ORIGINAL ARTICLE

Comparison of placebo and intrauterine lidocaine with/or without rectal diclofenac sodium suppositories used in office endometrial biopsy

Cengiz Kaya,[1] Elif Bengi Sener,[2] Ersin Koksal,[3] Yasemin Burcu Ustun,[4] Handan Celik,[5] Ali Haydar Sahinoglu[6]

Abstract

Objective: To compare the effects of intrauterine lidocaine, intrauterine lidocaine plus rectal diclofenac, and a placebo on analgesia and to determine the satisfaction of patients and surgeons in cases of endometrial biopsy.

Methods: The double-blind, randomised, placebo-controlled study was conducted in the Department of Obstetrics and Gynaecology of the Ondokuz Mayis University, Samsun, Turkey, from April 2013 to January 2014, and comprised patients scheduled for in-office endometrial biopsy. They were divided into three groups: Group P, 5ml of 0.9% saline intrauterine; Group L, 5ml of 2% lidocaine intrauterine; and Group LD, 5ml of 2% lidocaine intrauterine ±10min before the procedure plus 50mg of rectal diclofenac sodium. Haemodynamic changes and visual analogue scale scores were recorded during the preoperative period, when the cervix was grasped with a tenaculum, immediately after intrauterine instillation, during uterine curettage and at postoperative 10 min. The patient and the surgeon were questioned about their satisfaction 15 min after the procedure. SPSS 21 was used for statistical analysis.

Results: The 90 patients in the study were divided into three equal groups of 30(33.33%) each. There were no statistically significant inter-group differences in age, bodyweight, parity, number of postmenopausal patients, haemodynamic parameters and American Society of Anesthesiologists scores ($p>0.05$ in all categories). In Group P, the visual analogue scale score estimated when the cervix was grasped with the tenaculum was lower when compared with Group L and Group LD ($p=0.029$ and $p=0.007$, respectively). At other measurement time points, the scores did not differ between the groups. The groups did not differ with respect to patient and surgeon satisfaction and complication rates ($p>0.05$).

Conclusion: Intrauterine lidocaine or intrauterine lidocaine plus rectal diclofenac application had no effect on visual analogue scale scores, patient satisfaction and vasovagal reaction.

Keywords: Endometrium, Biopsy, Office Surgery, Analgesia. (JPMA 65: 29; 2015)

Introduction

Office endometrial biopsy has become a prevalent procedure in the investigation of abnormal uterine bleeding and intrauterine pathologies.[1-3] Avoidance of anaesthesia-related complications, shorter hospital stays, use of routine outpatient examination rooms, fewer complication rates and lower expenditures have greatly contributed to increasingly higher numbers of in-office gynaecological procedures.[4,5]

The most important reason for failed office gynaecological procedures is pain felt by the patient.[2] As a result, the cooperation of the patient decreases throughout the procedure, preventing completion of the procedure and achievement of the desired goal. As yet, there is no consensus in literature on optimal pain management during gynaecological procedures.[4,6] Although some studies have reported an acceptable level of pain during gynaecological procedures without using any anaesthetic, but not using anaesthetic raises concerns about bradycardia, hypotension, premature termination of the procedure or potential pain.[7-10]

Analysis of the neurophysiological mechanism of pain observed during in-office endometrial biopsies has revealed that painful stimuli stemming from the cervix and vagina are transmitted through pudendal and pelvic splanchnic nerves into S2-S4 spinal ganglia and that painful stimuli arising from the uterus are transmitted to T12-L2 spinal ganglia via hypogastric nerves.[11] Although the uterus and the cervix are insensitive to heat and slight touch, grasping and dilating the cervix with a tenaculum, uterine distension, endometrial destruction and biopsy elicit pain.[5,11] Prostaglandin release secondary to uterine and cervical manipulations also induces pain. Therefore, the use of prostaglandin synthetase inhibitors might be important for analgesia.[5]

Intrauterine (IU) anaesthesia is the blockage of nerve endings of the uterine body and fundus through IU instillation of a local anaesthetic agent.[12] Although some studies reported the achievement of analgesia using IU anaesthesia, but others did not.[2,3,12-14]

