Impact of intravenous infusion of lidocaine on intrapulmonary shunt and postoperative cognitive function in patients undergoing one-lung ventilation

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Abstract

Background. Intravenous infusion of lidocaine as an anesthesia adjuvant can improve patient outcomes, but its impact on intrapulmonary shunt during one-lung ventilation (OLV) has not been clarified.

Objectives. To determine the effect of intravenous lidocaine infusion on intrapulmonary shunt during OLV and postoperative cognitive function in video-assisted thoracoscopic surgery (VATS).

Materials and methods. Sixty patients who underwent OLV for thoracic surgery were randomized to receive intravenous infusion of lidocaine (lidocaine group, n = 30) or normal saline (control group, n = 30) for anesthesia induction. Arterial and venous blood gases were measured during two-lung ventilation and at 15 and 30 min after OLV (OLV + 15 and OLV + 30). The Mini-Mental State Examination was administered before the surgery and at postoperative 12 months to assess patient cognitive function.

Results. No significant difference was found in intrapulmonary shunt fraction (Qs/Qt) between the lidocaine group and the control group at OLV + 15 ($p = 0.493$) and OLV + 30 ($p = 0.754$). The lidocaine group used significantly lower doses of propofol and remifentanil compared to the control group (both $p < 0.001$). Furthermore, no significant difference was observed in the incidence of postoperative cognitive dysfunction between the lidocaine group and the control group at 1 year post-operation (3.3% vs 6.7%, $p = 0.554$).

Conclusions. Intravenous lidocaine administered in VATS had no significant impact on intrapulmonary shunt during OLV or postoperative cognitive function. However, it significantly reduced the doses of anesthetics used during the surgery.

Key words: cognitive function, lidocaine, one-lung ventilation, intrapulmonary shunt

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Background

One-lung ventilation (OLV) is necessary for improved visualization in video-assisted thoracoscopic surgery (VATS). However, it can increase intrapulmonary shunt, leading to postoperative pulmonary complications.[1,2] An intrapulmonary shunt is defined as the mixing of unoxygenated blood flow with oxygenated blood within the lungs. This phenomenon has the potential to reduce oxygenation levels and, consequently, may result in the development of hypoxemia. Hypoxic pulmonary vasoconstriction is an intrinsic homeostasis mechanism of the pulmonary vasculature. Pulmonary arteries contract due to alveolar hypoxia and transfer blood to the pulmonary segments with higher oxygenation, thereby optimizing ventilation-perfusion matching. In thoracoscopic surgery, hypoxic pulmonary vasoconstriction is an important mechanism of reducing intrapulmonary shunt and maintaining oxygenation in OLV.

Lidocaine is a promising agent used for enhanced recovery after surgery, showing benefits across various surgical procedures. Intravenous lidocaine is noninferior to thoracic epidural analgesia for acute postoperative pain control in major abdominal surgery at 24 h postoperatively.[3] It can also reduce the use of opioids in the perioperative period and alleviate postoperative nausea and vomiting in thoracic surgery.[4] However, the impact of lidocaine on hypoxic pulmonary vasoconstriction and intrapulmonary shunt in patients undergoing OLV is still unknown.

Our study aimed to investigate the impact of intravenous lidocaine on intrapulmonary shunt and cognitive function during OLV in VATS.

Materials and methods

Patients

This is a randomized, double-blind, placebo-controlled clinical trial evaluating the impact of intravenous infusion of lidocaine compared to normal saline on intrapulmonary shunt and postoperative cognitive function in patients undergoing OLV. This study complied with the Declaration of Helsinki and was approved by the ethics committee of Affiliated Hospital of Yangzhou University, China (approval No. 2018-YKL012-01). Informed consent was obtained from each participant. The inclusion criteria consisted of: 1) scheduled video-assisted thoracoscopic resection of pulmonary tumors under general anesthesia; 2) American Society of Anesthesiologists (ASA) physical status classification grades I–II; 3) age between 20 and 70 years; and 4) body mass index (BMI) between 18 and 25 kg/m^2. Patients were excluded for: 1) preoperative comorbidities involving vital organs (such as diabetes and severe liver and kidney diseases); 2) moderate or more severe anemia; and 3) the forced expiratory volume in the 1st 2nd/forced vital capacity ratio <65%.

Recruitment and randomization

Patients who underwent treatment for pulmonary tumors at our hospital between August 2018 and March 2020 were approached for recruitment. Each patient was randomly allocated in a 1:1 ratio to the lidocaine group or the normal saline group through a computer-generated randomization sequence. Normal saline and lidocaine were preprepared by an assistant and stored in indistinguishable vials. The assistant was not involved in matters other than drug preparation.

