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The effect of preoperative intravenous lidocaine on postoperative pain following hysteroscopy

A randomized controlled trial

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Abstract

Background: The use of hysteroscopy for the diagnosis and treatment of uterine and endometrial abnormalities is often associated with postoperative pain. This randomized controlled trial aimed to assess the efficacy of preoperative intravenous (IV) lidocaine in reducing pain after hysteroscopy.

Methods: In total, 138 patients undergoing elective hysteroscopy at the CHA Bundang Medical Center, Seongnam, Korea were randomly assigned to a control group (n = 69) or a lidocaine group (n = 69), which received normal saline or IV lidocaine at 1.5 mg/kg, respectively. The primary outcome was the incidence of postoperative pain.

Results: The incidence of pain was significantly lower in the IV lidocaine group than in the control group at the post-anesthesia care unit (27.3% vs 68.2%, $P < .001$). The visual analog scale (0–10) score (median [interquartile range]) was lower in the IV lidocaine group than in the control group (0 [0–2]) vs 2 [0–4]), $P < .001$). The use of rescue analgesics and postoperative nausea and vomiting were similar between the 2 groups. This study demonstrated that administering 1.5 mg/kg of preoperative IV lidocaine can be a simple method to reduce incidence of pain after hysteroscopy.

Conclusion: Preoperative bolus administration of 1.5 mg/kg of IV lidocaine may be used to decrease incidence of pain after hysteroscopy under general anesthesia.

Abbreviations: PACU = post-anesthesia care unit, PADS = post-anesthesia discharge scoring system, PONV = postoperative nausea and vomiting, VAS = visual analog scale.

Keywords: hysteroscopy, lidocaine, pain

1. Introduction

Hysteroscopic procedures are more commonly performed for the diagnosis and treatment of uterine and endometrial abnormalities in comparison to blind procedures.[1] For local anesthesia, the use of paracervical or intracervical injection with oral or intravenous (IV) analgesics, including opioids, is generally well tolerated and is less expensive than general anesthesia. Outpatient hysteroscopy has been done under local anesthesia over the last decade. Although guidelines recommend office hysteroscopy to avoid the use of general anesthesia,[2,3] the pain and difficulty in accessing the uterus can be considered disadvantages of office hysteroscopy.[4] Pain occurs due to the advancement of the hysteroscope through the cervical canal; the myometrium's contraction caused by distension medium; and the direct stimulation of the uterine walls due to contact with the device.[5] In addition, the uterus has complex innervation; the cervix is innervated via the S2 to S4 parasympathetic nerves, whereas the corpus is innervated from the T10-L2 sympathetic nerves.[6] The pain of local anesthetic injections can be more severe than the hysteroscopy itself,[7] and greater postoperative pain was also reported for office hysteroscopy than hysteroscopy under general anesthesia.[8,9]

Lidocaine is an amide-type local anesthetic, which has analgesic,[10] antihyperalgesic,[11] and anti-inflammatory effects.[12] Recent studies have reported that IV lidocaine reduced postoperative pain, thus reducing opioid analgesic requirements and improving recovery following gynecologic laparoscopy.[13] Furthermore, these effects were also demonstrated in abdominal surgeries, including both laparotomy and laparoscopy, through meta-analyses.[14,15] However, the effect of lidocaine on pain after hysteroscopy has not yet been studied. Therefore, we conducted a randomized controlled trial to examine whether IV lidocaine was effective in reducing postoperative pain. Our hypothesis for this study was that the

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administration of 1.5 mg/kg of preoperative IV lidocaine would reduce the incidence of pain in patients after hysteroscopy with general anesthesia.

2. Materials and methods

This study was approved by the institutional review board of CHA Bundang Medical Center, CHA University, Seongnam, Korea (CHAMC 2018–11–007) in accordance with the tenets of the Declaration of Helsinki,[16] and registered at the Clinical Research Information Service (https://cris.nih.go.kr/cris/index.jsp, KCT0003493, 12/05/2018) prior to the enrollment of the first patient. We obtained written informed consent from all subjects participating in this study. This study was conducted between December 11, 2018, and June 18, 2019. The inclusion criteria were as follows: patients who were between the ages of 19 and 65 with American Society of Anesthesiologists physical status I or II and who were scheduled for an elective hysteroscopy. The exclusion criteria were as follows: patients who were pregnant, were unable to express pain, had an allergy to lidocaine, had taken analgesics 24 hours prior to hysteroscopy, or had a body mass index $>30\,kg/m^2$. We randomly assigned the eligible patients to either the lidocaine or the control group using sealed envelopes. Randomization (1:1) was based on a computer-generated random numbers table.

