Pharmacokinetics of intravenous and topical lidocaine in patients undergoing thoracoscopic pulmonary resection: a comparative study

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Abstract. – **OBJECTIVE:** Lidocaine was the commonly used local anesthetic. The present study aimed to compare the pharmacokinetics of intravenous and topical lidocaine in patients undergoing thoracoscopic pulmonary resection.

PATIENTS AND METHODS: Sixty patients who were scheduled for thoracoscopic pulmonary resection were screened and randomly assigned to the intravenous lidocaine group and topical lidocaine group. After induction, the patient in the intravenous group was given an intravenous bolus of 1.5 mg/kg lidocaine, while the patient in the topical group was given 3.0 mg/kg lidocaine *via* the "spray-as-you-go" method. Arterial blood was sampled at preset intervals, and plasma concentrations of lidocaine and its metabolites [monoethylglycinexylidide (MEGX) and glycinexylidide (GX)] were measured by ultra-performance liquid chromatography-tandem mass spectrometry.

RESULTS: Following intravenous administration, plasma lidocaine concentration reached its peak with a time to reach C_{max} (T_{max}) of 0.05 h and then decreased in a biphasic manner with a very short half-life time ($T_{1/2}$) of 1.85 h. After topical administration, lidocaine was well absorbed, with T_{max} of 0.21 h and bioavailability of 71.02%. The mean T_{max}, C_{max}, and area under the curve from the time (AUC0-t) of MEGX and GX were higher in the topical group than in the intravenous group. There were no obvious differences in the C_{max}, $T_{1/2}$, clearance, or apparent volume of distribution of lidocaine between the two groups. No obvious adverse events were observed.

CONCLUSIONS: Topical administration of 3 mg/kg lidocaine *via* the spray-as-you-go" method is an effective and safe technology for patients undergoing thoracoscopic pulmonary resection.

Introduction

Thoracoscopic pulmonary resection is a modern lung surgical technique that originated in the 1990s. In 1992, it was performed the first lobectomy on a specific patient using thoracoscopic technology[1]. With the advancement of thoracoscopic technology, its advantages, such as smaller incisions, less blood loss, shorter recovery time, and lower pain, have increased sharply[2-4]. Sihoe[5] reported that video-assisted thoracoscopic surgery was the gold standard for lung cancer surgery. In addition, growing evidence has demonstrated that thoracoscopic pulmonary resection can be used to treat various types of lung diseases[6-9].

Double-lumen tube (DLT) intubation is commonly used to achieve intraoperative single-lung ventilation and lung collapse in thoracoscopic pulmonary resection. However, due to the larger diameter and hardness of the double tube, DLT directly stimulates the carina and the inner wall of the trachea and induces more severe cardiovascular responses[10,11]. The cardiovascular response was the most severe when the endotracheal catheter entered the trachea for approximately 30-45 s, and the reaction lasted for 3-5 min[12]. Although this stress response duration is relatively short, it has a potentially fatal risk for patients with cardiovascular and cerebrovascular diseases. Therefore, many drugs, including opioids[13], dexmedetomidine[14,15], esmolol[16], and lidocaine[17-19],

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have been used to attenuate the cardiovascular response. Among these drugs, lidocaine is the ideal anesthetic for reducing cardiovascular responses during DLT intubation owing to its favorable pharmacokinetic characteristics with minimal tissue toxicity, wide safety margin, and short half-life[20].

Lidocaine is a medium-effect amide local anesthetic; it acts as a local anesthetic by inhibiting the sodium ion channels of nerve cell membranes; on the other hand, it can reduce the cardiovascular stress response by increasing the permeability of the cell membrane to potassium ions. In addition, it can also effectively alleviate and suppress the cough reflex during anesthesia induction[20]. The pharmacokinetics of drugs depend on the location and technique of drug administration[21,22]. Lidocaine can be delivered intravenously and topically. Administered topically, lidocaine has been reported to be delivered to patients by nebulization[23], mucosal atomization[24], and "spray-as-you-go" (SAYGo) technique[18,25]. The pharmacokinetics of atomized and non-atomized lidocaine in a randomized clinical trial[26] have also been reported. However, there is no pharmacokinetic study comparing a single intravenous injection of lidocaine with the airway topical anesthesia method of SAYGo.

