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Original Article

Determination of the median effective dose of intravenous lidocaine for pain on awakening after pediatric tonsillectomy: a randomized controlled trial

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Abstract: Objectives: We investigated whether intravenous lidocaine reduces pain on awakening in a dose-dependent manner and aimed to determine the median effective dose (ED_{50}) of lidocaine in 160 children aged 3-12 years (American Society of Anesthesiologists physical status I-II) undergoing elective tonsillectomy with or without adenoidectomy at Yichang Central People's Hospital. Methods: Patients were randomized into four dose groups (A-D: 0.0, 1.0, 1.5, and 2.0 mg/kg, respectively) and underwent the same anesthetic induction and maintenance protocols. The primary outcome was pain on awakening, while secondary outcomes included pain scores at 1, 4, 12, and 24 hours after awakening; incidences of laryngospasm, bronchospasm, or perioperative stridor; and time to extubation. Intraoperative cardiac events were classified as safety events. Data were analyzed using ANOVA with Bonferroni correction. Intravenous lidocaine reduced pain on awakening in a dose-dependent manner. Results: The ED_{50} of intravenous lidocaine for pain on awakening was 1.75 mg/kg. Significant differences were observed between Groups A and D ($P \leq 0.001$). No incidents of laryngospasm, bronchospasm, or perioperative stridor were observed. Furthermore, significant between-group differences were observed in time to extubation ($P \leq 0.05$). Conclusion: These findings demonstrate that lidocaine dose-dependently reduced pain on awakening in children undergoing tonsillectomy with or without adenoidectomy (ED_{50} = 1.75 mg/kg), with no severe adverse events.

Keywords: Lidocaine, pain on awakening, pediatrics, tonsillectomy

Introduction

Tonsillectomy is one of the most common surgical procedures performed in children, in which general anesthesia via tracheal intubation is used [1, 2]. Although it is a common and generally safe procedure, pain on awakening is frequently observed and, if untreated, may persist, restricting oral fluid and medication intake, and potentially extending postoperative length of stay [3-5].

Lidocaine is a commonly used adjuvant in pediatric general anesthesia [6]. However, there is considerable controversy regarding its efficacy in reducing pain after elective surgery under general anesthesia [7-9]. Previous studies have demonstrated that the risk-benefit ratio of lidocaine varies with patient factors and have recommended that lidocaine be regarded as a high-risk medication [10]. The median effective dose (ED_{50}) of intravenous lidocaine in children remains unknown, and it is unclear whether lidocaine reduces pain on awakening in a dose-dependent manner.

We hypothesized that intravenous lidocaine dose-dependently reduces pain on awakening and sought to determine the ED_{50} of lidocaine in children undergoing tonsillectomy with or without adenoidectomy. The primary outcome, pain on awakening, was selected to provide a clinically meaningful outcome with potential therapeutic benefits.

Methods

Ethics statements

Ethical approval for this study was obtained from the Institutional Review Board of Yichang Central People's Hospital (HEC-KYJJ-2020-

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038-02), chaired by Ke-jun Yan, on September 17, 2021. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki (1975), as revised in 2013. Written informed consent was obtained from the parents or legal guardians of all participants.

Study design and patients

This single-center, parallel-group, double-blind, randomized controlled trial was registered at www.chictr.org.cn (Trial registration: ChiCTR-2100053006) on November 8, 2021 and conducted between December 1, 2021 and June 30, 2022 at Yichang Central People's Hospital in accordance with the CONSORT guidelines. Randomization was computer-generated, and each patient was assigned a code. The random numbers were generated using SPSS (version 26.0.0.0; IBM Corp., Armonk, NY, USA). A total of 160 random numbers were arranged in ascending order, and patients were allocated into four groups: Group A (1-40), Group B (41-80), Group C (81-120), and Group D (121-160). Patients were randomized to receive anesthesia with saline or three additional doses of lidocaine in a 1:1:1 ratio. On the day of the study, a nurse anesthetist who was blinded to the study protocol opened the sealed envelope containing the sequential allocation number, prepared the study drug, and assigned a randomization code only known to the participant. The allocation code was concealed from the patients and investigators collecting the clinical data until data analysis completion.

The inclusion criteria were children aged 3-12 years (American Society of Anesthesiologists physical status I-II) scheduled for elective tonsillectomy with or without adenoidectomy. Participants were allocated into four groups according to the intravenous lidocaine dose administered: A (0.0 mg/kg), B (1.0 mg/kg), C (1.5 mg/kg), and D (2.0 mg/kg). The exclusion criteria encompassed chronic cough, history of steroid or bronchodilator treatment, reactive airway disease, upper airway infection 2 weeks prior to surgery, angiotensin-converting enzyme inhibitor therapy, gastroesophageal reflux, morbid obesity, known allergy to any of the study drugs, use of medications or nutraceuticals known to affect blood pressure and heart rate, surgery lasting > 2 hours, unexpected bleeding, and the need for more than two intubation attempts.

