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CLINICAL TRIAL REPORT

Effect of Intravenous Lidocaine Infusion on Propofol Dose and Perioperative Pain During Moderate Sedation-Analgesia for Hysteroscopy: A Randomized Controlled Trial

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Purpose: In China, the majority of hysteroscopic procedures require moderate sedation and analgesia. The efficacy of intravenous lidocaine in reducing the need for sedatives and alleviating perioperative pain during hysteroscopy remains equivocal. This study aims to determine whether the intravenous administration of lidocaine can reduce the required dose of propofol and enhance perioperative pain management.

Patients and Methods: We conducted a prospective, single-center, double-blind randomized controlled trial involving patients with ASA I–II undergoing hysteroscopy. Forty patients were randomly assigned in a 1:1 ratio to either receive an intravenous bolus dose of 1.5 mg/kg lidocaine, followed by a continuous intravenous infusion at 4 mg/kg/h until the conclusion of the procedure, or an equivalent volume of normal saline. Propofol was then titrated to maintain a MOAA/S score of ≤ 2.

Results: Compared with the control group, the lidocaine group showed a 13.8% decrease in the total dose of propofol (140.0[120.0, 155.0] mg vs 162.5[140.0, 197.5] mg), which was statistically significant ($P = 0.014$). The induction dose of propofol was 1.37 (1.29, 1.56) mg/kg in the lidocaine group and 1.61 (1.48, 1.94) mg/kg in the control group, respectively ($P = 0.001$). However, no significant differences were observed between the groups regarding the supplemental dose of propofol ($P = 0.062$), the number of involuntary movements during hysteroscopy ($P = 0.384$), or postoperative pain scores (T0: $P = 0.628$; T1: $P = 0.886$; T2: $P = 0.711$). Additionally, the incidence of intraoperative hypoxia ($P = 1.000$) and fatigue scores (T0: $P = 0.878$; T1: $P = 0.401$; T2: $P = 0.056$) between the two groups were not statistically significant.

Conclusion: Intravenous lidocaine reduces the dose requirements of propofol during the induction phase of anesthesia. However, it does not have a significant influence on alleviating intraoperative and postoperative pain during hysteroscopic procedures.

Keywords: analgesia, hysteroscopy, lidocaine, propofol, sedation

Introduction

Hysteroscopy is the leading choice for diagnosing and treating gynecological conditions, providing intuitive and precise evaluations of hemorrhagic diseases and intrauterine lesions. Despite ongoing debates regarding the necessity of sedation and analgesia during hysteroscopy, a recent survey report indicates that more than half of hysteroscopic procedures in China are performed under anesthesia.[1] The use of moderate sedation during hysteroscopy is both feasible and safe, reducing the patient's pain score and enhancing overall satisfaction.[2]

Propofol, characterized by its rapid onset, minimal body accumulation, and quick recovery, is the preferred sedative for hysteroscopy and is suitable for use either alone or in combination with opioid drugs.[1] However, adverse events such

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as respiratory depression and hypotension can occur during propofol sedation, and if severe, these complications can lead to catastrophic outcomes.[3] The occurrence of adverse events caused by propofol is often dose-dependent.[3] Reducing the dose of propofol can theoretically lower the incidence of adverse events associated with propofol sedation. Consequently, studies aimed at reducing the dose of propofol during procedural sedation for hysteroscopy or gastroscopy are continuously being reported.[4–9]

Currently, an increasing number of studies have demonstrated that intravenous lidocaine has an opioid-sparing effect.[10–13] However, this perspective remains a subject of debate within the academic community.[14] Recently, a study conducted by Forster et al found that intravenous lidocaine can reduce the dose requirements of propofol during colonoscopy. The possible mechanism is that lidocaine has an effect on relieving visceral pain.[9] The hysteroscopic procedure involves multiple anatomical regions, including the vagina, cervix, and uterus. The surgical procedures include grasping the cervix, cervical dilation, uterine distension, and endometrial curettage.[15,16] Furthermore, the procedure itself can induce uterine contractions and the release of prostaglandins,[16] making the pain characteristics of this surgery relatively complex. Colonoscopy-induced discomfort predominantly arises from visceral pain due to colonic distension, which contrasts significantly with the pain mechanisms experienced during hysteroscopy.[9] In light of this, the analgesic and propofol-sparing effects of intravenous lidocaine observed during colonoscopy may not necessarily be present in hysteroscopy. Currently, there is a significant lack of clinical research data regarding the use of intravenous lidocaine as an adjunct to sedation and analgesia with propofol and sufentanil during hysteroscopy.