Therefore, we designed this study to explore and compare the pharmacokinetic profiles of intravenous *vs.* topical lidocaine in patients undergoing thoracoscopic pulmonary resection.

Patients and Methods

Subjects

The study was conducted in the Department of Anesthesiology, Affiliated Hospital of North Sichuan Medical College. The inclusion criteria were as follows: planning to general anesthesia for thoracoscopic pulmonary resection, American Society of Anesthesiology (ASA) grade I-III, age 18-65 years, body mass index (BMI) between 18.5 and 25 kg/m². Exclusion criteria were as follows: allergy to lidocaine, severe cardiac or pulmonary disease, severe hepatic or renal disease, complicated with asthma or myasthenia gravis, anticipated difficult airway. The exit criteria were as follows: transferred to open chest surgery, serious cardiovascular events, and delivery to the intensive care unit after surgery.

This study was strictly conducted in accordance with the Declaration of Helsinki. This study was approved by the Medical Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (No.: 2022ER501-1). The trial was registered in the China Clinical Trial Registration Center (No.: ChiCTR2300069747). Written informed consent was obtained from all patients before the study.

Study Design and Anesthesia

All patients fasted for at least 8 hours and refrained from water for 4 hours before surgery. Routine monitoring included electrocardiogram (ECG), heart rate (HR), non-invasive blood pressure (NIBP), and pulse oxygen saturation (SpO₂). Radial artery catheterization was performed to collect blood samples. All patients received an intravenous infusion of 10 mL/kg compound sodium chloride solution after the establishment of a peripheral venous channel. Each patient was given mask oxygen inhalation for 3 minutes with oxygen flow at 6 L/min. General anesthesia induction was carried out by 0.2-0.3 μg/kg sufentanil (Yichang Renfu, Pharmaceutical Company, Hubei, China), 2.0-3.0 mg/kg propofol (AstraZeneca Pharmaceutical Company, London, UK), and 0.6 mg/kg rocuronium (Xianju Pharmaceutical Co, Ltd, Zhejiang, China).

Patients were randomly assigned to an intravenous group and a topical group (Figure 1).

After induction of anesthesia, patients in the intravenous group received an intravenous injection of 2% lidocaine (Suicheng Pharmaceutical Co, Ltd, Zhengzhou, China) at a dose of 1.5 mg/kg for 3 min. Patients in the topical group received 3 mg/kg of 2% lidocaine *via* the "spray-as-you-go" technique[27]. The "Spray-as-you-go" technique was performed using fiberoptic bronchoscopy, which consisted of a flexible intubation scope (FIS) and an epidural catheter. FIS can offer high visibility. It can gradually complete the airway mucosal surface anesthesia from the subglottic trachea to the carina by spraying lidocaine through the epidural catheter in the working channel of the FIS. The operating steps were as follows: an assistant placed the dental pads and lifted the chin; then, the operator slowly placed the endoscope of fiberoptic bronchoscopy in the subglottic trachea, advanced in the trachea, and to the carina while continuously spraying 3 mg/kg of 2% lidocaine. Then, mild manual ventilation was given at a frequency of 10 times per minute, and the air pressure did not exceed 20 cm H₂O.

