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CLINICAL RESEARCH

Effect of intravenous lidocaine on short-term pain after hysteroscopy: a randomized clinical trial

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Abstract
Background: The role of intravenous lidocaine infusion in endoscopic surgery has been previously evaluated for pain relief and recovery. Recently, it has been shown to reduce postoperative pain and opioid in patients undergoing endoscopic submucosal dissection. Similar to endoscopic submucosal dissection, operative hysteroscopy is also an endoscopic surgical procedure within natural lumens. The present study was a randomized clinical trial in which we evaluated whether intravenous lidocaine infusion would reduce postoperative pain in patients undergoing hysteroscopic surgery.
Objective: To evaluate whether intravenous lidocaine infusion could reduce postoperative pain in patients undergoing operative hysteroscopy.
Methods: Eighty-five patients scheduled to undergo elective hysteroscopy were randomized to receive either an intravenous bolus of lidocaine 1.5 $mg.kg^{-1}$ over 3 minutes, followed by continuous infusion at a rate of 2 $mg.kg^{-1}$. h^{-1} during surgery, or 0.9% normal saline solution at the same rate. The primary outcome was to evaluate postoperative pain by Visual Analog Scale (VAS). Secondary outcomes included remifentanil and propofol consumption.
Results: In the lidocaine group, the VAS was significantly lower at 0.5 hour ($p = 0.008$) and 4 hours ($p = 0.020$). Patients in the lidocaine group required less remifentanil than patients in the control group ($p < 0.001$). However, there was no difference between the two groups in the propofol consumption. The incidence of throat pain was significantly lower in the lidocaine group ($p = 0.019$). No adverse events associated with lidocaine infusion were discovered.
Conclusion: Intravenous lidocaine infusion as an adjuvant reduces short-term postoperative pain in patients undergoing operative hysteroscopy.

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Introduction

Operative hysteroscopy is performed under General Anesthesia (GA), which benefits both physicians and patients. First, GA can reduce potential difficulties of intrauterine access compared with local anesthesia.[1] Second, although a few studies have reported that non-pharmacological approaches to pain control for hysteroscopic procedures (including distension methods and physical stimuli) have contributed to improving patient satisfaction, hysteroscopy continues to be painful for a very high percentage of patients.[2] Obviously, GA has been demonstrated to alleviate patients' experience of pain during hysteroscopy.

Intraoperative lidocaine infusion has been widely accepted as an alternative to GA, as it can achieve opioid sparing, good pain relief, decreased postoperative nausea and vomiting, and excellent recovery.[3,4] Furthermore, recent studies have shown that intravenous lidocaine infusion can reduce postoperative pain and opioid requirements in patients undergoing Endoscopic Submucosal Dissection (ESD).[5] Similar to ESD, operative hysteroscopy is an endoscopic procedure within natural lumens. However, to the best of our knowledge, the efficacy of intravenous lidocaine in operative hysteroscopy has not been fully elucidated. Therefore, our study explored whether the administration of intravenous lidocaine can reduce postoperative pain, and propofol and remifentanil requirements in patients undergoing operative hysteroscopy.

Methods

Study population

The study protocol was conducted in compliance with the Helsinki Declaration and approved by the Hospital Ethics Committee of Renmin Hospital of Wuhan University. Written informed consent was obtained from 85 patients with an American Society of Anesthesiologists (ASA) classification of I–II undergoing operative hysteroscopy. The exclusion criteria were as follows: less than 18 years old; hypersensitivity to lidocaine; only performing diagnostic hysteroscopy; chronic abuse of opioid or nonsteroidal anti-inflammatory drug; chronic pain; mis- or lack of understanding of oral information about the study; other severe systemic diseases; and serious surgical complications. The study was registered under the Clinical Trials Register number ChiCTR1800016857.

Study group

Patients were categorized into two study groups using a random number table method performed by an Independent Anesthetist (IA) not involved in the treatment or follow up. The study drugs were prepared in syringes with an identical appearance by the same IA as follows: a 20 mL syringe contained 1% lidocaine solution or 0.9% normal saline solution (for the bolus), and a 50 mL syringe contained 1% lidocaine solution or 0.9% normal saline solution (for the continuous infusion). The treatment and follow-up anesthetists were all blinded to patient assignment until analysis completion. The IA would cease the blinding if the patient experienced abnormal conditions (such as serious complications) during the trial. All operative procedures were performed by the same surgeon, including the same hysteroscopic instrumentation.

