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ORIGINAL RESEARCH

ED50 and ED95 of Propofol Combined with Different Doses of Intravenous Lidocaine for First-Trimester Uterine Aspiration: A Prospective Dose-Finding Study Using Up-and-Down Sequential Allocation Method

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Purpose: This study aimed to test the effect of different doses of intravenous lidocaine on the median effective dose (ED50) and 95% effective dose (ED95) of propofol-induction dose and identify the optimal dose.

Patients and Methods: Patients undergoing first-trimester uterine aspiration were screened and randomly enrolled into the following groups: saline (L_0), 0.5 mg/kg lidocaine ($L_{0.5}$), 1.0 mg/kg lidocaine ($L_{1.0}$), and 1.5 mg/kg lidocaine ($L_{1.5}$). Anesthesia was induced with 1.0 μg/kg fentanyl. Prepared lidocaine or saline solution was injected later according to allocation, followed by propofol. The dose of propofol for each patient was determined using the up-and-down sequential study design. The primary end point was the ED50 and ED95 of the propofol-induction dose. The total propofol doses, awakening time, and adverse events were recorded.

Results: The ED50 (95% confidence interval) of propofol was significantly lower in groups $L_{1.0}$ and $L_{1.5}$ than group L_0 (1.6 [1.5–1.7] mg/kg and 1.8 [1.6–1.9] mg/kg, versus 2.4 [2.3–2.5] mg/kg, respectively; $p<0.001$). There was no significant difference in ED50 between groups $L_{1.0}$ and $L_{1.5}$ ($p>0.05$). However, surprisingly, the ED50 was significantly higher in group $L_{0.5}$ than L_0 (2.8 [2.6–3.0] mg/kg vs 2.4 [2.3–2.5] mg/kg; $p<0.05$). The total doses of propofol in groups $L_{1.0}$ and $L_{1.5}$ were lower than those in groups L_0 and $L_{0.5}$ ($p<0.05$). The systolic blood pressure (SBP) decline after anesthesia induction in group $L_{0.5}$ was greater than that in group L_0 ($p<0.01$). The incidence of respiratory depression in group $L_{0.5}$ was greater than that in groups L_0 and $L_{1.0}$ ($p<0.05$).

Conclusion: In patients who underwent first-trimester uterine aspiration, intravenous lidocaine 1.0 mg/kg prior to propofol injection significantly reduced the ED50 of propofol induction dose without severe side effects, equivalent to the effect of 1.5 mg/kg dose. We recommend 1.0 mg/kg as the optimal dose.

Keywords: lidocaine, propofol, uterine aspiration, median effective dose

Introduction

Propofol has been commonly used as an intravenous anesthetic to provide sedation in outpatient surgery, given its significantly shorter half-life than other agents.[1,2] However, sedation with propofol alone in a large dose is related to adverse respiratory and circulatory events. Higher doses of propofol can increase the risk of apnea, upper airway collapse, and hypotension;[3–7] whereas, lower doses can lead to inadequate sedation. Propofol administered in combination with other drugs may decrease the risk of respiratory and circulatory complications and provide safe and satisfactory sedation. Thus, an effective adjunct for attenuating the response to surgery and reducing the propofol requirement is

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needed. In recent years, both midazolam and dexmedetomidine have been used in outpatient surgery, but the half-life of midazolam is relatively long, and the induction of dexmedetomidine is slow and the preparation is cumbersome, so the application is limited.[8,9]

Lidocaine is a widely used local anesthetic in clinical practice.[10] Previous studies have found that intravenous lidocaine could enhance the sedative effect of propofol-based anesthesia.[11–15] Other perioperative benefits of intravenous lidocaine include alleviated propofol injection pain, reduction of opioid requirement, accelerated recovery of gastrointestinal function after surgery, and decreased incidence of postoperative chronic pain.[16–19] Intravenous lidocaine has a short half-life (90–120 min), and its blood concentrations reported in clinical studies remained below toxic concentrations (>5 μg/mL).[20,21] Foo et al recommended in their newly published consensus guidelines that if intravenous lidocaine was used, an initial dose of no more than 1.5 mg/kg calculated using the patient's ideal body weight was safe.[21] A study by Lili et al already proved that administration of bolus intravenous lidocaine 1.5 mg/kg before anesthesia induction resulted in a 36% reduction in ED50 of propofol for attenuating the response to cervical dilation in patients undergoing operative hysteroscopy.[22] Liu et al also demonstrated that the addition of intravenous lidocaine 1.5 mg/kg significantly reduced the ED50 of propofol induction dose during gastroscopy in adult patients without any dramatic compromise of hemodynamic and respiratory profiles.[23]

Therefore, this study was designed to test the effect of different doses of intravenous lidocaine on the ED50 and ED95 of propofol induction dose during first-trimester uterine aspiration, and to identify the optimal dose, which, to our knowledge, has not yet been explored in previous studies.