Anesthesia protocol

Patients were attached to a standard ASA monitor. Under ultrasound guidance, the radial artery and right internal jugular vein were accessed. The right internal jugular vein catheter measured 18 cm in length, with the catheter tip positioned in the right atrium confirmed with transthoracic echocardiography. Invasively measured mean arterial pressure (MAP), heart rate, oxygen saturation measured with pulse oximetry (SpO_2), and central venous pressure were monitored. The Narcotrend index (NI) was monitored using a Narcotrend® monitor (MT MonitorTechnik GmbH & Co. KG, Hannover, Germany).

For anesthesia induction, a bolus of 1.5 mg/kg lidocaine was administered in the lidocaine group, followed by continuous infusion of 1.5 mg/kg/h lidocaine combined with 0.05 mg/kg midazolam, 1.5–2 mg/kg propofol, 0.3 μg/kg sufentanil, and 0.15 mg/kg cisatracurium. Normal saline instead of lidocaine was administered in the control group, with the doses of other anesthetic agents unchanged.

Intubation was performed with a double-lumen endobronchial tube. Patients were mechanically ventilated with a tidal volume of 8 mL/kg, an inhaled oxygen concentration (FiO_2) of 100%, a respiratory ratio of 1:2, and a respiratory rate of 10–12 breaths/min. During OLV, the non-ventilated branch of the double-lumen tube was open to the atmosphere. The respiratory rate was adjusted to 14–16 breaths/min, while other respiratory parameters remained unchanged, and the partial pressure of end-tidal carbon dioxide ($PETCO_2$) was maintained at 35–45 mm Hg.

Propofol, remifentanil and cisatracurium (0.1 mg/kg/h) were used for the maintenance of anesthesia. The doses of propofol and remifentanil were tuned to keep the NI between 26 and 46 and the MAP within ±20% of the baseline blood pressure. The central venous pressure was maintained at 5–12 cm H_2O with intravenous rehydration (crystalline : colloidal = 2 : 1). Cisatracurium was stopped approx. 30 min before the end of surgery, and other anesthetics were discontinued upon completion of the procedure.

Blood gas analysis

Blood samples were collected from the radial artery and internal jugular vein while the patient was in a lateral

position with two-lung ventilation (TLV), after 15 min of OLV (OLV + 15) and after 30 min of OLV (OLV + 30). Blood gas analysis was performed using a GEM 3500 blood gas analyzer (Instrumentation Laboratory Company, Bedford, USA). The total doses of propofol and remifentanil (TLV to OLV + 30) and the post-anesthesia recovery time (the time from drug withdrawal to extubation) were recorded. The extubation criteria were: patients had regained consciousness; spontaneous breathing frequency >12 breaths/min; $PETCO_2 \leq 45$ mm Hg; $SpO_2 > 95\%$; tidal volume >6 mL/kg; patients could elevate their head for a min of 5 s.

Outcome measures

Intrapulmonary shunt

The intrapulmonary shunt fraction (Qs/Qt) was calculated as $Qs/Qt = (CcO_2 - CaO_2)/(CcO_2 - CvO_2) \times 100\%$, where CcO_2 is the pulmonary capillary oxygen content, CaO_2 is the arterial oxygen content and CvO_2 is the mixed venous oxygen content (replaced with the oxygen content in the right atrium):

$$CcO_2 = 1.36 \times Hb \times SaO_2 + PaO_2 \times 0.0031$$

$$CaO_2 = 1.36 \times Hb \times SaO_2 + PaO_2 \times 0.0031$$

$$CvO_2 = 1.36 \times Hb \times SvO_2 + PvO_2 \times 0.0031$$

In these formulas, 1.36 is the oxygen-carrying capacity of hemoglobin (mL/g); SaO_2 is the alveolar capillary oxygen saturation, which was approximated by the arterial oxygen saturation; PaO_2 is the alveolar oxygen partial pressure, which was calculated by using the formula,

$$PaO_2 = FiO_2 \times (Pb - PH_2O) - (PaCO_2/R) + [PaCO_2 \times FiO_2 \times (1 - R)/R],$$

where Pb is the atmospheric pressure (760 mmHg), PH_2O is the water vapor pressure at 37°C (47 mm Hg), R is the respiratory quotient (0.8), and $PaO_2 = 713 - PaCO_2$ when $FiO_2 = 100\%$; SaO_2 is the arterial oxygen saturation; SvO_2 is the mixed venous oxygen saturation, which was equal to the saturation of the blood sample extracted from the right atrial ($SvcO_2$); PvO_2 is the mixed venous oxygen partial pressure, which was equal to the partial pressure of oxygen in the right atrium ($PvcO_2$).