Interventions

All patients received the study drugs prepared by IA with a bolus dose of 0.15 $mL.kg^{-1}$ over 3 minutes prior to anesthesia induction, followed by continuous infusion at a rate of 0.2 $mL.kg^{-1}.\ h^{-1}$ until the end of the surgery. Patients were treated under the same anesthetic protocol without premedication. Standard monitoring included five-lead electrocardiography, oxygen saturation, noninvasive blood pressure, continual end-tidal carbon dioxide and Narcotrend (NT) monitoring (MT Monitor Technik GmbH & Co, KG, D-24576 Bad Bramstedt, Germany). The Narcotrend Index (NTI) determined by the Narcotrend monitoring system is a dimensionless continuous variable ranging from 0 to 100 that reflects the depth of anesthesia. Based on the NTI, the depth of anesthesia ranges from stage A (awake) to stage F (very deep anesthesia), with stage D (37–64) indicating the routine depth of anesthesia for surgery.

Anesthesia was induced with propofol 2.5 $mg.kg^{-1}$ and then with remifentanil 1.5 $\mu g.kg^{-1}$ within one minute followed by the placement of a paraffin oil-lubricated laryngeal mask (ALMA type, HangZhou FuShan Medical Appliances Co, Ltd. China). The specific size of advanced laryngeal mask airway (ALMA) was selected according to the weight of the patient (3# for 30–50 kg; 4# for 50–70 kg; 5# for 70–100 kg), the intracuff pressure of ALMA was the pressure that has been set at the factory (< 2 cm H_2O). We did not deflate before inserting the laryngeal mask, and generally did not inflate after inserting it. If the airway pressure is too high (more than 30 mmHg) or obviously leaking in mechanical ventilation after implantation, adjust the position of the laryngeal mask or proper inflation of air (less than 20 mL), observe the airway pressure, and check the end-breathing carbon dioxide partial pressure to ensure the correct position. 180-degree rotation was used for insertion of laryngeal mask by all anesthesiologists.

Patients were placed on given mechanical ventilation or were converted to assisted ventilation when they resumed spontaneous breathing. Anesthesia was maintained with continuous remifentanil and propofol infusion. Remifentanil was adjusted at a rate of 5–10 $\mu g.kg^{-1}.\ h^{-1}$, and the rate of propofol was adjusted according to the following NTI target values: during maintenance in a range from 37–64; 5 minutes before the end of surgery in a range from 65–79. In the case of intraoperative patient movement, additional remifentanil (1 $\mu g.kg^{-1}$) was injected immediately. Anesthesia was performed by the attending anesthesiologist for more than 5 years.

Outcomes and adverse events observation

Mean Blood Pressure (MAP), Heart Rate (HR), and NTI data were collected at six separate time points: before intravenous the study drugs prepared by IA e (T0); before anesthesia induction (T1); 5 and 10 minutes after surgery (T2 and T3); at the end of surgery (T4); and at the time of