Materials and Methods

Trial Registration

After finished designing this clinical trial, we had missed the previous ethics review within West China Second University Hospital, and the next one was still months away. Therefore, we applied for ethical review to the Chinese Ethics Committee of Registering Clinical Trials, an independent institutional ethics committee organized by the Chinese Clinical Trial Registry. The protocol of this study was approved by the Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT20210401), and registered in the Chinese Clinical Trial Registry (ChiCTR2100049263). The study was carried out in accordance with the Declaration of Helsinki from September 2021 to May 2022, and we have obtained written informed consent from the 100 study participants prior to study commencement.

Patients

This prospective study was carried out in patients who were scheduled to undergo outpatient first-trimester uterine aspiration under anesthesia at West China Second Hospital of Sichuan University. Patients with ASA physical status I or II, aged 18–50 years, and in a fasted state up to 6 h (for solids) and up to 2 h (for liquids) before surgery were included. Exclusion criteria were as follows: patients with body mass index (BMI) >28 kg/m^2 or BMI <18 kg/m^2; patients with body weight <40 kg; patients with a history of vaginal delivery and those who had undergone cervical dilation within 6 months; patients allergic to local anesthetics, propofol, fentanyl, or other drugs related to this study; patients with severe liver and kidney dysfunction, endocrine diseases, metabolic diseases, cardiovascular diseases, respiratory system diseases, or central nervous system diseases; patients who received long-term sedatives, analgesics, and drugs that may affect the metabolism of local anesthetics or received within 7 days; patients who received other experimental drugs or participated in other clinical trials within 3 months before the study; patients addicted to alcohol or recreational drugs; and patients with Mallampati score III–IV. All participants were informed about the purpose of the trial.

Randomization and Blinding

Briefly, 100 patients were randomized into the L_0, $L_{0.5}$, $L_{1.0}$, and $L_{1.5}$ groups, according to a computer-generated random sequence with a block size of four. The unique number was sealed in an opaque envelope. The anesthesiologist who prepared and administered the medication was aware of the group allocation. The investigator who collected data, the patients, and the surgeon and nurses were blinded to the group allocation.

Study Protocol

No other drug was given before anesthesia induction. A 22-gauge cannula was inserted into the vein and an infusion of Ringer's lactate (2 mL/kg/h) was started. Once inside the operating room, patients were given mask oxygen inhalation of 10 L/min for 3 min before induction, and the invasive blood pressure, electrocardiogram, respiratory rate and peripheral capillary oxygen saturation (SpO_2) were monitored until the patients woke up from anesthesia and were transferred to the postoperative anesthesia care unit. SpO_2, heart rate (HR), and invasive blood pressure were recorded according to the following three time points: on the examining table ready for anesthesia induction (T_0), on finishing anesthesia induction (T_1), and on finishing cervical dilation (T_2). All drugs were prepared and stored at room temperature and used immediately. Lidocaine (Sinopharm Rongsheng Pharmaceutical Co., China) 0.5 mg/kg, 1.0 mg/kg, and 1.5 mg/kg was diluted with normal saline to 10 mL in a 10-mL syringe. An equal volume of normal saline was also prepared in a 10-mL syringe. Anesthesia induction was started with a single bolus of 1.0 ug/kg fentanyl (Yichang Humanwell Pharmaceutical Co., China). One minute later, the prepared lidocaine or saline solution was injected in approximately 30 seconds according to allocation, followed by propofol (Corden Pharma S.P.A., Italy) at a speed of 0.4 mL/s in all patients. The first patient in every group received propofol 2.0 mg/kg. In subsequent patients, the dose of propofol was increased or decreased by 0.2 mg/kg according to the response of the previous patient. Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) was used to assess the depth of sedation.[24] The MOAA/S scale is a 6-point scale and it is described as 5: Responds readily to name spoken in normal tone; 4: Lethargic response to name spoken in normal tone; 3: Responds only after name is called loudly and/or repeatedly; 2: Responds only after mild prodding or shaking; 1: Responds only after painful trapezius squeeze; 0: No response after painful trapezius squeeze. After the MOAA/S score was <1, the surgeon was allowed to begin placement of the vaginal speculum, which signaled the start of the operation. All operations were performed by the same surgeon. If the MOAA/S score was ≥1 after the first dose of propofol or if bodily movement was observed from the beginning until cervical dilation, the result was defined as ineffective; otherwise, it was effective. For ineffective cases, the propofol of the subsequent patient was increased by 0.2 mg/kg. For effective cases, the propofol of the subsequent patient was decreased by 0.2 mg/kg. If the MOAA/S score was ≥1 or bodily movement was observed during the surgery, 0.5 to 1.0 mg/kg of propofol was given based on the clinical needs. After anesthesia induction, if apnea was longer than 1 min, it was defined as respiratory depression, and assisted face mask ventilation was applied until spontaneous respiration was restored. If upper airway obstruction was observed, the mandible was lifted to ensure ventilation. If SpO_2 <92%, hypoxia was defined and the procedure was stopped, and an assisted face mask ventilation was applied to normalize the oxygen saturation. If the HR was <50 beats/min, atropine 0.5 mg was administered. Hypotension was defined as SBP, diastolic blood pressure (DBP), or mean arterial pressure (MAP) decreased by more than 20% of the baseline, or SBP<80 mmHg. When hypotension occurred, metahydroxyamine 0.2–0.4 mg or ephedrine 5–10 mg was injected as appropriate. The total dose of propofol, surgery duration, and awakening time at the end of surgery were recorded. Myoclonus after propofol and side effects of local anesthetic such as tinnitus, perioral numbness, and heart palpitations were also recorded.