[1-4,6]Anesthesiology and Reanimation Department, [5]Gynecology and Obstetrics Department, Faculty of Medicine, Ondokuz Mayis University, Samsun, Turkey.
Correspondence: Cengiz Kaya. Email: raufemre@yahoo.com

The current study attempted to determine an optimal method of analgesia. We reviewed the literature and having taken into account the controversial effects of IU local anaesthetic instillation and the lack of the prostaglandin component involving mechanisms of pain, the use of non-steroidal anti-inflammatory drugs (NSAIDs) was considered. NSAIDs are generally subjected to critically important first-pass metabolism in the liver.[15] To improve the bioavailability of the drug used, a rectal application, which bypasses portal circulation, is preferable.[16] Therefore in our study the rectal route of application, the use of which we hadn't previously encountered in similar procedures, was preferred with the aim of achieving more effective analgesia.

Patients and Methods

The double-blind, randomised, placebo-controlled study was conducted in the Department of Obstetrics and Gynaecology of the Ondokuz Mayis University, Samsun, Turkey, from April 2013 to January 2014, and comprised patients scheduled for in-office endometrial biopsy.

To determine an adequate study sample, literature was used as a guide[17] on the basis of which an analysis of the statistical power was made based on a visual numerical rating scale parameter. To achieve a statistical power of 97% (Cronbach's=0.05) within 95% confidence interval (95% CI=0.824-1) for each group, 30 cases were deemed to be adequate.

Those included in the study had indications of abnormal uterine bleeding and dysmenorrhea. Those excluded were virgin patients; patients classified as having a risk greater than II according to the American Society of Anaesthesiologists (ASA); patients with a genital infection (acute cervicitis), hypersensitivity to NSAIDs, peptic ulcers, inflammatory bowel disease, porphyria, a history of previous cervical surgery, anti-arrhythmic drug use, epilepsy, hepatic dysfunction or cervical stenosis. Pregnant women, patients requiring endocervical curettage and patients who did not understand how to rate the 10cm visual analogue scale (VAS) were also excluded.

Before randomisation of the patients into three groups, signed informed consent was obtained from all the patients. The study drugs were allocated among the groups as follows: Group P, 5ml of 0.9% saline IU; Group L, 5ml of 2% lidocaine IU (Jetocaine simplex ampoule; Adeka Pharmaceutical Company, Istanbul, Turkey); and Group LD, 5ml of 2% lidocaine IU ±10 min before the procedure plus 50mg of rectal diclofenac sodium (Dikloron supp; Deva Company, Istanbul, Turkey). The patients did not receive any pre-medication. Randomisation was made using codes in the random number list. These codes were enclosed in opaque, sealed envelopes. An independent assistant blinded to the study opened the envelopes, prepared suitable medications and administered the rectal applications to the patients in Group LD. The physical appearance of the formulated solutions was similar (colourless and clear), and these solutions were administered in 10ml unmarked disposable injectors. Thus, the gynaecologist and the assistant keeping the records of the patients had no knowledge about the anaesthetic/analgesic agent used. The procedure was performed by the same gynaecologist to minimise risks and technical variations.

VAS was used to evaluate the patient's pain score by marking a cross on a 10cm line, with 0 on the left side indicating no pain and 10 on the right side indicating the worst imaginable pain. The patients were informed about the scoring system prior to the commencement of the study. Heart rate, blood pressure and respiratory rate were monitored continuously in all the groups. A 20-gauge cannula was inserted into the back of the hand. The women in all the groups were placed in the lithotomy position, and a bimanual examination was done. The cervix, fornix and vagina were cleansed with an antiseptic solution. After cleaning and draping, a bivalved speculum was inserted to expose the cervix, and the anterior lip of the cervix was grasped with a single-tooth tenaculum. Then, an 18-gauge Angiocath (Bicakcilar, Istanbul, Turkey) was slowly advanced through the cervical canal, and its hub was engaged so as to obstruct ectocervix's opening. The study drug was then instilled into the uterine cavity through a catheter, and the catheter was held in position for 5min to prevent backflow of the instilled solution.