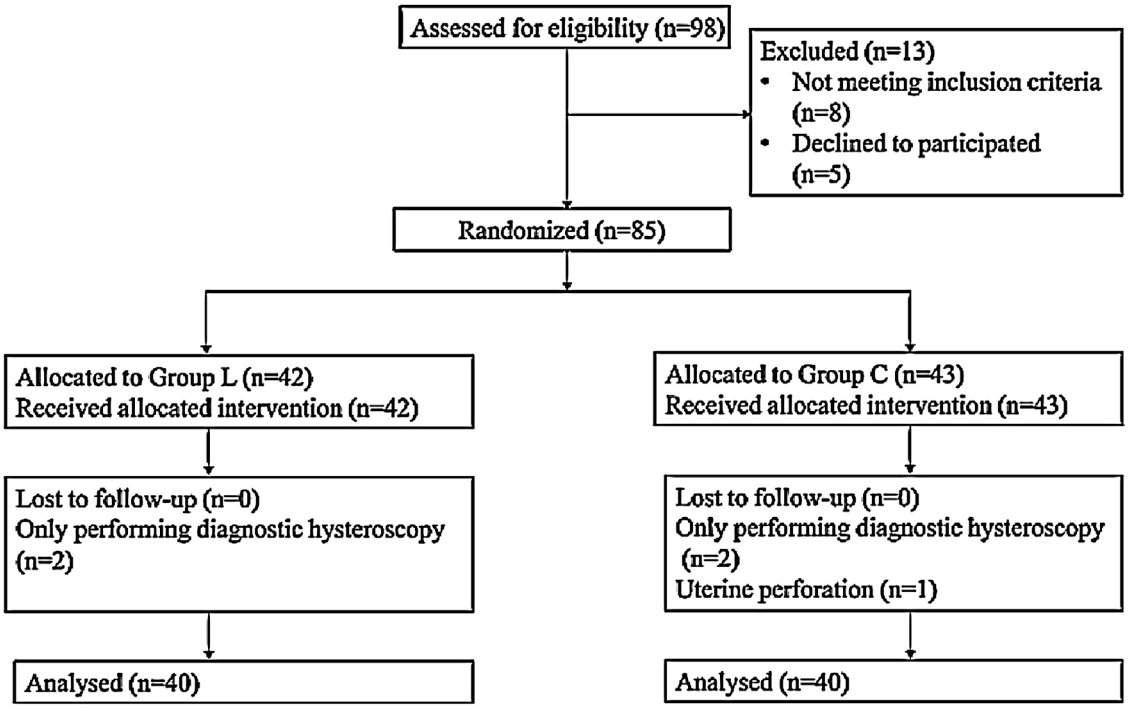

Figure 1 Flow diagram of patient recruitment.

laryngeal mask removal (T5). The total administered doses of remifentanil and propofol were recorded. Postoperative pain at rest was evaluated at 0.5 hour (T6), 4 hours (T7), and 24 hours (T8) after surgery by the visual analogue scale (VAS, 0 = no pain, 10 = unbearable pain). In the case of a VAS score $\geq$ 6, 50 mg of flurbiprofen was given intravenously. The incidence of throat pain was assessed using the VAS within 24 hours after surgery (any VAS score $\geq$ 2 was considered to represent a sore throat). The incidence of postoperative nausea or vomiting was also recorded up to 24-hours after the procedure.

Statistical analysis

The primary outcome variable was postoperative pain. The sample size was calculated based on the 0.5 hour postoperative VAS score of 5 patients (mean = 2.3; Standard Deviation −SD = 1.5) administered saline in a preliminary study. To demonstrate a 35% difference in the mean VAS score at 0.5 hour postoperatively between the two groups with a two-tailed α of 0.05 and a power of 80%, 36 candidates in each group were required. To compensate for the possibility of dropout for various reasons, we initially enrolled 85 patients in total for randomization. Statistical analysis was performed using GraphPad Prism version 6 (GraphPad Software Inc.). The Kolmogorov-Smirnov test was used to test the assumption of normal distribution. Normally distributed data are reported as mean $\pm$ SD and were compared among groups using unpaired *t*-test. Non-normally distributed data are reported as median (minimum−maximum) and were compared between groups using the Mann-Whitney U test. Repeated-measured data within the group, such as VAS, HR, MBP, and NIT were analyzed with two-way analysis of variance. When the interaction was statistically significant, sidak's multiple comparisons test was performed. Categorical data were compared between groups with Chi-Square test. p-values less than 0.05 were considered to represent a statistically significant difference.

Results

The study flowchart is shown in Figure 1. Of 98 patients assessed for eligibility, 85 patients were enrolled and randomly assigned to two groups. Five patients (2 in Group L and 3 in Group C) were excluded from the analysis because only diagnostic hysteroscopy or uterine perforation was performed. Patient characteristics were similar between the groups (Table 1). For MAP, HR and NTI data at the corresponding time points no significant differences were found between the two groups (Figure 2).

Details regarding VAS scores, drugs administered, and postoperative events were shown in Table 2. In the lidocaine group, the VAS was significantly lower at 0.5 hour (p = 0.008) and 4 hours (p = 0.020) postoperatively, compared to the control group. The total administered dose of remifentanil was 13% lower in Group L than in Group C, 232 (185−410) vs. 259 (190−420); $p < 0.001$. There was no difference between the two groups in the propofol requirement. No patients were given flurbiprofen after surgery. Regarding to postoperative effects, the lidocaine group had less throat pain (22.5% vs. 47.5%, p = 0.019). The groups did not differ with respect to the incidence of nausea or vomiting. No case of lidocaine-related local anesthetic systemic toxicity was reported.

Table 1 Baseline characteristics of study subjects.

	Group L (n = 40)	Group C (n = 40)	*p*-value
Age (years)	31.38 ± 7.37	32.85 ± 7.73	0.385
Weight (kg)	50 (40–78)	51 (42–82)	0.206
Height (cm)	160.10 ± 7.05	159.20 ± 8.19	0.600
ASA physical status, n (%)			0.485
I	24 (60%)	27 (67.5%)	
II	16 (40%)	13 (32.5%)	
Surgical indication, n (%)			0.819
Polyp	15 (37.5%)	17 (42.5%)	
Intrauterine adhesion	11 (27.5%)	9 (22.5%)	
Submucous myoma	8 (20%)	10 (25%)	
Placenta remnant	3 (7.5%)	1 (2.5%)	
Cesarean scar pregnancy	1 (2.5%)	2 (5%)	
Uterine septum	2 (5%)	1 (2.5%)	
Duration of surgery (min)	25 (18–55)	25 (15–48)	0.357

Values are shown as mean ± SD, median (minimum–maximum) or number of patients (proportion). ASA, American Society of Anesthesiologists.