Measurements

The primary end point was the ED50 and ED95 of the propofol-induction dose. The secondary end points were total dose of propofol, awakening time from the end of surgery, respiratory depression, upper airway obstruction, hypoxia, bradycardia, hypotension, and myoclonus after propofol.

Sample Size

The non-independence and unknown distribution of data of an up-and-down sequential methodology study prevent the formulation of theoretically strict rules for calculating sample size.[25] The sample size is decided according to the stop rule. Patients should be enrolled until at least six pairs of ineffective results have turned to effective results. Simulation studies suggested that including at least 20–40 patients could provide stable estimates of the target dose for most scenarios. Other anesthesia trials using this methodology also typically had 20–40 patients.[26,27] In our study, each group included 25 patients, which was sufficient for statistical analysis.

Statistical Methods

SPSS 26.0 (IBM Inc., Armonk, NY, USA) was used to analyze the results. The Shapiro–Wilk test was used to determine whether the data were normally distributed. Continuous normally distributed variables were presented as mean±standard deviation, and compared using one-way ANOVA between groups. Non-normally distributed data were presented as median (interquartile range) and compared using Wilcoxon rank-sum test. Categorical data were represented as n (%) and analyzed using chi-square testing. The ED50 (95% CI) of propofol was calculated as the average of midpoints of ineffective-effective crossovers and analyzed by one-way ANOVA, and Bonferroni method was used for comparison between groups. The ED95 (95% CI) was estimated by using probit regression. For all analyses, $p<0.05$ was considered to indicate statistically significant differences.

Results

In all, 121 patients were enrolled and screened. Among them, 100 patients were divided randomly into four groups and included in the final analysis (Figure 1). There were no significant differences among the four groups with respect to patient baseline characteristic data including age, BMI, HR (T_0), SBP (T_0), DBP (T_0), and MAP (T_0) (Table 1).

The up-and-down sequences showing the doses and responses of patients are presented below (Figure 2). The mean propofol induction doses in L_0, $L_{0.5}$, $L_{1.0}$, and $L_{1.5}$ groups were 2.3±0.2, 2.7±0.3, 1.6±0.2, and 1.7±0.2 mg/kg, respectively. Figure 3 shows the dose-effect analysis of lidocaine and propofol on patients' responses in the four groups. Table 2 shows the ED50 and ED95 (with 95% CI) of propofol in the four groups, based on the Dixon–Massey up-and-down sequential allocation method and probit regression, respectively. The ED50 of propofol in groups $L_{1.0}$ and $L_{1.5}$ were significantly less than that in group L_0 (1.6 [1.5–1.7] mg/kg; 1.8 [1.6–1.9] mg/kg vs 2.4 [2.3–2.5] mg/kg, $p<0.001$). The value of ED50 was higher in group $L_{0.5}$ than in group L_0 (2.8 [2.6–3.0] mg/kg vs 2.4 [2.3–2.5] mg/kg, $p<0.05$). There was no significant difference in ED50 of propofol between groups $L_{1.0}$ and $L_{1.5}$ ($p>0.05$).