Before entering the operating room, we did not administer premedication to the patients. In the operating room, standard monitoring was applied for all patients, including pulse oximetry, electrocardiography, and noninvasive blood-pressure monitoring. After IV injection of midazolam 2 mg and fentanyl 50 μg for anxiolysis, the patients' perineum and vagina were prepared for hysteroscopy using Betadine. For the lidocaine group, 2% lidocaine 1.5 mg/kg was injected intravenously. The same volume of normal saline was injected for the control group. There was no restriction on the injection speed of the lidocaine bolus dose, as has been reported previously.[14,15,17] The syringes containing lidocaine or saline were identical and without a drug label. A registered nurse who did not prepare the drug administered the injection. If the patient felt numbness, metallic taste, light headedness, or tinnitus, she was to be referred to the anesthesiologist, who was not blinded, for proper management of possible side effects of the lidocaine. Then, IV propofol 2.0–2.5 mg/kg was administered for anesthesia induction followed by continuous infusion of propofol 6–10 mg/kg/h, which was used for anesthesia maintenance. Patients' breathing was secured through the nasal airway, and O_2 5 L/min was supplied to spontaneously breathing patients via a fitted facemask using straps on hook, and bag mask ventilation was applied if needed. If the blood pressure of the patient had increased to more than 20% of the baseline measurement, fentanyl 50 μg would be administered, additionally. The anesthesia induction, maintenance, and emergence were conducted by the anesthesiologist who was blinded to the randomization.

A speculum was placed on the anterior lip of the cervix to stabilize the cervix. Hegar dilators were used to induce cervical os dilatation. Then, a 2.9-mm hysteroscope with a 22-Fr (7.33 mm) operating sheath (Bettocchi, Karl Storz, Tuttlingen, Germany) or a 4-mm resectoscope with a 27-Fr (9 mm) outer sheath (Gynecare Versapoint System; Ethicon, Somerville, NJ) was inserted and the speculum was removed. The intrauterine distension pressure was maintained using 0.9% normal saline administered from 1 m above the patients' uterus by gravity. The surgeries included polypectomy, biopsy, myomectomy, curettage, etc. When the hysteroscope was used, polyps were removed directly or divided into smaller fragments using scissors and the fragments were removed by forceps. When the resectoscope was employed, a bipolar loop resecting electrode was used. Removed tissues were sent for histological diagnosis.

Patient demographics, including indication for hysteroscopy, were noted prior to the operation if the patients had obstetric history, including vaginal delivery, postmenopausal status, dysmenorrhea, and were administered oral misoprostol 400 μg for cervical ripening. Operative details, including the type of instrument, position of uterus, duration of procedure, intraoperative IV fluid volume and propofol dose, dose and adverse effect of lidocaine for the lidocaine group, number of patients who were administered uterotonics and rescue fentanyl, and main procedure of hysteroscopy, were recorded after the operation.

Postoperative pain was assessed at the post-anesthesia care unit (PACU) after surgery using a visual analog scale (VAS), which consisted of a 10-cm line ranging from "no pain" to "worst possible experienced pain." IV ketorolac 30 mg was administered in the PACU if the VAS score was $\geq$4. If the pain did not subside, IV propacetamol 1 g was additionally administered. If postoperative nausea and vomiting (PONV) occurred, IV ondansetron 4 mg was administered. The incidence of PONV, antiemetic and analgesic administration, and time to discharge readiness were also recorded. Discharge readiness was assessed by using the post-anesthesia discharge scoring system (PADS)[18] every 10 minutes. The PADS is based on 5 criteria: vital signs, ambulation, nausea/vomiting, pain, and surgical bleeding. Each of these criteria is scored as 0 to 2, with a maximal score of 10. Patients were considered as ready for discharge when the score was $\geq$9. These PADS, including VAS score and PONV, were assessed by the anesthesiologist who was blinded to the randomized group. For pain control after discharge, oral mefenamic acid 250 mg was administered thrice a day for 3 days.