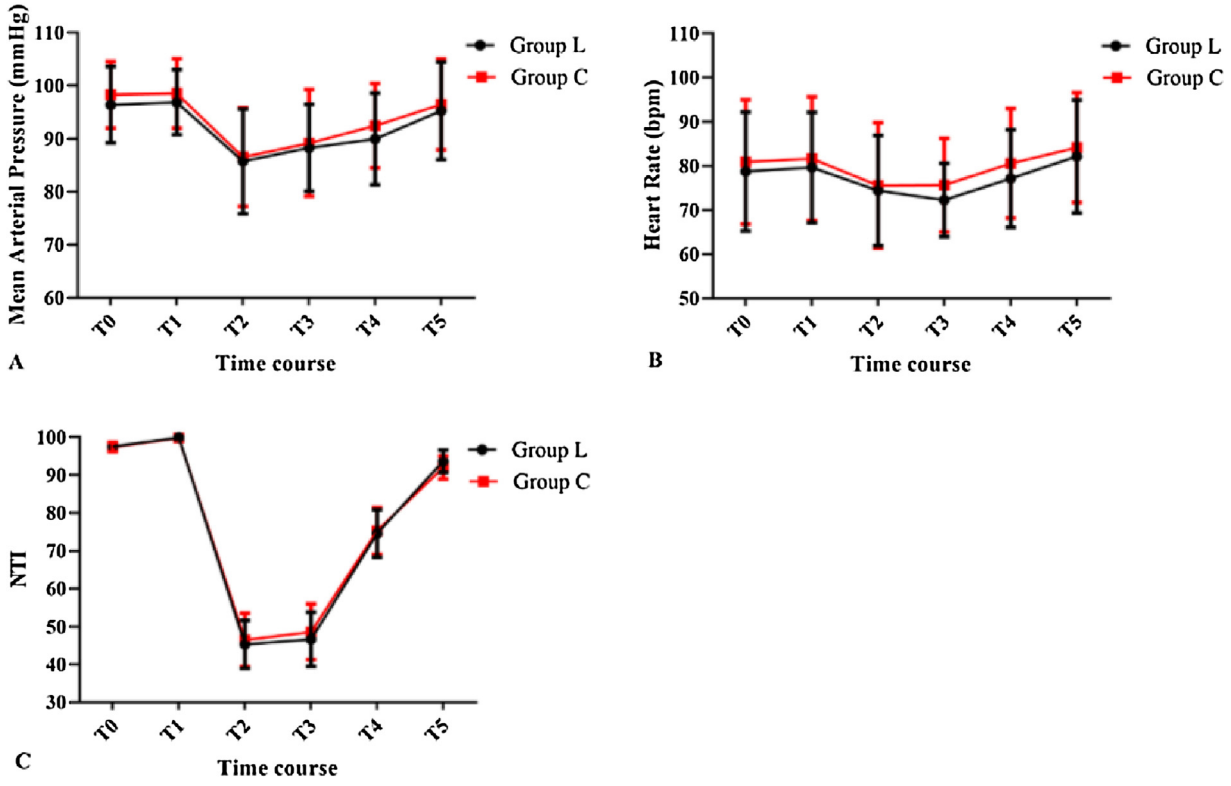

Figure 2 Changes in (A) mean blood pressure, (B) heart rate and (C) NTI. T0, Before intravenous the study drugs; T1, Before anesthesia induction; T2, 5 minutes after the start of the surgery; T3, 10 minutes after the start of the surgery; T4, The end of the surgery; T5, The time to remove the laryngeal mask; NTI, Narcotrend Index. Data are expressed as mean ± SD.

Discussion

Hysteroscopic procedures could be performed under mild sedation, local anesthesia, or GA. In this randomized, double-blinded, placebo-controlled trial, we selected GA for use during operative hysteroscopy, with intravenous lidocaine administered as a bolus of 1.5 $mg.kg^{-1}$ and then a continuous infusion at 2 $mg.kg^{-1}.\ h^{-1}$. We found that this strategy reduces the severity of short-term postoperative pain. Moreover, lidocaine administration also reduces the remifentanil requirement and the incidence of throat pain during operative hysteroscopy.