Cognitive assessment

All patients were evaluated for cognitive function using a validated Chinese version of the Mini-Mental State Examination before the surgery and at 12 months postoperatively. A reduction of ≥2 points from the baseline cognitive score was regarded as postoperative cognitive dysfunction. The cognitive assessment was performed by a single anesthesiologist who was blinded to patient assignment.

Sample size

The primary outcome was intrapulmonary shunt fraction (Qs/Qt), which was 13.24 ±5.48% in the lidocaine group and 22.36 ±5.35% in the control group in a previous study.[4] With a bilateral α of 0.05 and a power of 90%, the sample size was calculated as N1 = N2 = 14 for each group. Our study finally included a total of 60 patients.

Statistical analyses

Measurement data were expressed as mean and standard deviation (SD), or median and interquartile range (IQR). Categorical data were expressed as percentage. Comparisons between the lidocaine and control groups were made using the Mann–Whitney U test, 2 independent-samples Student's t-test or χ^2 test. Homoscedasticity was verified using Levene's test. Continuous variables were checked for normal distribution with the Shapiro–Wilk test due to the small sample size. Non-normally distributed data ($p < 0.05$) were analyzed with the Mann–Whitney U test, whereas normally distributed variables were compared using the 2 independent-samples t-test. All statistical analyses were performed using SPSS v. 23.0 (IBM Corp., Armonk, USA). A $p < 0.05$ indicated a statistically significant difference.

Results

The final analysis included 60 patients with 30 in each group. The flowchart of participant inclusion is shown in Fig. 1. No patients died or were lost to follow-up during the study. No significant difference was found in the basic characteristics between the control group and the lidocaine group (Table 1). The homoscedasticity test results are shown in Supplementary Table 1 (doi.org/10.5281/zenodo.13683171).

The blood gas analysis parameters of PaO_2 and Qs/Qt (intrapulmonary shunt fraction) in the lidocaine group and

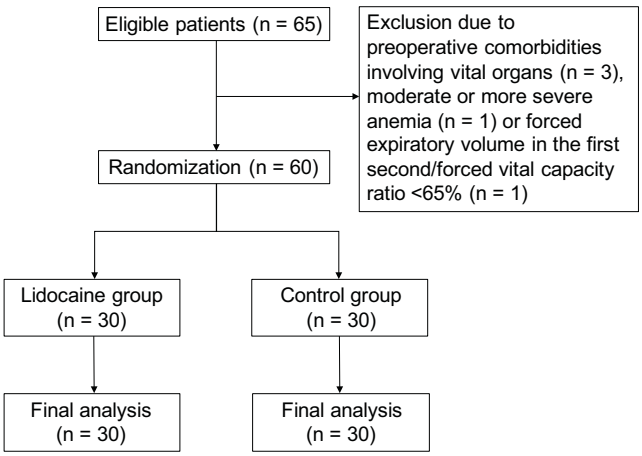

Fig. 1. Flowchart of participant inclusion

Table 1. Characteristics of the patients

Item	Control (n = 30)	Lidocaine (n = 30)	U/t	df	p-value
Age [years], median (IQR)*	48 (38, 54.8)	54.5 (40.3, 59.5)	349	/	0.135
Male/female (n)†	15/15	14/16	0.067	1	0.796
BMI [kg/m^2], median (IQR)*	23.7 (22.1, 24.3)	23.05 (21.1, 23.9)	367.5	/	0.222
FEV1 (% predicted), median (IQR)*	91 (87.3, 98.8)	94.5 (89, 101.8)	369.5	/	0.233
FVC (% predicted), mean ±SD (95% CI)#	116.7 ±10.7 (112.7, 120.7)	121.6 ±9.5 (118.1, 125.2)	–1.88	58	0.065
FEV1/FVC (%), mean ±SD (95% CI)#	80.0 ±4.9 (78.2, 81.9)	78.7 ±4.7 (77.0, 80.5)	1.51	58	0.298
Right/left lung operation (n)†	13/17	14/16	0.600	1	0.439
OLV time [min], mean ±SD (95% CI)#	59.5 ±17.2 (53.1, 65.9)	57.8 ±17.2 (51.4, 64.3)	0.38	58	0.703
Bleeding volume [mL], median (IQR)*	80 (66.25, 90.75)	70 (61.25, 83.75)	351.5	/	0.144
Intraoperative fluid [mL], mean ±SD (95% CI)#	921.0 ±232.6 (834.1, 1007.9)	896.0 ±211.9 (816.9, 975.1)	0.435	58	0.665

df – degrees of freedom; IQR – interquartile range; SD – standard deviation; 95% CI – 95% confidence interval; BMI – body mass index; FEV1 – forced expiratory volume in 1 s; FVC – forced vital capacity; OLV – one-lung ventilation; *Mann–Whitney U test; #two-sample t-test; †Pearson's χ^2 test of independence.