Thus, this study aims to investigate whether intravenous lidocaine administered during sedation-analgesia for hysteroscopy can reduce the dose of propofol, minimize intraoperative involuntary movements, and alleviate post-operative pain.

Materials and Methods

This study was approved by the Ethics Committee of the General Hospital of Ningxia Medical University, Yinchuan, China (November 11, 2020; File No.2020–1000) and conformed to the provisions of the Helsinki Declaration. Written informed consent was obtained from all participants in the trial. The trial was registered at clinicaltrials.gov prior to patient enrollment (Trial ID: NCT04633577, Principal investigator: H.-X. Ma, Date of registration: 18/11/2020). This manuscript adheres to the applicable CONSORT guidelines.

Participants

After obtaining written informed consent from patients, 40 female patients undergoing hysteroscopy were enrolled in this prospective, randomized, controlled, double-blind clinical trial. In this study, hysteroscopic procedures were conducted under the following circumstances: 1) for conditions such as abnormal uterine bleeding, both diagnostic and therapeutic interventions were performed using endometrial curettage; 2) in cases where endometrial pathology was suspected, endometrial tissue sampling via curettage was used to assess for precancerous lesions and to identify specific malignant transformations; 3) endometrial curettage was employed to treat small polyps. The exclusion criteria were as follows: body mass index (BMI) ≥ 25 kg/m² or < 18.5 kg/m², American Society of Anesthesiologists physical status (ASA-PS) > II, age > 65 years or < 18 years, allergy to local anesthetics, a history of long-term sedative or analgesic drug use, severe arrhythmia or organic heart disease, and mental or neurological disorders. Patient data were excluded from analysis if they experienced any side effects that could disrupt the blinding of the study, including central nervous system symptoms (tinnitus, tongue numbness, dizziness, dysphoria, and convulsions) or cardiovascular adverse reactions (severe arrhythmias and hypotension).

Randomization and Blinding

Patients were randomly allocated to one of two groups using a computer-generated 1:1 randomization sequence, which was concealed in sequentially numbered, sealed, opaque envelopes (numbered 1 to 40). When a patient was enrolled, the study drug was prepared using identical 20 mL syringes by a research nurse according to the random sequence, and then it was delivered to the anesthesiologist in charge. The patients, the anesthesiologist who administered the anesthesia and assessed outcomes, and the healthcare providers were all blinded to the drug used.

Protocol for Sedation

Peripheral venous access was established with an 18G needle after the patients had entered the room. Oxygen was supplied to the patients at a rate of 4 L/min through a mask. Non-invasive blood pressure, peripheral oxygen saturation (SpO_2), and the electrocardiogram were routinely monitored. Vital signs were measured and recorded before anesthesia induction and then at 5-minute intervals. In the lidocaine group, a bolus of 1.5 mg/kg of 1% lidocaine (2% lidocaine hydrochloride injection, Anhui Changjiang Pharmaceutical Co., Ltd., Anhui, China) was slowly administered intravenously (within 30 seconds). Two minutes later, a bolus of 1 mg/kg of propofol (propofol injection long chain triglyceride, 200 mg/20 mL/ampule, Fresenius Kabi Deutschland, Bad Homburg, Germany) was administered. Subsequent boluses of 10 mg propofol were given at 10-second intervals until loss of the eyelash reflex and no response to loud verbal stimuli. Then, a continuous infusion of lidocaine at 4 mg/kg/h was administered until the end of the procedure. Following thirty minutes of administration at the current rate, it has been demonstrated that the plasma concentration of lidocaine remains significantly below the toxic threshold of 5 μg/mL.[17] The control group received normal saline and propofol using the same dosing regimen as the lidocaine group. Three minutes before the intravenous injection of lidocaine or normal saline, all patients in both groups received an intravenous injection of 0.1 μg/kg sufentanil (sufentanil citrate injection, 50 μg/1 mL/ampule; Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China). An additional 0.25–0.5mg/kg of propofol was administered if there were any signs of inadequate anesthesia, such as involuntary movement, grimacing, or an increase in heart rate (HR) by ≥ 20 beats/min during hysteroscopy. The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale was used to assess the depth of anesthesia during both induction and maintenance, with a target score of ≤ 2 being maintained. Spontaneous breathing was maintained throughout the anesthesia. When patients suffered from hypoxia (defined as SpO_2 < 93%), either jaw thrust or assisted mask ventilation was applied to improve oxygenation. Anesthesia was administered by the same anesthesiologist who was blinded to the patient allocation, and the dose of propofol and intra-procedure conditions were recorded. At the end of the procedure, the administration of supplementary medications was discontinued, and the patient was monitored for spontaneous eye opening. Once the patient could verbally state their name and follow directed movements (Aldrete Score ≥ 9), they were transferred to the recovery room. Upon entering the recovery room, pain and fatigue scores following hysteroscopy were assessed using a 0–10 visual analog scale (VAS) by an anesthesiologist who was not involved in the anesthesia management and was unaware of the patient allocation.