For the endometrial biopsy, a 4mm vacuum suction curette (Karmen Cannula, Plastimed, Istanbul, Turkey) was inserted into the uterine cavity. A 20ml injector was then mounted onto the cannula, and negative pressure was created to gently curette all the mucosal surface. The patient was kept in the observation room for 20 minutes after the procedure.

Heart rate, mean arterial blood pressure, respiratory rate and VAS were recorded during the preoperative period, when the cervix was grasped with a tenaculum, immediately after the IU instillation, during uterine curettage and at postoperative 10min.

Side effects were observed and treated. Vasovagal reaction was defined as bradycardia (pulse <60 per min) or hypotension (>20% fall from baseline), along with nausea, vomiting, sweating, dizziness or fainting. The patient and the surgeon were questioned about their satisfaction 15 minutes after the termination of the

procedure, and satisfaction was rated as good to excellent, moderate or poor.

Data was analysed using SPSS 21. In inter-group comparisons, mean pain scores, age, bodyweight, and parity were evaluated using a nonparametric analysis of variance test (Kruskal-Wallis) with Bonferroni correction, while ASA, complications, number of postmenopausal complications, patient and surgeon satisfaction were assessed by chi-square test. For specific purposes, analysis of variance (ANOVA) was also used.

Results

Out of the total 410 patients who had consultations at the Clinic for endometrial biopsy 90(22%) were included in the study to meet the sample size requirement. Those included were divided into three equal groups of 30(33.3%) each.

There were no statistically significant inter-group differences in age, bodyweight, parity, number of postmenopausal patients, haemodynamic parameters and ASA scores (p>0.05 each) (Table-1). Biopsies were performed in 1(3.33%) patient in Group L and 1(3.33%) patient in Group LD for dysmenorrhoea, while the remaining patients underwent biopsy because of abnormal uterine bleeding.

In Group P, the visual analogue scale score estimated when the cervix was grasped with the tenaculum was lower when compared with Group L and Group LD (p=0.029 and p=0.007, respectively). At other measurement time points, the scores did not differ between the groups (Table 2).

The groups did not differ with respect to patient and surgeon satisfaction and complication rates (p>0.05).

The complication rates did not differ between the groups. 2(6.66%) patients in Group L and Group LD had a vasovagal episode, suffering from hypotension, or felt like fainting and became pale. The patients recovered

Table-1: Demographic Characteristics.

	Group P (n=30) Median (Max-Min)	Group L (n=30) Median (Max-Min)	Group LD (n=30) Median (Max-Min)	p
Age (years)	48 (78-34)	45 (80-30)	46 (85-33)	0.405
Weight (kg)	74.5(101-47)	80(110-48)	73.5(103-43)	0.722
Parity	3 (9-0)	2(7-0)	3(9-2)	0.201
Number of postmenopausal women	4 (%13,3)	4 (%12,9)	7 (%23,3)	0.466

Table-2: Visual Analogue Scale scores.

	Group P (n=30) Median (Max-Min)	Group L (n=30) Median (Max-Min)	Group LD (n=30) Median (Max-Min)	p
Preoperative	0 (3-0)	0 (3-0)	0 (3-0)	0.09
Grasping of cervix	0 (10-0)*	2 (10-0)	3 (8-0)	0.005
Uterine instillation	2 (8-0)	2 (10-0)	3(8-0)	0.060
Curettage	4 (10-1)	6 (10-0)	7 (10-0)	0.299
Postoperative 10 min	0 (4-0)	1 (7-0)	1,5 (7-0)	0.066

*: p<0.05 when compared to Group L and Group LD.

Table-3: Mean Arterial Blood Pressure.

	Group P (n=30) Median (Max-Min)	Group L (n=30) Median (Max-Min)	Group LD (n=30) Median (Max-Min)	p
Preoperative	93.46±18.30	95.58±13.43	102.36± 17.61	0.099
Grasping of cervix	95.36±18.30	99.22±15.62	105.43±15.66	0.065
Uterine instillation	97.60±19.37	99.67±15.73	108.76±16.11	0.051
Curettage	104.26±17.84	102.96±18.97	110.86±19.99	0.227
Postoperative 10 min	90.70±19.81	94.29±12.81	99.16±16.21	0.143

following intravenous administration of 5mg of ephedrine and infusion of fluids.