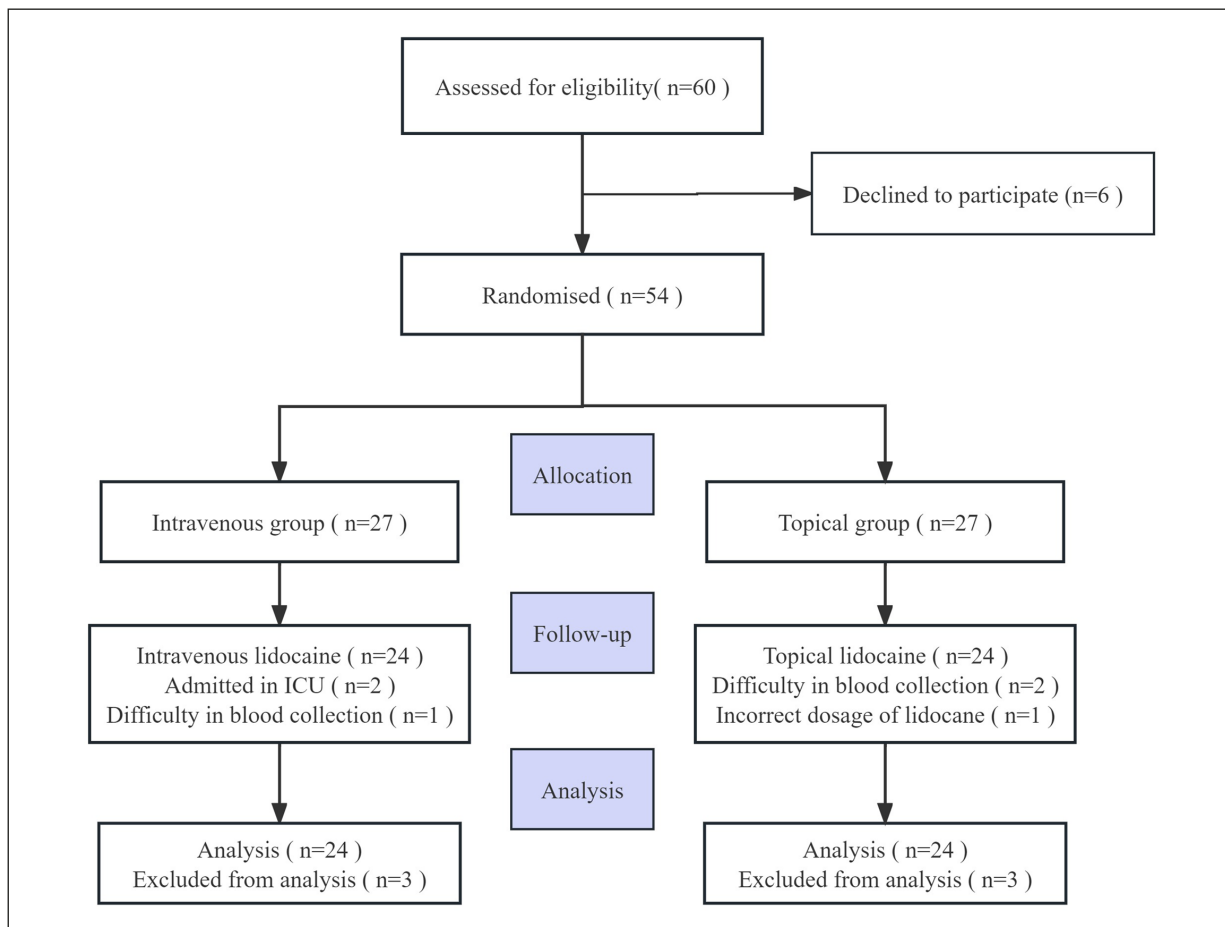After administering lidocaine, the patient was intubated by a senior anesthesiologist using vi-

748

Figure 1. Flow diagram of the study.

sual laryngoscopy with DLT. A 35 Fr and 37 Fr DLT were used in female and male patients, respectively. After locating by auscultation of both lungs and fiberoptic bronchoscopy, mechanical ventilation was performed, and the oxygen concentration was set at 100% at a flow rate of 2 L/min, tidal volume of 6-8 mL/kg, and inspiratory-to-expiratory ratio of 1:2. The respiratory rate was adjusted to maintain $PetCO_2$ at 35-45 mmHg. General anesthesia was maintained with 1-3% sevoflurane, sufentanil, and rocuronium. After the operation, when the patient was awake and had sufficient spontaneous respiration, the DLT was removed. Then, the patient was transferred to the post-anesthesia care unit (PACU) for observation.