The patients were also blinded as to which group they belonged to. The primary endpoint was the incidence of postoperative pain (VAS score $\geq$1). The secondary endpoints were the administration of analgesics for a VAS score $\geq$4 and the incidence of PONV at the PACU. The highest value of VAS score was used among the values assessed by 10 minutes.

3. Statistical analysis

According to a previous study, about 45% of patients undergoing hysteroscopy under general anesthesia complained of postoperative pain,[19] and if the number of patients who complained of pain decreased by half, then the sample size was calculated to be 65 per group at a power of 0.8 and an alpha value of 0.05; thus, 138 patients were recruited to compensate for possible dropouts. All statistical calculations were carried out using SPSS version 25.0 for Windows (IBM Corp., Armonk, NY, USA). For the continuous data, the independent *t* test or the Mann-Whitney *U* test was performed. For categorical data between the 2 groups, the chi-square or Fisher exact test was used. Data were described as mean $\pm$ SD, median (range [interquartile range, IQR]), or number of patients (%). Results were considered as statistically significant for a *P*-value less than .05.

4. Results

A total of 138 patients were randomized and 132 patients completed this study (Fig. 1). The patient demographics, including American Society of Anesthesiologists classification, obstetric

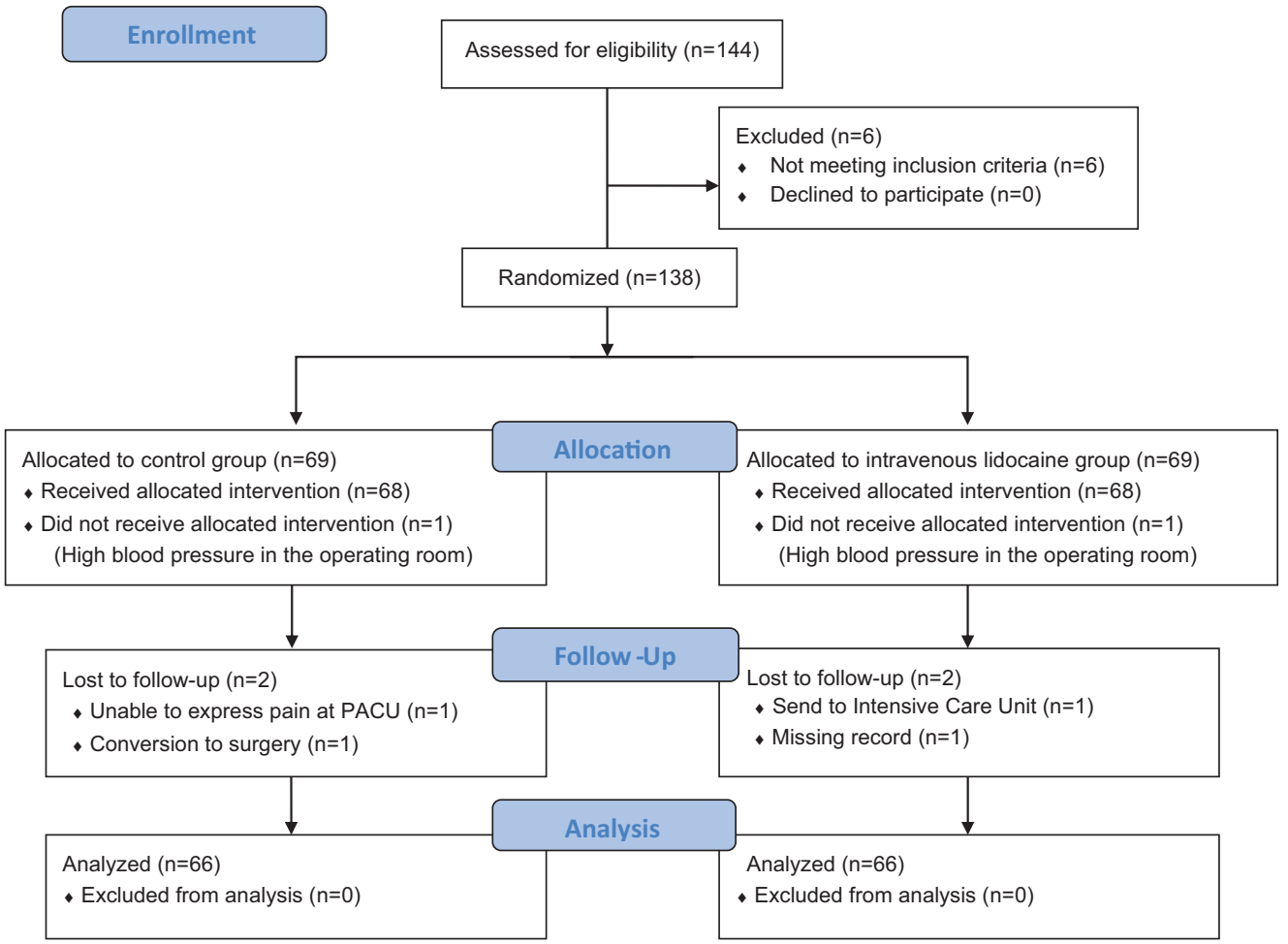

Figure 1. CONSORT flow diagram.

Table 1

Patient demographics.

	Control (n = 66)	Lidocaine (n = 66)	*P* value
Age (yr)	39.9 ± 8.5	41.1 ± 6.9	.36
Height (cm)	158.6 ± 5.9	160.1 ± 5.0	.12
Weight (kg)	58.2 ± 9.5	60.2 ± 8.3	.18
Body mass index (kg/m^2)	23.2 ± 3.9	23.5 ± 3.1	.60
ASA physical status (I /II)	55/11	52/14	.51
Previous obstetric history			.79
Cesarean	12 (18.2%)	10 (15.2%)	
Vaginal	19 (28.8%)	22 (33.3%)	