Table 2. Comparisons of hemodynamics between the lidocaine group and the control group

Variable	Control (n = 30)	Lidocaine (n = 30)	U/t	df	p-value
PaO_2 [mm Hg] median (IQR)*					
OLV + 15	196.5 (140.8, 300.5)	210.0 (125.8, 280.8)	442.5	/	0.912
OLV + 30	198.5 (103.8, 269.5)	198.0 (102.8, 264.8)	426	/	0.723
Qs/Qt (%), mean ±SD (95% CI)#					
OLV + 15	25.8 ±6.1 (23.6, 28.1)	24.7 ±6.4 (22.3, 27.1)	0.689	58	0.493
OLV + 30	26.6 ±8.6 (23.4, 29.8)	26.0 ±6.9 (23.4, 28.6)	0.315	58	0.754

*Mann–Whitney U test; #two-sample t-test; df – degrees of freedom; OLV – one-lung ventilation; IQR – interquartile range; SD – standard deviation; 95% CI – 95% confidence interval.

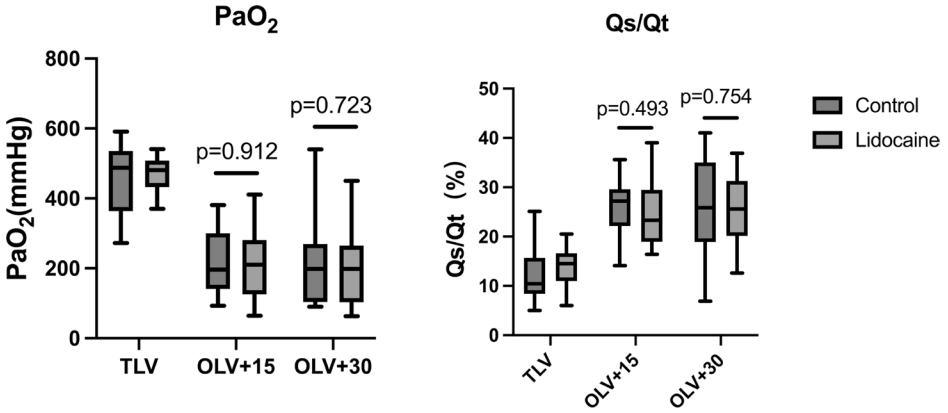

Fig. 2. Comparisons of hemodynamics between the control group and the lidocaine group during video-assisted thoracoscopic resection of pulmonary tumors

PaO_2 – alveolar oxygen partial pressure; Qs/Qt – intrapulmonary shunt fraction.

the control group are shown in Fig. 2. During OLV, there was no significant difference between the lidocaine group and the control group in the levels of PaO_2 and Qs/Qt (Table 2).

Compared to the control group, the lidocaine group had significantly higher doses of propofol (Mann–Whitney U test, U = 28.5, p < 0.001) and remifentanil (Mann–Whitney U test, U = 63.0, p < 0.001) infused from TLV to OLV + 30. The post-anesthesia recovery time did not differ significantly between the 2 groups (2-sample t-test, t = –0.635, p = 0.528) (Table 3). Also, the 1-year incidence of postoperative cognitive dysfunction was not significantly different between the lidocaine group and the control group (1/30, 3.3% vs 2/30, 6.7%; χ^2 test of independence with Yates's correction, χ^2 = 0, df = 1, p = 1.0).