Safety Evaluation

Safety was evaluated through the occurrence of adverse events, and the concentrations of lidocaine and active metabolites [monoethylglycinex-ylidide (MEGX) and glycinexylidide (GX)]. The assessment of adverse events consisted of nausea, drowsiness, dizziness, visual hallucination, tinnitus, severe arrhythmia, allergic reaction, convulsions, and circumoral numbness. Severe adverse events were defined as patients experiencing severe organ dysfunction or even death. In addition, it is necessary not only to evaluate whether the concentration of lidocaine exceeds 5 μg/mL,[28] but also to evaluate the potential toxicity of the contribution of MEGX and GX[28-29].

Pharmacokinetics Assessment

Arterial blood samples (4 mL) were collected at 1, 3, 5, 7, 10, 15, 20, 30, 45, and 60 min and every 60 min after administration until patients left the PACU. Blood samples were centrifuged at 3,000 rpm for 10 min, and plasma samples were transferred to polyethylene tubes and kept at −80°C until measurement. The fully validated UPLC−MS/MS method was used to measure

plasma concentrations of lidocaine, MEGX, and GX[30]. The pharmacokinetic parameters of lidocaine and its metabolites were determined by Phoenix WinNonlin software (version 7.0, Certara Pharsight, Princeton, NJ, USA). The data were analyzed by noncompartmental analysis. The pharmacokinetic parameters included the maximum concentration (C_{max}), time to reach C_{max} (T_{max}), half-life ($T_{1/2}$), clearance (CL), apparent volume of distribution (V_d), area under the curve from time (AUC_{0-t}), and AUC from time zero to infinity ($AUC_{0-\infty}$).

Statistical Analysis

The Shapiro-Wilk (S-W) test was used to test the distribution of continuous data. Continuous variables with a normal distribution are expressed as the mean ± standard deviation (SD), and comparisons between the two groups were performed by Student's t-test. Continuous data that did not conform to the normal distribution were expressed as the median (interquartile range) and then compared by using the Wilcoxon Mann-Whitney test. Categorical data are expressed as frequencies (n) and percentages (%), and comparisons were performed by χ^2 test or Fisher's exact test as appropriate. Statistical analyses were conducted with SPSS software (version 25.0, IBM Corp., Armonk, NY, USA). $p < 0.05$ was considered statistically significant.

Results

Demographic Characteristics

A total of 60 patients were included in this study. Two patients were excluded because they were admitted to the intensive care unit after surgery. Three participants were excluded due to difficulty in blood collection. One individual was also excluded due to an incorrect dosage of lidocaine. Moreover, six patients dropped out of the study at the beginning of anesthesia because they refused to participate. Finally, 48 patients were included in the statistical analysis (Figure 1). There were 9 males and 15 females in the intravenous group and 14 males and 10 females in the topical group. The ASA grade of most patients was level II in the intravenous and topical groups [n=20 (83.3%) vs. n=18 (75.0%)]. There were no significant differences in age, weight, height, BMI, or clinical biochemical indexes. Furthermore, there was still no significant difference in surgery-related content, including surgical time, anesthesia time, and type of lung resection. The total dose of lidocaine in the topical group was higher than that of the intravenous group (Table I).

Table I. Demographic and operation characteristics.

Characteristics	Intravenous group	Topical group	p-value
Gender, male/female	9/15	14/10	0.149
ASA physical status, n (%)			
I	1 (4.2)	2 (8.3)	
II	20 (83.3)	18 (75.0)	
III	3 (12.5)	4 (16.7)	
Age (years)	50.46 ± 6.64	53.58 ± 4.06	0.055
Height (cm)	161.00 ± 0.73	165.29 ± 0.10	0.089
Weight (kg)	59.92 ± 7.66	63.21 ± 11.26	0.243
BMI (kg/m^2)	23.03 ± 1.54	23.03 ± 1.81	1.00
Hemoglobin (g/L)	131.33 ± 10.63	145.75 ± 69.47	0.320
AST (U/L)	20.67 ± 5.44	24.79 ± 9.19	0.065
ALT (U/L)	23.96 ± 14.90	25.50 ± 16.51	0.736
CR (mmol/L)	59.91 ± 12.42	64.92 ±12.93	0.178
BUN (mmol/L)	4.69 ± 1.11	5.03 ± 1.21	0.327
Total lidocaine (mg)	90.35 ± 11.77	194.04± 35.94	0.001
Surgical duration (min)	93.83 ± 27.83	110.54 ± 34.61	0.072
Anaesthesia duration (min)	132.33 ± 33.50	150.25 ±30.14	0.086
Lobectomy site			
Left lobe of lung, n (%)	11 (45.83)	10 (41.67)	
Right lobe of lung, n (%)	13 (54.17)	14 (58.33)	