Both	0 (0%)	1 (1.5%)	
Nulliparous	35 (53%)	33 (50%)	
Postmenopausal status	7 (10.6%)	5 (7.6%)	.55
Dysmenorrhea	28 (42.4%)	35 (53.0%)	.22
Indication for hysteroscopy			.63
Abnormal bleeding	36 (54.5%)	39 (59.1%)	
Infertility	24 (36.4%)	24 (36.4%)	
Others	6 (9.1%)	3 (4.5%)	
Administered misoprostol	39 (59.1%)	38 (57.6%)	.86

Values are presented as mean ± SD or number of patients (%).
ASA = American Society of Anesthesiologists.
Others include intrauterine synechiae, retained placenta, intrauterine device and cervical mass.

history, indications for hysteroscopy, and the number of patients who had a postmenopausal status and were administered oral misoprostol prior to hysteroscopy, were similar between the 2 groups (Table 1). Furthermore, similarities were found between the 2 groups, including the type of instrument, position of uterus, duration of procedure, intraoperative IV fluid volume and propofol dose, the number of patients who were administered uterotonics and rescue fentanyl, and main procedure of hysteroscopy (Table 2). For the lidocaine group, the mean injected lidocaine dose was 90.1 ± 12.0 mg, and no adverse effect was observed.

The incidence of postoperative pain and VAS scores were lower in the lidocaine group than in the control group. The number of patients who were administered analgesics was similar between the 2 groups. The incidence of PONV and the number of patients who were administered antiemetics were similar between the 2 groups (Table 3). Four patients in the control group and 2 patients in the lidocaine group were administered propacetamol 1 g in addition to ketorolac 30 mg before the pain subsided ($P = .664$). The time to discharge readiness was similar between the 2 groups (Table 3).

5. Discussion

This is the first randomized controlled trial to demonstrate the efficacy of IV lidocaine in patients who underwent hysteroscopy

Table 2

Operative details.