Measurements

The primary outcome measures included the total dose of propofol (comprising both the induction and supplemental doses), the number of involuntary movements during hysteroscopy, and the pain scores at three time points: immediately upon admission to the recovery room (T0), 15 min (T1), and 30 min later (T2). Secondary outcome measures included the incidence of intraoperative hypoxemia, as well as evaluations of mean arterial pressure (MAP) and heart rate (HR) at 5, 10, and 15 minutes post-induction. Additionally, fatigue scores were recorded immediately upon entry into the recovery room (T0) and at subsequent intervals of 15 minutes (T1) and 30 minutes (T2).

Statistical Analysis

According to our pilot study, the total propofol requirement for hysteroscopy was 171 ± 45 mg. We estimated that a sample size of 18 patients per group would provide 90% power to detect an expected 30% difference in propofol requirements between the two groups at a two-sided α of 0.05. Considering a 10% dropout rate, a total of 20 patients per group were eventually enrolled in the study. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). The normality of the variables was confirmed using the Shapiro–Wilk test, and Levene's test was subsequently applied to assess the equality of variances. Continuous data were expressed as mean (SD) for normal distribution variables and as median (IQR) for non-normally distributed variables. Categorical variables were presented as numbers and percentages. The propofol dose, post-hysteroscopy pain and fatigue scores, MAP, and HR were compared using the Independent samples *t*-test when the assumptions of normality and equal variances were met, Welch's *t*-test when variances were unequal, and the Mann–Whitney *U*-test when the data were not normally distributed. The weight, number of involuntary movements, height, age and duration

of procedure were compared using Mann–Whitney *U*-test. The ASA-PS scores and the incidence of hypoxia were compared using the Fisher exact test. $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

This trial was initiated on November 12, 2020. The first patient was enrolled on November 20, and the last patient was enrolled on December 25, 2020. A total of 40 patients were enrolled in this study. Among the enrolled patients, one patient refused follow-up immediately upon admission to the recovery room, resulting in 39 patients being included in the per-protocol analysis. No adverse reactions related to lidocaine were observed during the study. A flowchart of the study was presented in Figure 1. The general characteristics were well balanced between the two groups (Table 1).

Primary Outcome Measures

The total and induction doses of propofol were significantly lower in the lidocaine group compared to the control group (total dose: 140.0 [120.0, 155.0] mg vs 162.5 [140.0, 197.5] mg, $P = 0.014$; induction dose: 1.37 [1.29, 1.56] mg/kg vs 1.61 [1.48, 1.94] mg/kg, $P = 0.001$). However, there were no significant differences between the two groups in terms of supplemental dose ($P = 0.062$), involuntary movements during hysteroscopy ($P = 0.384$), or pain scores at three time points after entering the recovery room (T0: $P = 0.628$; T1: $P = 0.886$; T2: $P = 0.711$) (Table 2).