Data are expressed as mean±standard deviation (SD) or number (percentage of patients). ASA, American Society of Anesthesiologists; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, creatinine; BUN, blood urea nitrogen.

Safety

After 7-10 minutes of topical administration, plasma lidocaine concentration in three patients exceeded the toxic concentration (5 μg/mL). Among three patients, only one patient suffered from drowsiness, and the symptoms significantly improved on the first day after surgery. The remaining patients did not show any toxic reactions. The plasma concentration of lidocaine in one patient exceeded 5 μg/mL following intravenous administration. There were no patients experiencing hemodynamic instability or serious adverse events.

Pharmacokinetics

The plasma concentration-time curves of lidocaine, MEGX, and GX are depicted in Figure 2, and the pharmacokinetic parameters are listed in Table II.

Following intravenous administration, plasma lidocaine concentration reached its peak immediately with a T_{max} of 0.05 h and then began to decrease in a biphasic manner with a very short $T_{1/2}$ of 1.85 h. The CL was 36.19 L/h, and V_d was 95.62 L. After topical administration, lidocaine was rapidly and well absorbed through the airway, with a T_{max} of 0.21 h and
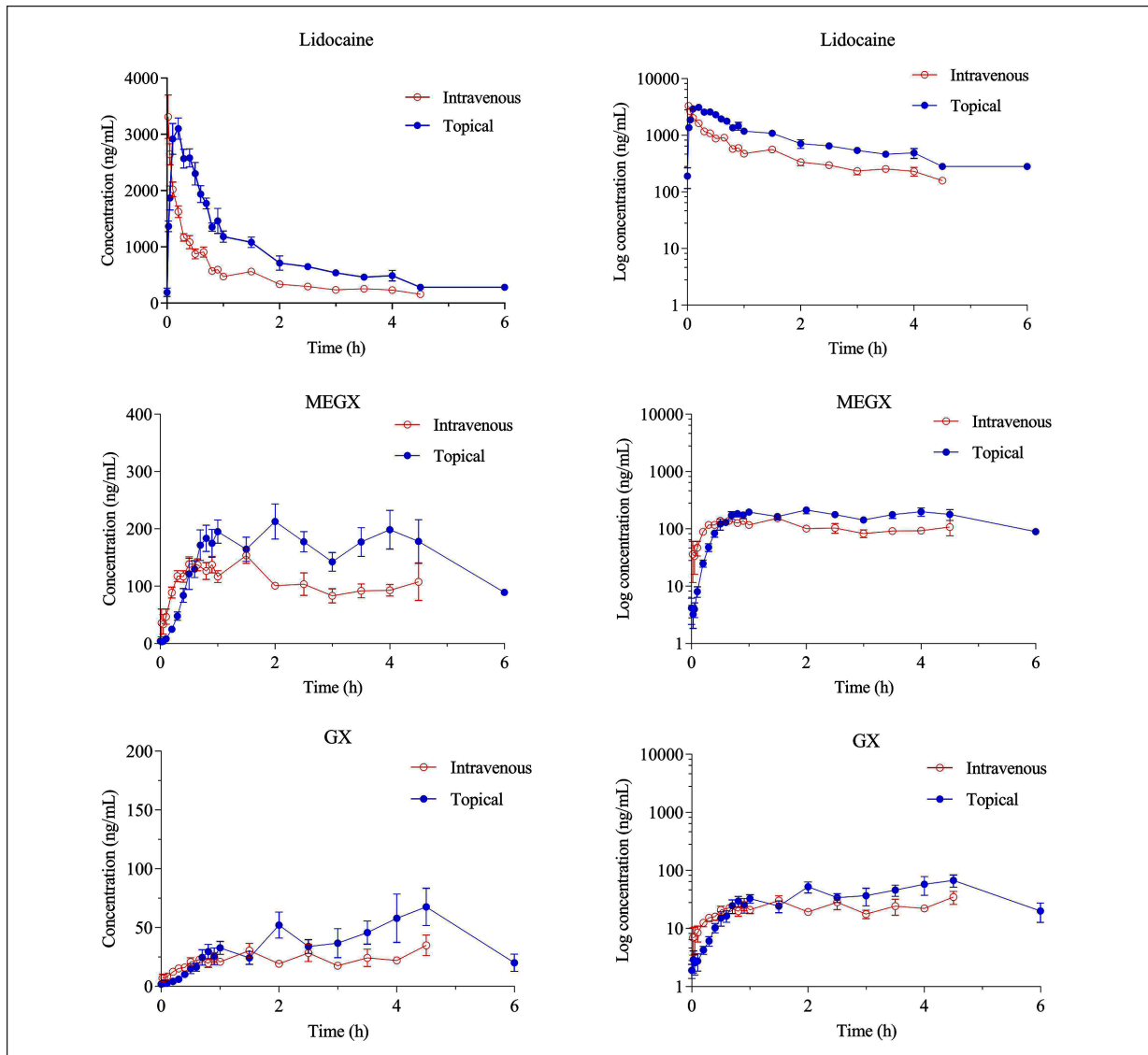