Intravenous lidocaine infusion has shown efficacy in controlling postoperative pain.[6] The analgesic mechanisms are multifactorial, including sodium channel blockade, reduction in spinal cord sensitivity, synergistic effects with the GA agents and intrinsic systemic anti-inflammatory properties.[7,8] The analgesic efficacy of intravenous lidocaine

Table 2 Perioperative data of study subjects.

	Group L (n = 40)	Group C (n = 40)	*p*-value
VAS			
T6	1.83 ± 1.24	2.43 ± 1.11	0.032
T7	1.98 ± 0.95	2.63 ± 1.23	0.018
T8	0.90 ± 0.81	1.20 ± 0.85	0.490
Total remifentanil (μg)	232 (185–410)	259 (190–420)	< 0.001
Total propofol (mg)	248.5 (175–342)	255 (170–335)	0.229
Throat pain, n (%)	9 (22.5%)	19 (47.5%)	0.019
Nausea or vomiting, n (%)	4 (10%)	9 (22.5%)	0.130

Values are presented as mean ± SD, median (minimum–maximum) or number of patients (proportion). VAS, Visual Analogue Scale (0 = no pain, 10 = unbearable pain). T6, 0.5 hour after surgery; T7, 4 hours after surgery; T8, 24 hours after surgery.

has been observed mainly in abdominal surgeries, including colectomy,[9] gastrectomy,[10] and cholecystectomy.[11] Moreover, Kim et al. confirmed the postoperative analgesic effects of intravenous lidocaine after ESD,[5] an endoscopic surgical procedure with natural lumens similar to operative hysteroscopy. They also estimated that the analgesic effects of lidocaine were mainly on visceral pain.[5] Therefore, we hypothesized that intravenous lidocaine would be beneficial for controlling visceral pain caused by operative hysteroscopy. In our study, administration of intravenous lidocaine resulted in reduced earlier postoperative hypogastric pain intensity and less remifentanil consumption during operative hysteroscopy, which is consistent with a previous study reporting that intravenous lidocaine had a positive impact on pain scores in the early postoperative phase.[4] It has been confirmed that the half-life of lidocaine is only 1.5–2 hours after bolus injection.[8] This may explain why analgesic effects were noted in the earlier postoperative phase rather than at 24 hours postoperatively in our study.

Remifentanil is a preferred drug for endoscopy because of its rapid onset and offset of action, and minimal adverse effects on cardiovascular and respiratory parameters.[12] To observe earlier postoperative analgesic effects of intravenous lidocaine, another advantage of remifentanil is its ability to avoid interference with the use of other opioid drugs. The administration of intravenous lidocaine has been shown to have an opioid sparing effect during GA, including on fentanyl,[13] sufentanil,[14] and morphine.[15] In a recent study, a remifentanil-sparing effect of intravenous lidocaine in the intraoperative period was found,[16] which is consistent with our findings. However, another study reported that perioperative intravenous lidocaine infusion had no significant effect on the remifentanil requirement during hypotensive anesthesia for an elective transsphenoidal endoscopic hypophyseal adenoma excision procedure.[17] Previous studies reported that intravenous lidocaine had a propofol-sparing effect during GA.[18,19] In this study, we ensured that each patient was at a constant anesthetic depth during surgery via Narcotrend monitoring, and we found that there was no difference in the propofol requirement between the two groups. These differences were likely due to the distinct types of surgery performed and different regimes for anesthetic management.

We used a laryngeal mask for mechanical ventilation or assisted ventilation to ensure respiratory safety in this study. In addition, placement of the laryngeal mask could also provide us with another way to observe the analgesic effects of lidocaine. The administration of intravenous lidocaine reduced the incidence of throat pain caused by the laryngeal mask from 47.5% to 22.5% in this study. Our observation is in keeping with the finding of several studies showing that the administration of intravenous lidocaine was effective in reducing throat pain after ESD[5] and postoperative throat soreness caused by tracheal intubation.[20] Last, we did not observe any significant differences in the incidence of postoperative nausea or vomiting, which is consistent with previous reports.[21,22]

There are some limitations to our study. We did not measure the plasma level of lidocaine in our patients. However, the protocol for administering a loading dose followed by the continuous intravenous infusion of lidocaine during GA has been used previously at several centers and reported to result in a level well below the toxic level.[23,24] Another limitation is the small number of patients. A larger-scale trial will provide further details to validate our findings. Finally, our unit did not have the nociception level index or analgesia nociception index monitoring equipment. The use of these devices may provide more accurate results in future studies.

In conclusion, intravenous lidocaine infusion as an adjuvant reduces short-term postoperative pain in patients undergoing operative hysteroscopy.

Conflicts of interest

The authors declare no conflicts of interest.

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