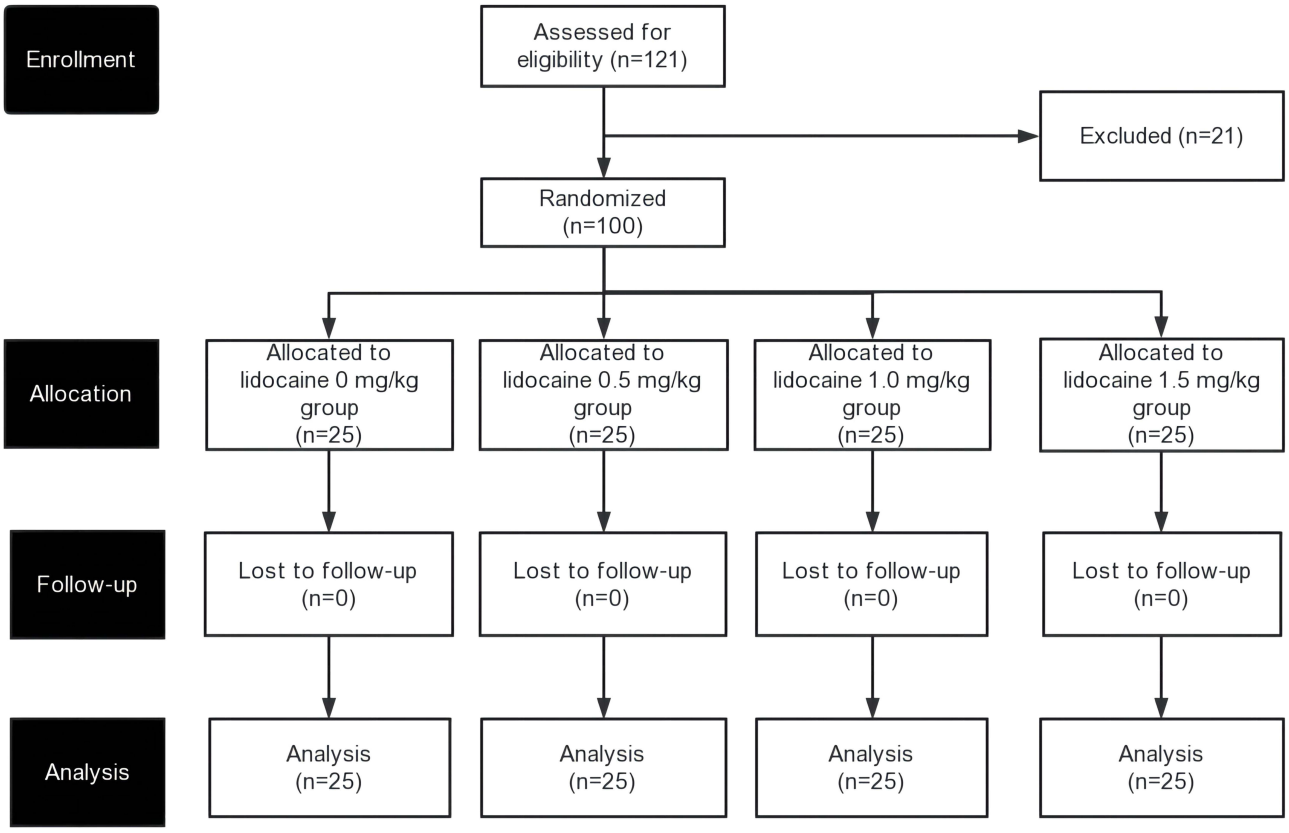

Figure 1 Flow diagram of included participants.

Table 1 Baseline Characteristic Data of Study Participants (n=25 per Group)

	L_0 (Lidocaine 0 mg/kg)	$L_{0.5}$ (Lidocaine 0.5 mg/kg)	$L_{1.0}$ (Lidocaine 1.0 mg/kg)	$L_{1.5}$ (Lidocaine 1.5 mg/kg)	*P* value
Age	31.3 (4.5)	30.3 (4.0)	31.6 (4.1)	30.2 (5.0)	0.568
BMI	0.5 [19.5;23.9]	20.9 [19.6;23.0]	22.2 [20.8;23.5]	20.1 [19.5;21.7]	0.08
HR (T0)	79.8 (11.3)	81.0 (11.0)	80.2 (10.2)	80.5 (12.1)	0.986
SBP (T0)	114 (10.9)	117 (9.7)	117 (9.9)	117 (6.7)	0.63
DBP (T0)	70.3 (7.5)	70.9 (7.5)	72.3 (9.0)	72.6 (9.4)	0.732
MAP (T0)	83.4 (7.2)	84.5 (7.4)	85.4 (8.3)	85.1 (8.2)	0.79

Notes: Data are presented as median [Q1: Q3] for non-normal distribution variables, mean (SD) for normal distribution variables, and n (%) for categorical variables. A value of p<0.05 was considered to indicate statistical significance.