Figure 2. Mean plasma concentration-time curves of lidocaine, MEGX, and GX after intravenous boluses (1.5 mg/kg) and after topical doses (3 mg/kg).

Table II. Pharmacokinetic parameters of lidocaine and its active metabolites following intravenous and topical administration.

Parameters	Intravenous group	Topical group	*p*-value
Lidocaine			
$T_{1/2}$ (h)	1.85 ± 0.65	1.98 ± 0.83	0.571
T_{max} (h)	0.05 ± 0.03	0.21 ± 0.12	0.001
C_{max} (ng/mL)	3,267.73 ± 980.47	3,615 ± 916.64	0.157
AUC_{0-t} (h·ng/mL)	2,838.11 ± 3,976.93	3,643.25 ± 932.38	0.339
$AUC_{0-\infty}$ (h·ng/mL)	3,477.58 ± 4,032.46	4,939.48 ± 1,235.55	0.096
CL (L/h)	36.19 ± 12.40	40.55 ± 8.80	0.167
Vd (L)	95.62 ± 48.58	115.70 ± 57.61	0.198
F (%)	n/a	71.02 ± 0.15	n/a
MEGX			
Tmax (h)	0.66 ± 0.77	1.34 ± 0.80	0.004
Cmax (ng/mL)	148.57 ± 49.05	199.96 ± 86.7	0.015
AUC_{0-t} (h·ng/mL)	323.7 ± 154.42	565.6 ± 286.23	0.001
GX			
T_{max} (h)	2.35 ± 1.24	3.23 ± 0.99	0.009
C_{max} (ng/mL)	25.43 ± 13.74	44.54 ± 32.09	0.012
AUC_{0-t} (h·ng/mL)	61.91 ± 45.09	115.34 ± 91.65	0.017

Data are expressed as mean ± standard deviation. $T_{1/2}$, elimination half-life; T_{max}, peak time; C_{max}, peak concentration; AUC_{0-t}, the area under the curve from the time of dosing to the time of last concentration measurement; $AUC_{0-\infty}$, the AUC from time zero to infinity and the sum of the AUC_{0-t} and extrapolated area (C_{0-t}/λ); CL, the total body clearance; Vd, the volume of distribution; F, bioavailability.

bioavailability of 71.02%. The topical CL/F was 40.55 L/h, and V_d/F was 115.70 L. Notably, a biphasic absorption pattern was observed in some patients following topical administration. The lidocaine plasma concentration in the topical group decreased slightly slower than that in the intravenous group within 1-hour following administration; however, the decreasing trend in both groups gradually slowed down one hour after administration. The C_{max} of lidocaine in the intravenous group and topical group was 3,220±985.12 ng/mL and 3,615±916.64, respectively. In addition, there were no obvious differences in the $T_{1/2}$, CL, and Vd of lidocaine between the two groups.