	Control (n = 66)	Lidocaine (n = 66)	*P* value
Instrument			1.00
Hysteroscope	35 (53%)	35 (53%)	
Resectoscope	31 (47%)	31 (47%)	
Position of uterus			1.00
Anteverted	50 (75.8%)	50 (75.8%)	
Retroverted	16 (24.2%)	16 (24.2%)	
Duration of procedure (min)	13.3 ± 8.3	14.7 ± 8.5	.34
Intraoperative fluid (mL)	198.5 ± 92.0	212.9 ± 81.5	.34
Administered uterotonics	10 (15.2%)	16 (24.2%)	.19
Main procedure			.76
Polypectomy	41 (62.1%)	37 (56.1%)	
Biopsy	9 (13.6%)	11 (16.7%)	
Myomectomy	7 (10.6%)	8 (12.1%)	
Curettage	3 (4.5%)	6 (9.1%)	
Others	6 (9.1%)	4 (6.1%)	

Values are presented as mean ± SD or number of patients (%).
Hysteroscope = a 2.9-mm hysteroscope with a 22-Fr (7.33 mm) operating sheath (Bettocchi, Karl Storz, Tuttlingen, Germany).
Resectoscope = a 4-mm resectoscope with a 27-Fr (9 mm) outer sheath (Gynecare Versapoint System; Ethicon, Somerville, NJ, USA).
Others include adhesiolysis, and removal of intrauterine device and cervical mass.

Table 3

Perioperative profiles.

	Control (n = 66)	Lidocaine (n = 66)	*P* value
In the operating room			
Propofol (mg)	237.7 ± 77.3	237.9 ± 72.7	.98
Rescue fentanyl 50 μg	4 (6.1%)	2 (3.0%)	.68
In the post anesthesia care unit			
Pain incidence (VAS ≥ 1)	45 (68.2%)	18 (27.3%)	< .001
Pain (VAS)	2.00 (0–7 [0–4])	0 (0–5 [0–2])	< .001
Rescue analgesics	17 (25.8%)	14 (21.2%)	.54
Postoperative nausea and vomiting	0 (0%)	1 (1.4%)	>.99
Time to discharge readiness (min)	61.9 ± 21.0	56.9 ± 23.3	.20

Values are presented as mean ± SD, median (range [IQR]), or number of patients (%).
VAS = visual analog scale.
Time to discharge readiness was assessed using postanesthesia discharge scoring system (PADS) for every 10 minutes.

with general anesthesia. This study suggests that a preoperative single bolus dose of IV lidocaine could reduce postoperative pain.

Lidocaine is a local anesthetic that blocks the voltage-gated sodium channels in the neuronal tissue. This interrupted neuronal transmission is demonstrated clearly when the drug is in contact with neural tissues.[20] This is concordant with a recent meta-analysis that reported lidocaine paracervical block was the most effective method for reducing pain after outpatient hysteroscopy under local anesthesia.[21] While the systemic effects of lidocaine might act in a similar way to local anesthesia, the exact mechanism remains largely elusive. The analgesic effects of lidocaine, especially in terms of suppressing increased sensitivity to pain, were proven clinically.[14] Recent studies have demonstrated that IV lidocaine reduced postoperative pain following various surgeries, including gynecologic laparoscopy,[13] abdominal surgeries,[14,15,22] prostatectomy,[23] and brain tumor surgery.[24] The lidocaine doses applied for these studies were 1 to 2 mg/kg for an initial bolus and 1 to 2 mg/kg/h for continuous infusion, which were mostly within the recommended doses, according to meta-analyses.[14,15,17] In contrast, we administered only a single bolus dose as the duration of the procedure was around 10 minutes, which is considered a short time to elicit the effect of a maintenance dose of lidocaine. According to a previously reported systematic review, IV lidocaine reduced postoperative pain in abdominal surgeries, as evidenced by a VAS score reduction,[14] which is comparable to our findings.