There were no inter-group differences found in mean arterial pressure, heart rate or respiratory rate ($p>0.05$) (Table-3).

Discussion

The study evaluated the effects of IU lidocaine, IU lidocaine + rectal diclofenac, and a placebo on analgesia and on patient and surgeon satisfaction in patients who underwent in-office endometrial biopsy. Based on their VAS scores, IU lidocaine or IU lidocaine + rectal diclofenac did not demonstrate any analgesic efficacy. However, the VAS scores estimated at the time of grasping the cervix with a tenaculum were significantly lower in Group P.

One study demonstrated that when compared with a placebo, VAS scores estimated during 5ml of IU 2% lidocaine instillation were lower, without any statistically significant difference between them.[18] Another study also found no difference in the VAS scores in patients administered 5ml of 2% lidocaine IU or a placebo.[12] However, another study demonstrated improved VAS scores with 2ml of 2% mepivacaine IU compared to those in the placebo group.[19] As the study included only postmenopausal women, however, this finding cannot be generalised to premenopausal women.[20] Another study also demonstrated higher effectiveness of 5ml of 2% mepivacaine IU compared to a placebo.[21] However, as the study population was small (n=45), the results were not found to be statistically significant. As is the case in our study, the lack of efficacy of the IU instillation of local anaesthetic agent can be attributed to the IU applications not having any effect on the sensorial fibres associated with paracervical and uterosacral ligaments.[5] In addition, a waiting period of 5min after IU instillation might not be sufficient for the blockage of the nerve endings, which are located deep within the myometrium, cervical stroma and visceral peritoneum.[4]

Oral doses of diclofenac are subject to hepatic first-pass metabolism, and only 60% of the administered drug enters the systemic circulation.[16] However, with rectal applications, the portal circulation can be bypassed. As a result, the average bioavailability of diclofenac reaches 78%. Therefore, we used a rectal formulation of diclofenac sodium in the present study.[16]

In our study, the highest VAS scores were obtained in the IU lidocaine + rectal diclofenac group. The relatively higher number of postmenopausal patients in our study might have contributed to this outcome. Indeed, endometrial biopsies are more painful in postmenopausal women because of the development of uterine involution and cervical stenosis associated with hormonal changes occurring during the postmenopausal period.[17,22]

One study compared 500mg of oral mefenamic acid and placebo and found that mefenamic acid was ineffective during the procedure, yielding decreased VAS scores after the procedure.[1] Cervical and uterine manipulation leads to prostaglandin release, which might induce postprocedural pain. Therefore, it has been asserted that the use of NSAIDs rather than procedural analgesia is a more logical approach for the relief of late-term postprocedural pain.[5] In our study, we monitored the patients for only 10 minutes after the procedure. Thus, we could not evaluate the long-term effects of diclofenac on pain relief.

One study compared 25mg of oral dexketoprofen and an intracervical application of 5ml of 2% mepivacaine in postmenopausal women and found comparable efficacy of both drugs during diagnostic hysteroscopy as assessed with VAS scores.[22] The effectiveness of dexketoprofen depends on the timing of its administration (1 hour before the procedure) and the onset of its mechanism of action. In our study, the ineffectiveness of diclofenac might be related to its administration 10min before the procedure. According to one study, diclofenac reaches peak plasma levels 20-60 minutes after its administration.[5] In our study, due to a large patient load in the department of gynaecology and obstetrics, a limited number of patient beds in the ward and a large number of procedures, we could administer the rectal diclofenac suppository only 10min before the office endometrial biopsy. This was the allotted waiting period for the patients to lie on the bed to allow absorption of the drug.