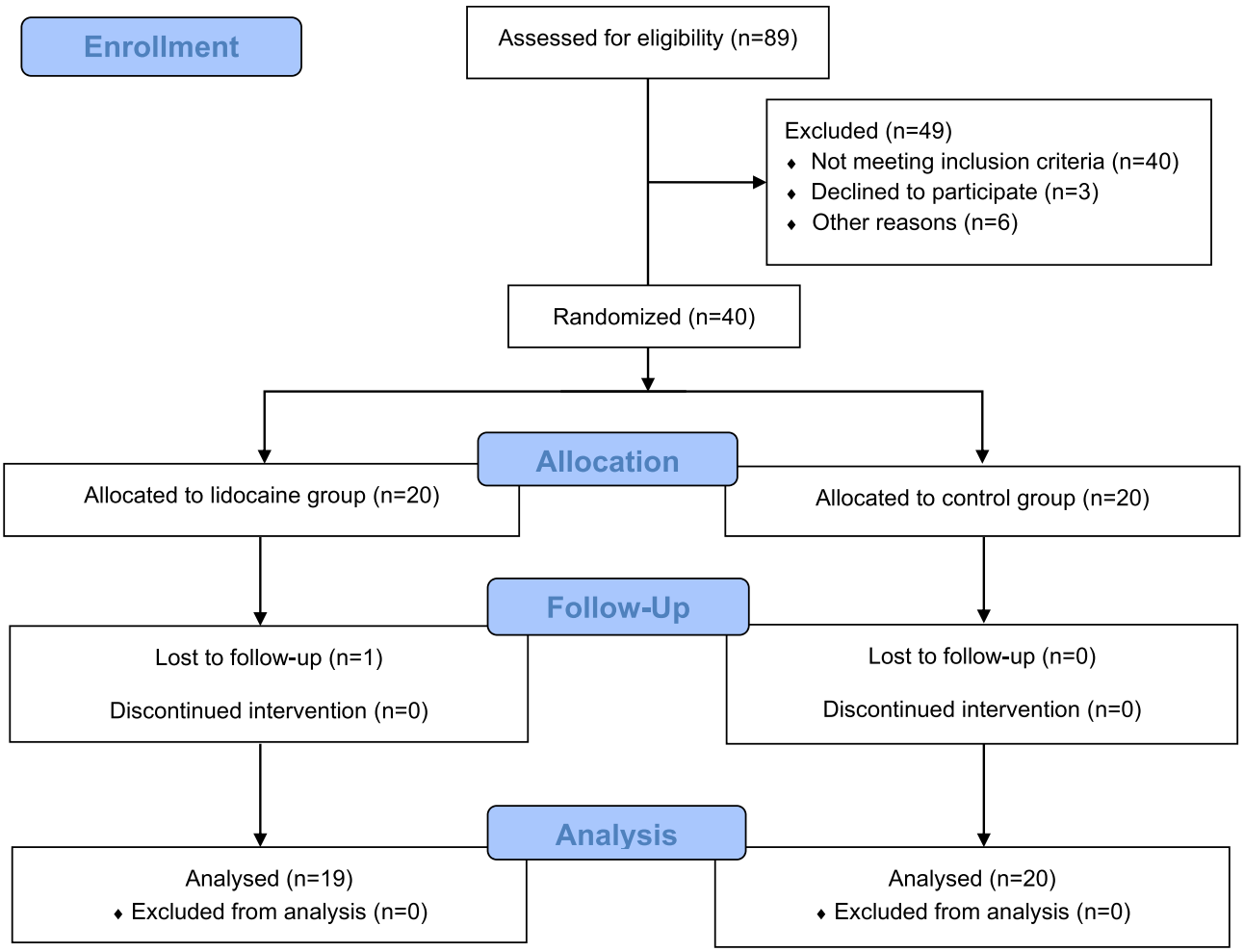

Figure 1 Consolidate Standards of Reporting Trials (CONSORT) flow diagram for this trial.

Table 1 General Characteristics and Duration of Procedure Between the Two Groups

	Lidocaine Group	Control Group
Weight, median(IQR), kg	55.0(51.0, 64.0)	55.5(50.0, 67.8)
Height, median(IQR), cm	162.0(156.0, 166.0)	160.0(157.2, 160.0)
Age, median(IQR), y	40.0(35.0, 50.0)	49.0(36.2, 52.8)
ASA-PS, No.(%)		
I	3(15.8)	3(15.0)
II	16(84.2)	17(85.0)
Duration of procedure, median(IQR), min	8.8(6.5, 10.5)	8.5(6.5, 10.0)

Notes: Continuous data are expressed as mean(SD) or median(IQR). Categorical variables were present as No.(%).
Abbreviation: ASA-PS, American Society of Anesthesiologists physical status.