There were no significant differences among groups in surgery duration and awakening time as listed in Table 3 (p>0.05). The mean doses of total propofol required for the whole surgery were significantly greater in groups L_0 and $L_{0.5}$ than the other two groups (p<0.05, Table 3). There were no significant differences among groups in the occurrence of upper airway obstruction (p>0.05). The incidence of respiratory depression in group $L_{0.5}$ was greater than that in groups L_0 and $L_{1.0}$ (p<0.05). There were no significant differences among groups in the occurrence of hypotension (p>0.05), but the SBP decline after anesthesia induction in group $L_{0.5}$ was greater than that in group L_0 (p<0.01). No patient developed bradycardia and hypoxia. No patient reported nausea, tinnitus, perioral numbness, and heart palpitations. Patient number 20 in group $L_{1.0}$ experienced facial myoclonus after the first dose of propofol 1.8 mg/kg, while patient number 10 in group $L_{1.5}$ developed myoclonus in the face and extremities after the first dose of propofol 1.4 mg/kg. The myoclonus stopped after 30–60 s. There were no significant differences among groups in the incidence of myoclonus (p>0.05).

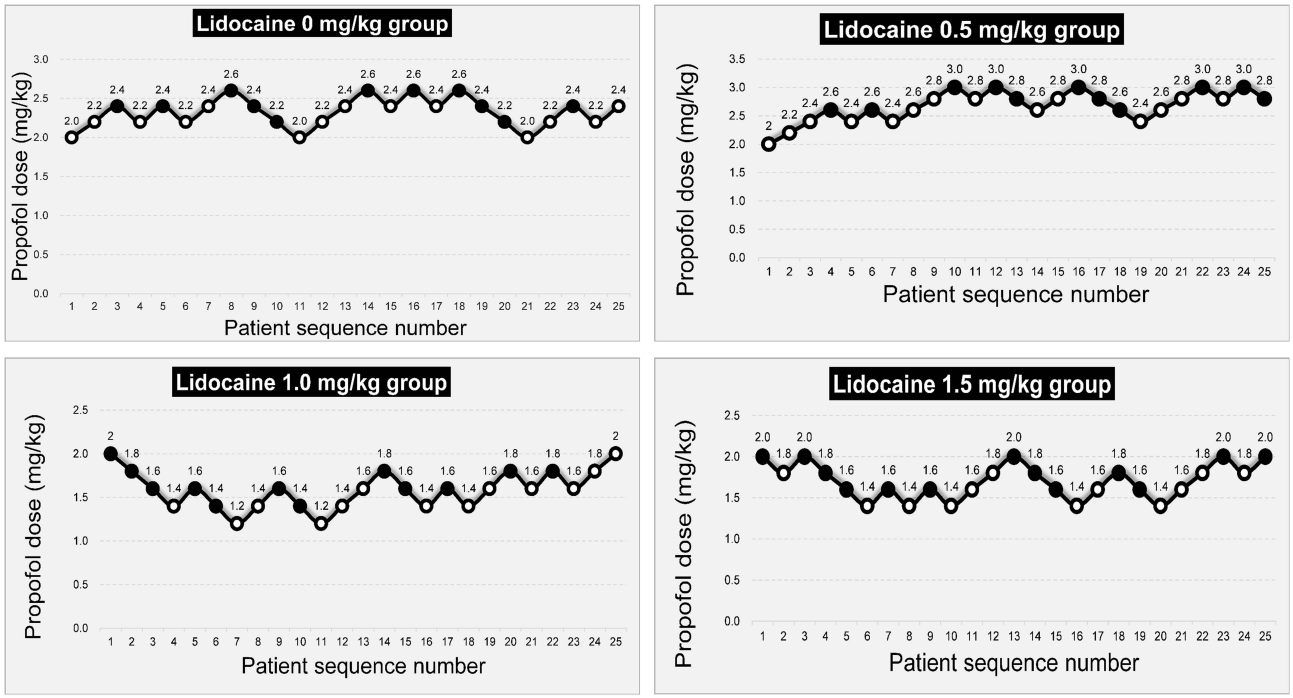

Figure 2 Dixon up-and-down plots for four groups. "●" represents effective, and "○" represents ineffective.