Plasma concentrations of MEGX and GX in both groups began to decline approximately 4 hours after lidocaine administration. Due to insufficient and limited sampling time, the $T_{1/2}$, CL and V_d of MEGX and GX could not be calculated. The peak concentration of MEGX in the intravenous group appeared earlier than that in the topical group (0.66±0.77 h *vs.* 1.34±0.80 h). The mean C_{max} and AUC_{0-t} of MEGX were higher in the topical group than that in the intravenous group (199.96±86.7 ng/mL *vs.* 148.57±49.05 ng/mL and 565.6±286.23 h·ng/mL *vs.* 323.7±154.42 h·ng/mL, respectively). Similarly, the mean T_{max}, C_{max} and AUC_{0-t} of GX were also higher in the topical group than that in the intravenous group

(3.23±0.99 h *vs.* 2.35±1.24 h, 44.54±32.09 ng/mL *vs.* 25.43±13.74 ng/mL, 115.34±91.65 h·ng/mL *vs.* 61.91±45.09 h·ng/mL, respectively).

Discussion

This is the first study to investigate and compare the pharmacokinetics of intravenous *vs.* topical lidocaine in patients undergoing thoracoscopic pulmonary resection.

It is well recognized that DLT can directly stimulate the respiratory tract through mechanical stimulation, resulting in cardiovascular responses[30]. Most simulation receptors are located below the epithelium[31]; therefore, local anesthetics administered topically can effectively attenuate cardiovascular responses. In addition, intravenous lidocaine blocks the passage of mechanoreceptors in the trachea by inhibiting the sympathetic adrenal system. Growing pharmacodynamics studies[11,22,32] have reported that delivery of lidocaine topically or intravenously is an effective method for minimizing cardiovascular responses.

In the clinical setting, 2% and 4% lidocaine solutions are commonly used in airway topical anesthesia. A previous pharmacodynamics study[18] demonstrated that endotracheal spraying of both 2% and 4% lidocaine by a SAYGo tech-

nique could be effective in reducing the intubation response. Clearly, both the dosage and the resulting plasma concentrations of 2% lidocaine are lower than those of 4% lidocaine. Therefore, 2% lidocaine was chosen to conduct this trial. In addition, the 3 mg/kg dose was used based on the recommendation that endotracheal drug administration should be 2 to 2.5 times the IV lidocaine dose of 1 to 1.5 mg/kg[33].

Lidocaine plasma concentration is a pivotal indicator for evaluating the safety following administration. Lung temporarily extracted 40% lidocaine when it first passed through the lung following intravenous administration[34]. This could be explained by the fact that lidocaine is a weak base with a cationic molecule with an ionization constant (pKa) of 7.9, and the pH in the lung was far lower than that in plasma, these factors make lidocaine more likely to remain in the lungs.

In addition, lidocaine is a poorly hydrosoluble drug that can easily penetrate cell membranes and distribute to the vascularized lung. The aforementioned lung trapping and "shooting effect" might explain the subsequent lack of lidocaine-related toxicity. Following intravenous administration, one patient had a lidocaine concentration of 5.46 µg/mL after 1 minute. By 3 minutes, the concentration rapidly decreased to 2.98 µg/mL, and no adverse reactions were observed. It is noteworthy that the unexpected C_{max} of three patients reached the toxic range in the topical group. However, only one patient experienced drowsiness, and the remaining patients did not show any lidocaine-related adverse reactions. This phenomenon could be partly explained by the fact that the correlation between plasma lidocaine concentrations and toxic reactions is not entirely reliable[27]. Hence, a 3 mg/kg dose is considered a relatively safe dose for endotracheal administration. Additionally, in contrast to the intravenous group, the plasma lidocaine concentration of the aforementioned 3 patients approached 5 µg/mL within 3 min after C_{max} in the topical group with minimal reduction. Therefore, this could be one reason why the patient had lidocaine-related toxicity.