An inability to adjust the time interval between the administration of a drug and the onset of the procedure can have a serious effect on outcomes. A study compared the efficacy of sublingual buprenorphine, which is 35 times more potent than morphine, and a placebo in cases of in-office hysteroscopy and endometrial biopsy and found similar pain scores in both groups.[23] In that study, buprenorphine was administered 40min before the procedure, and the peak effect of the drug became apparent 1-2 hours after its injection. One study compared 50mg of oral diclofenac with a placebo in patients who underwent in-office hysterectomy and an endometrial biopsy, and they reported comparable effectiveness as assessed by VAS scores.[2] They also attributed the result to the inappropriate time interval between the drug administration and the onset of the procedure. Diclofenac was administered 1-2 hours before

the procedure, and it exerted a suboptimal effect during and after the procedure.[4] In our study, the time interval between the application of diclofenac and the onset of the procedure was not properly adjusted. Therefore, we cannot make precise interpretations about the effectiveness of diclofenac.

Another surprising outcome of our study was the relatively lower VAS scores in Group P. In fact, the VAS scores (<4) in all the groups were low, and the patients did not require additional analgesic drugs. Therefore, we think that the minor inter-group differences that we observed do not have any clinical significance. In addition, the perception of pain has sensorial, emotional and cognitive components. Biological, psychological and social factors have an important role in the expression of painful stimuli. The complex interaction between these factors complicates the interpretation of studies investigating pain responses.[8,24] Other factors reported to affect pain scores are anxiety levels of patients, study expectations, individual characteristics of the patients, the approach of the operators to the patients, previous therapeutic experiences of the patients and pain-relieving effects of placebos.[25] However, we did not evaluate these factors in our study. Thus, we cannot make inferences about the impact of these on the study outcomes.

In many studies, the authors were unable to demonstrate blockage of vasovagal reactions following the application of local anaesthesia.[10,12,17,19,26] The same was true in our study, with blockage of vasovagal reactions seen in only two patients. Therefore, we cannot draw sound conclusions about this complication.

We observed no inter-group differences in mean arterial pressure values. This outcome might be related to the comparable VAS scores of the drug group and to the lower VAS scores obtained in all the groups. The relatively lower VAS scores in all the groups and the routine application of these procedures by gynaecologists without analgesia might have contributed to the comparable patient and surgeon satisfaction rates between the groups.

We did not collect data on previous uterine biopsies, educational status, demographic characteristics and socioeconomic status. Lack of optimisation of the timing of the drug delivery and the timing of the procedure may be additional limitations of our study. Since diclofenac reaches its peak plasma levels within 20-60mins, allowing adequate time for pain relief to take effect is very important for the accurate evaluation of drug effectiveness in studies performed using rectal diclofenac.

Conclusion

IU lidocaine or IU lidocaine + rectal diclofenac had no effect on VAS scores, patient satisfaction and vasovagal reactions.