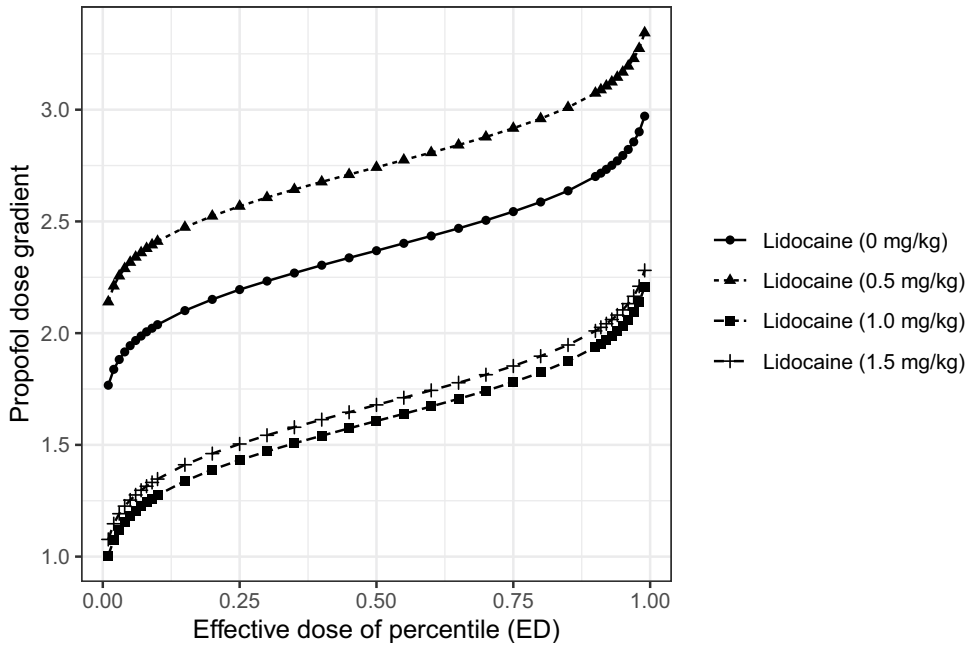

Figure 3 Dose-effect analysis of lidocaine and propofol on patients' responses in the four groups.

Discussion

To the best of our knowledge, this was the first prospective study to show the effect of different doses of intravenous lidocaine on ED50 and ED95 of propofol induction dose in patients undergoing first-trimester uterine aspiration. It demonstrated that intravenous lidocaine 1.0 mg/kg prior to propofol injection significantly reduced the ED50, ED95, and total doses of propofol, equivalent to the effect of 1.5 mg/kg dose. Therefore, we recommend a lower dose of 1.0 mg/kg as the optimal dose for effective adjunct therapy in propofol-based intravenous anesthesia. We were surprised to find that a dose of 0.5 mg/kg intravenous lidocaine increased the ED50 of propofol, which suggested a complex effect of lidocaine.

Propofol has been commonly used to provide sedation in outpatient surgery, owing to its rapid onset and recovery. However, higher doses of propofol can increase the risk of apnea, upper airway collapse, and hypotension, while lower doses can lead to inadequate sedation. Thus, an effective adjunct for attenuating the response to surgery and reducing propofol requirement is needed. In recent years, several studies have shown the analgesic benefits of intravenous lidocaine, including alleviated pain after

Table 2 ED50 and ED95 of Propofol (with 95% Confidence Intervals) in Four Groups, Based on the Dixon–Massey Up-and-Down Sequential Allocation Method and Probit Regression, Respectively

	L_0 (Lidocaine 0 mg/kg)	**$L_{0.5}$ (Lidocaine 0.5 mg/kg)**	**$L_{1.0}$ (Lidocaine 1.0 mg/kg)**	**$L_{1.5}$ (Lidocaine 1.5 mg/kg)**
ED50 (Dixon–Massey) (mg/kg)	2.4 (2.3–2.5)■#	2.8 (2.6–3.0)▲#	1.6 (1.5–1.7)▲■	1.8 (1.6–1.9)▲■
ED50 (Probit regression) (mg/kg)	2.4 (2.2–2.5)■#	2.7 (2.6–2.9)▲#	1.6 (1.5–1.8)▲■	1.7 (1.5–1.8)▲■
ED95 (Probit regression) (mg/kg)	2.8 (2.6–3.2)	3.2 (3.0–3.5)	2.0 (1.9–2.4)	2.1 (1.9–2.4)

Notes: A value of $p<0.05$ was considered significant between four groups. One-way analysis of variance: <0.001. Bonferroni multiple comparison test: group L_0 vs group $L_{0.5}$, $p<0.05$; group L_0 vs group $L_{1.0}$, $p<0.001$; group L_0 vs group $L_{1.5}$, $p<0.001$; group $L_{0.5}$ vs group $L_{1.0}$, $p<0.001$; group $L_{0.5}$ vs group $L_{1.5}$, $p<0.001$; group $L_{1.0}$ vs group $L_{1.5}$, $p>0.05$. "▲" represents the group had significant difference with group L_0 ($p<0.05$). "■" represents the group had significant difference with group $L_{0.5}$ ($p<0.05$). "#" represents the group had significant difference with group $L_{1.0}$ ($p<0.05$).