A biphasic absorption pattern with two maximal concentrations was observed in the concentration-time profile of some patients in the topical group. This phenomenon was consistent with previous related studies[32]. This phenomenon can partly account for the different rates of lidocaine absorption from the endobronchial mucosa and the alveolar-capillary membrane. Since we administered lidocaine to the depth of the tracheal carina, lidocaine may flow through the bronchi to the alveolar lumen and alveolar-capillary membrane. A study[35] also mentioned the possibility of drugs reaching the alveolar lumen and alveolar-capillary membrane during bronchial administration. Furthermore, we started adjuvant ventilation after administration; however, hyperventilation may affect the distribution of lidocaine in the trachea, resulting in two different absorption rates in the endotracheal/endobronchial mucosa and alveolar-capillary membrane[32].

Bioavailability is an important index of airway administration. The higher the bioavailability is, the lower the drug dose needed. The bioavailability of topical lidocaine administration depends on the drug delivery technique and location. No unified standard has been formed until now. Takaenoki et al[26] reported that the bioavailability of atomized lidocaine and a non-atomized technique in the airway was 80.1% and 55.9%, respectively. The satisfactory bioavailability of the SAYGo method in this study was approximately 71.02%. Compared with the non-atomized method, the SAYGo technique can increase spread throughout the respiratory tract by spraying drugs[36,37]. In addition, atomized liquid has the same spray advantage, but smaller atomized particles could explain the higher bioavailability[38,39].

When the drug was sprayed in the trachea, plasma concentrations of lidocaine were quickly detected (Figure 2). The initial plasma concentration was lower than intravenous administration, but its peak was higher. This result was consistent with a previous study[40]. In addition, administering topical lidocaine could maintain the effective plasma concentration range (1.4-5 µg/mL) for 30 min, while administering intravenous lidocaine only kept for 5 min. Moreover, a "shooting effect" might be observed after patients receive intravenous lidocaine. Topical spraying of lidocaine not only allows the drug to be absorbed quickly and completely (bioavailability: 71.02%) but also maintains the therapeutic concentrations for a longer time. In clinical scenarios, if patients encounter unexpected DLT intubation that requires a longer time, giving lidocaine topically can still weaken the cardiovascular response. Therefore, it is evident that the SAYGo technique is an alternative method of lidocaine administration when double-lumen endotracheal intubation is difficult in clinical practice.

Limitations

There are several limitations of this study. First, this study included patients aged 18-65

only, and it remains unclear whether the same dosing regimen can be applied to elderly patients. Second, the sample sampling point is not enough, leading to some PK parameters of MEXG and GX not being calculated. Last, the optimal dose of topical lidocaine is not available. Therefore, we need to optimize the study design for further research.

Conclusions

In conclusion, topical administration of 3 mg/kg lidocaine *via* the "spray-as-you-go" technique is an effective and safe delivery method for patients undergoing thoracoscopic pulmonary resection.

Authors' Contribution
Study design: ZYL, MZ, YJ, ZLW, FPT. Patient recruitment: ZYL, FPT. Patient treatment: ZYL, MZ. Data collection: YJ. Data analysis: ZYL, ZLW, FPT. Writing of first draft of paper: ZYL. Critical revision of the paper: MZ, YJ, ZLW, FPT. All authors read and approved the final manuscript.

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Data Availability
The data that support this study are available from the corresponding authors upon request.

Ethics Approval
The present study followed the Declaration of Helsinki. This study was approved by the Medical Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (No.: 2022ER501-1).

Informed Consent
Informed consent was obtained from all individual participants included in the study.

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