation with a validated method (VAS) of pain measurement in Pipelle endometrial sampling, the statistical evaluation of three different sub-groups according to their menopausal status, performing the procedure by only one and the same gynaecologist in order to avoid personal differences between operators. The limitations of this trial include the inadequate number of premenopausal, perimenopausal and postmenopausal subgroup samples for a power analysis and the shortness of the patient observation time after the endometrial biopsy for the tenoxicam administered group.

Conclusion

IUL, PBL and IVT reduced the pain associated with a Pipelle endometrial biopsy. Although similar pain score results were achieved with a PBL, IUL was superior in terms of the reduced risk of serious complications and the ease of application. IVT had a slightly lower effect than IUL and PBL during the early period after the procedure. Tenoxicam may be more effective if it is administered later than 30 minutes or its effect may be apparent much later than 30 minutes in terms of pain scoring. Further research that assesses the pain scores in later periods is needed.

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