Table 3 Surgery-Related Characteristics and Adverse Events

	L_0 (Lidocaine 0 mg/kg)	$L_{0.5}$ (Lidocaine 0.5 mg/kg)	$L_{1.0}$ (Lidocaine 1.0 mg/kg)	$L_{1.5}$ (Lidocaine 1.5 mg/kg)	*P* value
Surgery duration (min)	5.5 (1.9)	5.6 (1.4)	5.2 (1.8)	5.4 (1.4)	0.856
Awakening time (min)	1.0 [0.0;2.0]	1.0 [0.0;2.0]	1.0 [0.0;3.0]	0.0 [0.0;2.0]	0.594
Total dose of propofol (mg/kg)	169 (28.3)	179 (23.6)	146 (34.9)▲■	136 (33.9)▲■	<0.001*
Respiratory depression					0.001*
No	25 (100%)■	18 (72.0%)▲#	25 (100%)■	24 (96.0%)	
Yes	0 (0.0%)	7 (28.0%)	0 (0.0%)	1 (4.0%)	
Upper airway obstruction					0.296
No	19 (76.0%)	21 (84.0%)	18 (72.0%)	23 (92.0%)	
Yes	6 (24.0%)	4 (16.0%)	7 (28.0%)	2 (8.0%)	
Hypotension					0.689
No	17 (68.0%)	13 (52.0%)	16 (64.0%)	15 (60.0%)	
Yes	8 (32.0%)	12 (48.0%)	9 (36.0%)	10 (40.0%)	
SBP(T1)-SBP(T0) (mmHg)	−10.9 (8.1)	−19.5 (7.7)▲	−15.7 (8.9)	−16.4 (8.2)	0.004*
Myoclonus					1
No	25 (100%)	25 (100%)	24 (96.0%)	24 (96.0%)	
Yes	0 (0.00%)	0 (0.00%)	1 (4.00%)	1 (4.00%)	

Notes: Data are presented as median [Q1: Q3] for non-normal distribution variables, mean (SD) for normal distribution variable, and n (%) for categorical variable. *p<0.05 was considered significantly different between four groups. "▲" represents the group had significant difference with group L_0 (p<0.05). "■" represents the group had significant difference with group $L_{0.5}$ (p<0.05). "#" represents the group had significant difference with group $L_{1.0}$ (p<0.05).

propofol injection, reduced opioid requirement, and decreased incidence of postoperative chronic pain. Foo et al, in their published consensus guidelines, recommended that if intravenous lidocaine was used, an initial dose of no more than 1.5 mg/kg calculated using ideal body weight was safe. Recently, Liu et al and Yu et al proved that the administration of intravenous lidocaine before anesthesia induction resulted in a reduction in the ED50 of propofol in patients undergoing gastroscopy and hysteroscopy. Hence, our study aimed to test the effect of different doses of intravenous lidocaine to the ED50 and ED95 of propofol induction dose during first-trimester uterine aspiration and determine the optimal dose. We excluded patients had a history of vaginal delivery and those who had undergone cervical dilation within 6 months, because we speculated that stimulation of the cervix via surgical dilation was less in those with a history of vaginal delivery or cervical dilation procedure than in those without.[28] This likely led to more accurate results.

With a short distribution half-life of 5–8 min, the distribution of intravenous lidocaine starts from the vascular compartment into the peripheral tissues, passing first through highly perfused areas (heart, lung, liver, spleen), to the less perfused areas (muscles and adipose tissue).[10] In our study, we administered lidocaine just prior to propofol induction to maintain its plasma concentration within the effective range. The result is that 1.5 mg/kg lidocaine prior to propofol resulted in a 26% reduction in the ED50 of propofol, and 1.0 mg/kg lidocaine resulted in a 30% reduction. These results are consistent with the results of Liu and Xu, suggesting the analgesic and anti-hyperalgesic effects of these doses of lidocaine. However, surprisingly, the ED50 increased with