References

1. Nagele F, Lockwood G, Magos AL. Randomised placebo controlled trial of mefenamic acid for premedication at outpatient hysteroscopy: a pilot study. Br J Obstet Gynaecol 1997; 104: 842-4.
2. Tam WH, Yuen PM. Use of diclofenac as an analgesic in outpatient hysteroscopy: a randomized, double-blind, placebo-controlled study. Fertil Steril 2001; 76: 1070-2.
3. Cooper NA, Khan KS, Clark TJ. Local anaesthesia for pain control during outpatient hysteroscopy: systematic review and meta-analysis. BMJ 2010; 340: c1130.
4. Ahmad G, Attarbashi S, O'Flynn H, Watson AJ. Pain relief in office gynaecology: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2011; 155: 3-13.
5. Ahmad G, O'Flynn H, Attarbashi S, Duffy JM, Watson A. Pain relief for outpatient hysteroscopy. Cochrane Database Syst Rev 2010: CD007710.
6. O'Flynn H, Murphy LL, Ahmad G, Watson AJ. Pain relief in outpatient hysteroscopy: a survey of current UK clinical practice. Eur J Obstet Gynecol Reprod Biol 2011; 154: 9-15.
7. Hassan L, Gannon MJ. Anaesthesia and analgesia for ambulatory hysteroscopic surgery. Best Pract Res Clin Obstet Gynaecol 2005; 19: 681-91.
8. Wong AY, Wong K, Tang LC. Stepwise pain score analysis of the effect of local lignocaine on outpatient hysteroscopy: a randomized, double-blind, placebo-controlled trial. Fertil Steril 2000; 73: 1234-7.
9. Nagele F, O'Connor H, Davies A, Badawy A, Mohamed H, Magos A. 2500 Outpatient diagnostic hysteroscopies. Obstet Gynecol 1996; 88: 87-92.
10. Lau WC, Lo WK, Tam WH, Yuen PM. Paracervical anaesthesia in outpatient hysteroscopy: a randomised double-blind placebo-controlled trial. Br J Obstet Gynaecol 1999; 106: 356-9.
11. Moore KL, Agur AMR, Dalley AF. Pelvis and Perineum. Clinically orientated anatomy. 7.th North American eds. London: Lipincott Williams & Wilkins; 2013.
12. Lau WC, Tam WH, Lo WK, Yuen PM. A randomised double-blind placebo-controlled trial of transcervical intrauterine local anaesthesia in outpatient hysteroscopy. BJOG 2000; 107: 610-3.
13. Rattanachaiyanont M, Leerasiri P, Indhavivadhana S. Effectiveness of intrauterine anesthesia for pain relief during fractional curettage. Obstet Gynecol 2005; 106: 533-9.
14. Sharma JB, Aruna J, Kumar P, Roy KK, Malhotra N, Kumar S. Comparison of efficacy of oral drotaverine plus mefenamic acid with paracervical block and with intravenous sedation for pain relief during hysteroscopy and endometrial biopsy. Indian J Med Sci 2009; 63: 244-52.
15. Dugowson CE, Gnanashanmugam P. Nonsteroidal anti-inflammatory drugs. Phys Med Rehabil Clin N Am 2006; 17: 347-54
16. Davies NM, Anderson KE. Clinical pharmacokinetics of diclofenac. Therapeutic insights and pitfalls. Clin Pharmacokinet 1997; 33: 184-213.
17. Giorda G, Scarabelli C, Franceschi S, Campagnutta E. Feasibility and pain control in outpatient hysteroscopy in postmenopausal women: a randomized trial. Acta Obstet Gynecol Scand 2000;79: 593-7.
18. Costello MF, Horrowitz SD, Williamson M. A prospective randomized double-blind placebo-controlled study of local anaesthetic injected through the hysteroscope for outpatient

hysteroscopy and endometrial biopsy. Gynaecol Endosc 1998; 7: 121-6.
19. Cicinelli E, Didonna T, Ambrosi G, Schonauer LM, Fiore G, Matteo MG. Topical anaesthesia for diagnostic hysteroscopy and endometrial biopsy in postmenopausal women: a randomised placebo-controlled double-blind study. Int J Obstet Gynaecol 1997; 104: 316-9.
20. Yang J, Vollenhoven B. Pain control in outpatient hysteroscopy. Obstet Gynecol Surv 2002; 57: 693-702.
21. Zupi E, Luciano AA, Valli E, Marconi D, Maneschi F, Romanini C. The use of topical anesthesia in diagnostic hysteroscopy and endometrial biopsy. Fertil Steril 1995; 63: 414-6.
22. Mercorio F, De Simone R, Landi P, Sarchianaki A, Tessitore G, Nappi C. Oral dexketoprofen for pain treatment during diagnostic hysteroscopy in postmenopausal women. Maturitas 2002; 43: 277-81.
23. Lin YH, Hwang JL, Huang LW, Chen HJ. Use of sublingual buprenorphine for pain relief in office hysteroscopy. J Minim Invasive Gynecol 2005; 12: 347-50.
24. Dogan E, Celiloglu M, Sarihan E, Demir A. Anesthetic effect of intrauterine lidocaine plus naproxen sodium in endometrial biopsy. Obstet Gynecol 2004; 103: 347-51.
25. Turner JA, Deyo RA, Loeser JD, Von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. JAMA 1994; 271: 1609-14.
26. Cicinelli E, Didonna T, Schonauer LM, Stragapede S, Falco N, Pansini N. Paracervical anesthesia for hysteroscopy and endometrial biopsy in postmenopausal women. A randomized, double-blind, placebo-controlled study. J Reprod Med 1998; 43: 1014-8.