Table 2 Propofol Dose, Involuntary Movements, Pain Scores, Hypoxia and Fatigue Scores Between the Two Groups

	Lidocaine Group	Control Group	*P*
Total propofol dose, median(IQR), mg	140.0(120.0, 155.0)	162.5(140.0,197.5)	0.014
Induction dose, median(IQR), mg·kg-1	1.37(1.29, 1.56)	1.61(1.48,1.94)	0.001
Supplemental dose, median(IQR), mg	60.0(30.0, 65.0)	65.0(60.0, 97.5)	0.062
Lidocaine, median(IQR), mg	107.0(101.0, 114.0)	–	–
Involuntary movements, median(IQR), No.	2.0(1.0, 2.0)	2.0(2.0, 3.0)	0.384
Pain scores, mean(SD)/ median(IQR)			
T0	3.0(0.0, 4.0)	2.5(1.25, 4.0)	0.628
T1	2.37(1.77)	2.3(1.13)	0.886
T2	1.0(0.0, 2.0)	1.0(0.0,1.75)	0.711
Hypoxia, No.(%)	6.0(31.6)	7.0(35.0)	1.000
Fatigue scores, mean(SD)/median(IQR)			
T0	4.95(1.99)	5.05(2.14)	0.878
T1	3.84(1.68)	3.35(1.93)	0.401
T2	2.0(1.0, 3.0)	1.0(0.25, 2.75)	0.056

Notes: Continuous data are expressed as mean(SD) or median(IQR). Categorical variables were present as No.(%). $P < 0.05$ was considered statistically significant.

Secondary Outcome Measures

Additionally, there was no difference in fatigue scores at three time points after entering the recovery room between the lidocaine group and the control group (T0: $P = 0.878$; T1: $P = 0.401$; T2: $P = 0.056$) (Table 2). There were no meaningful differences in the incidence of hypoxia between the two groups (Lidocaine group: 6/19 [31.6%] vs Control group: 7/20 [35.0%]; odds ratio, 1.17; 95% CI, 0.31–4.43; $P = 1.000$). The MAP and HR at three time points after induction are presented in Table 3. There were no significant differences between the two groups in these indicators (MAP after

Table 3 The MAP and HR at Each Time Point After Induction Between the Two Groups

Timelines	MAP, Mean(SD)/ Median(IQR), mmHg			HR, Mean(SD)/ Median(IQR), Beats·min-1		
	Lidocaine Group	Control Group	*P*	Lidocaine Group	Control Group	*P*
Baseline	90.0(82.0, 97.0)	100.0(89.0, 110.8)	0.091	76.9(9.8)	77.2(11.4)	0.941
5 min	83.9(8.4)	86.4(18.2)	0.587	72.0(66.0, 74.0)	68.5(64.0, 78.5)	0.643
10 min	82.0(78.5, 89.0)	88.0(81.5, 96.3)	0.293	70.7(10.0)	69.3(11.0)	0.667
15 min	88.7(18.0)	90.6(15.8)	0.816	68.9(11.4)	76.4(13.2)	0.229

Notes: Continuous data are expressed as mean(SD) or median(IQR), $P < 0.05$ was considered statistically significant.
Abbreviations: MAP, mean arterial pressure; HR, heart rate.

induction: 5 min, $P = 0.587$; 10 min, $P = 0.293$; 15 min, $P = 0.816$; HR after induction: 5 min, $P = 0.643$; 10 min, $P = 0.667$; 15 min, $P = 0.229$).

Discussion

The findings of this study indicate that intravenous administration of lidocaine during hysteroscopy significantly reduced both the total and induction doses of propofol, with no observed adverse effects associated with lidocaine. Specifically, the average total amount of propofol used in hysteroscopy decreased by 13.8% with the intravenous administration of lidocaine. However, the study also found that intravenous lidocaine did not significantly affect the supplemental dose of propofol needed for anesthesia maintenance, the number of involuntary movements during hysteroscopy, postoperative pain conditions, hypoxia, and fatigue.

Several published studies have suggested that intravenous lidocaine can reduce the induction dose of propofol,[5,6,18] and our study's results also support this notion. The potential mechanisms may involve interactions between lidocaine and both excitatory and inhibitory neurotransmitter/receptor systems in the central nervous system. Nordmark et al have demonstrated that lidocaine potentiates GABA-mediated chloride ion influx by inhibiting GABA uptake, thereby inducing neuronal hyperpolarization.[19] Additionally, another study has shown that lidocaine exhibits a dose-dependent inhibitory effect on glutamate release evoked by 4-AP (4-aminopyridine).[20] Furthermore, several studies have demonstrated that the intravenous administration of lidocaine can result in a decreased requirement for propofol during the maintenance phase of anesthesia.[7,21] However, we did not observe a sparing effect on the propofol dose during the maintenance phase of anesthesia in hysteroscopy. The likely reason for this discrepancy may be related to the type of surgery performed. The subjects of this study are patients undergoing hysteroscopy, which may involve procedures that can cause pain and discomfort, including cervical dilation, hysteroscope insertion, uterine cavity distension, and endometrial curettage. Patients often exhibit involuntary movements during these procedural steps. In this study, there was no difference in the incidence of involuntary movements during hysteroscopy between the two groups of patients; therefore, it is not expected that the supplemental dose of propofol given to reduce these movements would differ significantly.