intravenous lidocaine 0.5 mg/kg, which suggested that the effect of the 0.5 mg/kg dose may be the opposite, and very low doses of intravenous lidocaine may be related to higher hypersensitivity and neuro-excitability. Lidocaine affects a multitude of molecular targets involved in acute and chronic nociception, including N-methyl-D-aspartate (NMDA) and muscarinic cholinergic (m1, m3) receptors, which were 100–1000-times more sensitive than other targets.[20,29] NMDA, m1 and m3 receptors remain sensitive at lidocaine concentrations below clinically relevant plasma concentrations. Lidocaine inhibits the activation of human NMDA receptors at nanomolar concentrations, reaching maximal inhibition in the millimolar range, resulting in analgesic effects. Lidocaine exerts its effect on muscarinic cholinergic receptors in a concentration- and time-dependent manner. The study by klas et al suggested that intravenous lidocaine 10 and 30 mg/kg increased the intraspinal release of acetylcholine and produced central anti-nociceptive effects through the activation on muscarinic receptors in rats, but a dose of 1 mg/kg lidocaine did not significantly increase the intraspinal release of acetylcholine.[30,31] Studies also showed that lidocaine at very low nanomolar concentrations (IC50 of 18 nM for m1 and 370 nM for m3) blocked m1 and m3 muscarinic receptors. Moreover, prolonged exposure to lidocaine at IC50 resulted in a biphasic time course of m1 and m3 receptors with initial inhibition, followed by enhanced signaling after 8 h.[32] Thus, our single bolus of very low dose of 0.5 mg/kg lidocaine without prolonged exposure may have been effective mainly via inhibition of m1 and m3 receptors. Inhibition of m1 and m3 receptors as a more significant effect may be why the ED50 increased in group $L_{0.5}$ in our study. However, we did not measure lidocaine plasma concentrations in our study. To support this speculation, further research and validation are needed.

The mean dose of total propofol required for the whole surgery was significantly higher in groups L_0 and $L_{0.5}$ than the other two groups. The incidence of respiratory depression in group $L_{0.5}$ was greater than that in groups L_0 and $L_{1.0}$. The SBP decline after anesthesia induction in group $L_{0.5}$ was greater than that in group L_0. No patient developed hypoxia, because we performed chin lift or mask ventilation in a timely manner. The increased dose of total propofol, incidence of respiratory depression, and SBP decline after anesthesia induction in group $L_{0.5}$ also indicated that higher doses of propofol can increase the risk of respiratory and circulatory depression. There were no differences in the occurrence of adverse events among the L_0, $L_{1.0,}$ and $L_{1.5}$ groups. However, given our study design, the mean propofol induction doses in each group were close to the ED50 but lower than the ED95. Thus, the incidence of adverse events may be higher if the ED95 dose of propofol (2.8 [2.6–3.2] mg/kg) in group L_0 was used for induction in patients. However, the effect of lidocaine resulted in the ED95 being 2.0 (1.9–2.4) mg/kg and 2.1 (1.9–2.4) mg/kg in groups $L_{1.0}$ and $L_{1.5}$, respectively, which were relatively much lower dose. The above discussion is why we considered the analgesic effect of intravenous lidocaine administered with appropriate doses and timing as beneficial in reducing complications of propofol-based anesthesia. There were no significant differences in the ED50, total propofol dose, awakening time, and adverse events between groups $L_{1.0}$ and $L_{1.5}$ in our study. Hence, we recommend a lower dose of 1.0 mg/kg of intravenous lidocaine as the optimal dose.

There are some limitations to our study. The first is that this study only recruited ASA I or II patients, but ASA III or IV patients may be more likely to suffer from respiratory and cardiovascular depression with propofol.[33] And the subjects of this study are all pregnant women, the results might be different in male population due to physiological difference. Second, we applied MOAA/S score as indicators of sedation level instead of objective indicators, eg, BIS monitoring.[34] Third, lidocaine was given as a single bolus dose, and we did not measure plasma levels of lidocaine. Last, ED95 was determined from the ED50, so further research is needed to obtain more accurate data.

Conclusion

Our current findings showed that in patients who underwent outpatient first-trimester uterine aspiration under anesthesia, intravenous lidocaine 1.0 mg/kg prior to propofol injection significantly reduced the ED50, ED95, and total doses of propofol, equivalent to the effect of 1.5 mg/kg dose. We considered 1.0 mg/kg dose as the optimal dose. Surprisingly, a dose of 0.5 mg/kg intravenous lidocaine increased the ED50 of propofol, which suggested a complex effect of lidocaine. Future studies on the underlying mechanism are needed to validate our results.

Data Sharing Statement

The data generated during the study are available from the corresponding author (Juan Ni) by request.

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Disclosure

The authors report no conflicts of interest in this work.

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