Discussion

Our study showed that the use of intravenous lidocaine did not significantly increase intrapulmonary shunt during OLV in VATS. Previous animal studies showed that intravenous infusion of lidocaine enhanced the effect of hypoxic pulmonary vasoconstriction and affected intrapulmonary

Table 3. Doses of propofol and remifentanil and post-anesthesia recovery time

Item	Control (n = 30)	Lidocaine (n = 30)	U/t	df	p-value
Propofol [mg], median (IQR)#	194.9 (171.7, 212.9)	121.2 (104.1, 129.1)	28.5	/	<0.001
Remifentanil [μg], median (IQR)#	283.4 (256.8, 319.7)	129.8 (102.2, 173.1)	63	/	<0.001
Post-anesthesia recovery time [min], mean ±SD (95% CI)*	9.9 ±2.4 (9.0, 10.8)	10.3 ±2.8 (9.3, 11.4)	0.635	58.0	0.528

df – degrees of freedom; IQR – interquartile range; SD – standard deviation; 95% CI – 95% confidence interval; #Mann–Whitney U test; *two-sample t-test.

shunt.[5,6] However, there are conflicting opinions regarding the appropriate doses of lidocaine needed to enhance the effects of hypoxic pulmonary vasoconstriction. Also, further investigation has revealed that amide anesthetics, such as lidocaine, are vasoconstrictive at low concentrations and vasodilative at high concentrations.[7,8] This biphasic effect of lidocaine has also been observed in swine pulmonary arteries, where concentrations of 1 μg/mL led to vasoconstriction, and concentrations of 10–100 μg/mL resulted in vasodilation.[9] Our study found that intravenous lidocaine did not have a significant impact on intrapulmonary shunt during OLV. This lack of effect may be attributed to the relatively low dose of lidocaine used in our study.

We found that lidocaine significantly reduced the doses of propofol and remifentanil during video-assisted thoracoscopic resection of pulmonary tumors, likely due to its sedative effect. When administered intravenously to healthy individuals, lidocaine can provide a certain level of analgesia and induce dizziness in over half of the study participants once its plasma concentration reaches 1.5 μg/mL.[10] These results indicate that lidocaine, at clinically relevant concentrations, can induce sedation, leading to a deepening of anesthesia. Forster et al.[11] has also suggested that intravenous lidocaine can reduce propofol doses by half during painless colonoscopy, which is consistent with the results of our study. Additionally, we found that intravenous lidocaine did not prolong post-anesthesia recovery time, consistent with previous research.[12]

Animal studies have demonstrated that the intravenous infusion of lidocaine, in combination with adenosine and magnesium, significantly reduces cerebral oxygen consumption.[13] Additionally, in research focusing on cerebroprotection using an in vitro cerebral ischemia model, lidocaine was found to decrease neuronal damage during cerebral ischemia.[14] Despite the neuroprotective properties of lidocaine, the impact of continuous intravenous lidocaine infusion on postoperative cognitive function in patients remains a topic of debate. Wang et al.[15] conducted a study where patients received a continuous intravenous infusion of lidocaine at a rate of 2 mg/kg/h during laparoscopic colorectal cancer surgery until the conclusion of the procedure. Their findings revealed a significant reduction in the occurrence of cognitive dysfunction within 7 days post-surgery. However, in a multicenter trial involving lidocaine administration in cardiac surgery, where study participants were given 1 mg/kg of lidocaine after tracheal intubation followed by a continuous infusion, researchers discovered that the use of intravenous lidocaine during and after cardiac surgery did not diminish postoperative cognitive decline at 6 weeks.[16] Similarly, our study on continuous lidocaine infusion during pulmonary surgery found no impact on postoperative cognitive function within a year.

A meta-analysis summarized the dose ranges for intraoperative intravenous lidocaine, indicating a continuous infusion at a rate of 1.5–3.0 mg/kg/h after a bolus injection of 0–2.0 mg/kg.[17] It was found that the plasma concentrations of lidocaine were much lower than the toxic level of 5 μg/mL despite continuous infusion during surgeries.[18,19] Our study used the same dose of lidocaine and found no obvious adverse effects.

Limitations

There are some limitations to our study. First, our patients were relatively young because older patients are reluctant to participate in clinical trials. This may have compromised the generalizability of our findings. Second, the single-center design and small sample size are additional limitations that should be considered when interpreting the results. Third, the statistical analysis in this study is exploratory and does not incorporate multiple comparisons correction. Hence, the interpretation of the results should be exercised with caution due to the potential for uncontrolled type I error probability, which could also impact the validity of any future meta-analyses. This exploratory analysis provides a foundation for future research in this field.

Conclusions

Our study found that intravenous lidocaine had no significant impact on intrapulmonary shunt during OLV in VATS. However, it significantly reduced the doses of propofol and remifentanil required. Furthermore, the supplementary use of lidocaine in our patients did not lead to a decline in cognitive function at 1 year post-operation.

Supplementary data

The Supplementary materials are available at https://doi.org/10.5281/zenodo.13683171. The package includes the following file:

Supplementary Table 1. Tests of homogeneity of variances (based on mean).

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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