Local anesthetic systemic toxicity can manifest as mild central nervous system (CNS) symptoms or cardiovascular collapse depending on its concentration in the plasma. CNS toxicity includes perioral tingling, lightheadedness, mental status change, convulsions, coma, and respiratory depression. Cardiovascular system toxicity includes various arrhythmias, hypotension, and asystole. However, toxicity from perioperative IV lidocaine is extremely rare, and this was supported by the lack of adverse events in our study. According to a systematic review, incidence of IV lidocaine toxicity was not increased in most trials. Lightheadedness, dizziness, visual disturbances, and bradycardia were reported in a small number of trials.[14] Moreover, previous studies reported that the bolus dose and infusion of lidocaine reduced postoperative pain, while plasma concentration did not approach a toxic level of 5 μg/mL even after 24 hours of infusion.[22,23] We did not measure plasma concentration of lidocaine in our patients but from these studies, we can assume that none of them experienced a toxic concentration of the lidocaine.

Another strength of this study is that IV lidocaine reduced pain, without influencing time to discharge readiness at the same-day surgery center. This is consistent with a previous trial of lidocaine in ambulatory surgeries that has shown a similar time to discharge readiness between groups.[25]

In this study, the preoperative administration of 1.5 mg/kg of IV lidocaine reduced the median pain VAS score from 2 to 0 as well as the incidence of pain. As this VAS score was reduced approximately from 2 to 0 that could be categorized as "mild pain," which may not require IV analgesics to relieve pain, this result might not have clinical significance. However, because we assumed that the occurrence of pain itself, as well as the severity of pain, could have a significant effect on the patient's satisfaction, we decided that the primary end point be the incidence of pain in this study. As a result, this study demonstrated that IV lidocaine at 1.5 mg/kg significantly reduced the incidence of pain from 68% in the control group to 27% in the lidocaine group.

Previous randomized controlled trials using several agents for reducing pain following minor gynecological surgery, including hysteroscopy and curettage under general anesthesia, were conducted[26–28] and their results were controversial. Preoperative administration of rectal suppositories of tramadol 100 mg provided superior postoperative analgesia compared to rectal suppositories of indomethacin 100 mg after diagnostic curettage and early termination of pregnancy.[27] In contrast, preoperative oral administration of pregabalin 100 mg, which is commonly used for multimodal analgesia, did not reduce postoperative pain after hysteroscopy.[26] Preoperative administration of IV parecoxib 40 mg reduced only dynamic pain, but not resting pain, after minor gynecological surgery.[28]

This study has some limitations. First, for the patients who underwent hysteroscopy at the same-day surgery center, post-discharge pain should be managed in addition to pain experienced at the hospital. The most common complication

after ambulatory surgery is pain after discharge.[29] In addition, female patients have worse postoperative recovery, including pain sensitivity, than male patients following surgery.[30] We administered oral mefenamic acid 250 mg thrice a day for 3 days, but we did not check the pain score after discharge. According to a previous systematic review, the effects of lidocaine on pain scores were most obvious and evident within 4 hours, less obvious and evident within 24 hours, and not significant 48 hours after the operation.[14] Therefore, further research is needed to clarify whether IV lidocaine is effective in reducing pain after discharge. Second, we administered fentanyl 50 μg intravenously in the operating room routinely, prior to the start of hysteroscopy. Since the efficacy duration of fentanyl is 30 to 60 minutes, which is sufficient for this short procedure and recovery period, the pain might have been mild after the hysteroscopy. And the intraoperative dose of fentanyl during the procedure was similar between the 2 groups, so the analgesic effect of the fentanyl could be equally considered. If we did not use preoperative fentanyl routinely, the effect of IV lidocaine might have been clarified by the difference in administered intraoperative rescue fentanyl and postoperative analgesics due to a VAS score ≥ 4, which was not the case in ours. Third, we did not evaluate the pelvic pain score prior to the operation. According to a previous study, chronic pelvic pain is a predictive factor for pain during hysteroscopy[31] and thus might affect postoperative pain after hysteroscopy, as dysmenorrhea,[32] menopause, and nulliparity[33] are risk factors for pain during and after hysteroscopy. Fourth, our institution's surgeons have always performed hysteroscopies under general anesthesia; thus, we did not include traditional transcervical/intrauterine instillation in the lidocaine group, which might have helped to clarify the effect of the administration method of lidocaine.

6. Conclusion

Preoperative bolus administration of 1.5 mg/kg of IV lidocaine decreased incidence of pain after hysteroscopy under general anesthesia.

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