Furthermore, our research findings suggest that intravenous lidocaine does not diminish the pain experienced following hysteroscopy. Several published studies have found that intravenous lidocaine can reduce both postoperative pain and the amount of opioid consumption required by patients.[9,22,23] The elimination half-life of intravenous lidocaine in healthy adults typically ranges from 80 to 110 minutes.[10] This study recorded patients' pain scores within 30 minutes postoperatively, a period during which the plasma concentration of lidocaine is theoretically still pharmacologically active. Postoperative pain following hysteroscopy may arise from traumatic pain, uterine contraction pain, or from prostaglandins released during the procedure.[16,24] Thus, the observed equivalence in postoperative pain scores between the two groups may be attributed to the limited efficacy of lidocaine in modulating the distinct characteristics and severity of pain associated with this surgical procedure. In light of this, pharmacological strategies could be considered, such as the vaginal administration of dinoprostone, misoprostol or isoniazid prior to the procedure to facilitate cervical preparation and reduce procedural pain.[25] Meanwhile, non-pharmacological strategies could also be adopted, including providing patients with ample pre-procedure information, utilizing active virtual reality technology and having them listen to music either before or after the hysteroscopic procedure, all aimed at ameliorating the pain experience of these patients.[25,26]

The results of this study indicate that intravenous lidocaine does not have a beneficial effect on the fatigue experienced following hysteroscopy. Fatigue, a common postoperative complication, is characterized by muscle weakness, malaise, depression, and an increased need for sleep.[27,28] A study has indicated that the primary risk factor for postoperative fatigue is postoperative pain, suggesting that interventions should focus on optimizing pain management.[29] In this study, intravenous administration of lidocaine did not improve intraoperative or postoperative pain in patients, which may explain the lack of difference in postoperative fatigue sensations between the two groups.

Our research found that the intravenous administration of lidocaine did not reduce the incidence of hypoxia observed during hysteroscopy. A previous study found that intravenous lidocaine reduced the incidence of hypoxemia during endoscopic retrograde cholangiopancreatography (ERCP) under propofol sedation.[8] Propofol significantly reduces the sensitivity of central chemoreceptors in response to hypercapnia, and the doses used for induction often result in respiratory depression and apnea.[30] Theoretically, reducing the propofol dose could lower the risk of respiratory depression. A possible

reason for the similar incidence of hypoxemia between the two groups in this study is that the patients undergoing hysteroscopy were positioned in lithotomy with the Trendelenburg position inverted, which can predispose the tongue to fall and be displaced posteriorly under the influence of gravity. Even though intravenous lidocaine reduces the induction dose of propofol, it remains difficult to prevent the occurrence of tongue falling back.

Our study has two limitations. Firstly, the study included only adult women aged 18–65, which means the findings cannot be generalized to all female patients. Secondly, since our study did not measure the plasma drug concentrations of the patients, it was not possible to accurately determine the lidocaine plasma concentration required to reduce the propofol induction dose.

Conclusion

Intravenous lidocaine reduces the dose requirements of propofol during the induction phase of anesthesia. However, it does not significant influence intraoperative and postoperative pain relief during hysteroscopic procedures. Additionally, the intravenous administration of lidocaine does not reduce the incidence of hypoxemia during hysteroscopy.

Abbreviations

BMI, Body mass index; ASA-PS, American Society of Anesthesiologists physical status; SpO_2, Saturation of peripheral oxygen; HR, Heart rate; VAS, Visual analog scale; MAP, Mean arterial pressure; ERCP, endoscopic retrograde cholangiopancreatography.

Data Sharing Statement

The anonymized data pertaining to individual participants that form the foundation of our findings can be accessed upon approval from the corresponding author, Hanxiang Ma, one year following the publication. Additionally, the study protocol, statistical analysis methods, and the full clinical study report will be made available for review.

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Disclosure

The author(s) report no conflicts of interest in this work.

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