Perioperative anesthetic care

Preoperatively, children fasted for 6 hours and were restricted from oral intake of clear fluids for 2 hours. The children entered the operating room, accompanied by their parents, to curb separation anxiety. Baseline measurements of blood pressure, heart rate, pulse oxygen saturation, bispectral index (BIS), and electrocardiography were performed using a multifunction monitor (GE Healthcare, Chicago, IL, USA). Blood pressure cuff width for each patient was approximately two-thirds of the length of the upper arm. After 5 minutes of stabilization, baseline heart rate, systolic/diastolic blood pressure, and mean arterial pressure values were obtained from the average of three measurements taken 2 minutes apart. A 22-gauge intravenous catheter was subsequently inserted into a vein on the back of the hand. Following preoxygenation, the drug of interest (lidocaine [Anhui Changjiang Pharmaceutical Co. Ltd., Wuhu City, China] or 0.9% saline) was administered intravenously over 10 minutes at a rate of 0.6 ml/kg/h. Blinding was ensured by matching the study drug volumes and avoiding light exposure during preparation. A nurse anesthetist, blinded to the study protocol, prepared the drug of interest to be administered through an infusion pump. General anesthesia was induced 2 minutes after administration, using the following induction protocol: sufentanil (0.25 μg/kg [Yichang Renfu Pharmaceutical Co. Ltd., Yichang City, China]), propofol (2.0 mg/kg [Fresenius Kabi Deutschland GmbH, Homburg, Germany]), and rocuronium (0.6 mg/kg [Zhejiang Xianju Pharmaceutical Co. Ltd., Taizhou City, China]). When the eyelash reflex disappeared, the patient's lungs were ventilated using a face mask with 100% oxygen. A cuffed tracheal tube was inserted, with size selected according to the widely used formula: 3.5 + [age (years)]/4. Patients were excluded from the study if difficulty occurred during face mask ventilation. Anesthesia was maintained with 2-3% sevoflurane (Maruishi Pharmaceutical Co. Ltd., Osaka, Japan) and 50% oxygen to maintain the BIS score between 40 and 60. All children received intraoperative analgesia according to the pain treatment protocol, which included ibuprofen

(10 mg/kg), acetaminophen (15 mg/kg), and tramadol (1 mg/kg) to manage postoperative pain.

At the end of the procedure, sevoflurane was discontinued, and neostigmine (0.04 mg/kg [Zhejiang Xianju Pharmaceutical Co. Ltd.]) and atropine (0.02 mg/kg [Suicheng Pharmaceutical Co. Ltd., Xinzheng City, China]) were administered to antagonize any residual neuromuscular blockade after confirming the cessation of the relaxant effect when the train-of-four (TOF) ratio was ≥ 0.5. Following surgery, oral suction was immediately performed while the patient was still under anesthesia. Extubation was performed by an experienced anesthetist who was blinded to the study after confirming adequate tidal volume, regular spontaneous respiratory patterns, purposeful behavior (eyes open upon request), and TOF ≥ 0.9. After extubation, an anesthetist not involved in the study assessed recovery, graded throat pain, and evaluated the cough response. Patients were monitored for at least 5 minutes, with 100% oxygen via a face mask, to allow regular spontaneous respiration. Patients were transferred to a post-anesthesia care unit (PACU) after extubation. The time to extubation (from sevoflurane discontinuation to tracheal extubation) was recorded. Electrocardiography, peripheral pulse oximetry, and non-invasive blood pressure measurements were also performed.

Postoperatively, the patients were monitored for at least 5 minutes to resume regular spontaneous respiration and were subsequently transferred to the PACU when their Steward score exceeded 4. An attending researcher, blinded to the study and trained in pain scoring, assessed post-anesthesia pain scores every 15 minutes. Patients were discharged from the PACU. Other postoperative care was performed according to the practices of local clinicians. If the pain (Face, Legs, Activity, Cry, and Consolability scale [children aged 3-4 years], Wong-Baker scale [children aged 4-7 years], or visual analogue scale [children aged ≥ 8 years]) score was ≥ 3 at rest [3], the attending PACU nurse administered intravenous propacetamol (30 mg/kg) as treatment. All scales ranged from 0 to 10. The use of other medications was restricted.

Outcomes

The primary outcome was pain on awakening after pediatric tonsillectomy, assessed immediately upon the patient's arrival in the recovery room [3]. Secondary outcomes included pain scores at 1, 4, 12, and 24 hours after awakening; incidences of laryngospasm, bronchospasm, or perioperative stridor; and time to extubation. Safety events included perioral numbness, muscle tremors, intraoperative cardiac events (arrhythmia, hypertension [mean arterial pressure > 90 mmHg]), and rescue treatment.

Statistical analysis

The sample size was calculated using G* Power (version 3.1.9.2; Heinrich Heine University, Düsseldorf, Germany) for a one-way ANOVA based on an expected pain on awakening score difference of 1 (clinically significant), with 80% power ($\alpha = 0.05$, $\beta = 0.2$), which indicated that 40 patients were required per group. Patient characteristics (including age, height, and weight); pain on awakening scores; incidences of laryngospasm, bronchospasm, or perioperative stridor; duration of surgery; and time to extubation are expressed as mean ± SD and analyzed using ANOVA, with $P < 0.05$ indicating statistical significance. Since ANOVA results revealed a significant difference between lidocaine dose and postoperative pain score ($P < 0.0001$), multiple post-hoc comparisons were performed using the Bonferroni method to correct the *P*-value. A linear regression model was applied to determine the ED_{50}. All statistical analyses were conducted using GraphPad Prism (version 8.0.2; GraphPad Software Inc., San Diego, CA, USA).

Results

Between December 1, 2021 and June 30, 2022, a total of 160 patients were enrolled and divided into four groups according to the dose of lidocaine administered (**Figure 1**). There were significant differences in time to extubation between Groups A and B ($P = 0.014$), A and C ($P = 0.015$), and A and D ($P = 0.017$). Patient characteristics and other operative data did not differ significantly between groups (**Table 1**).

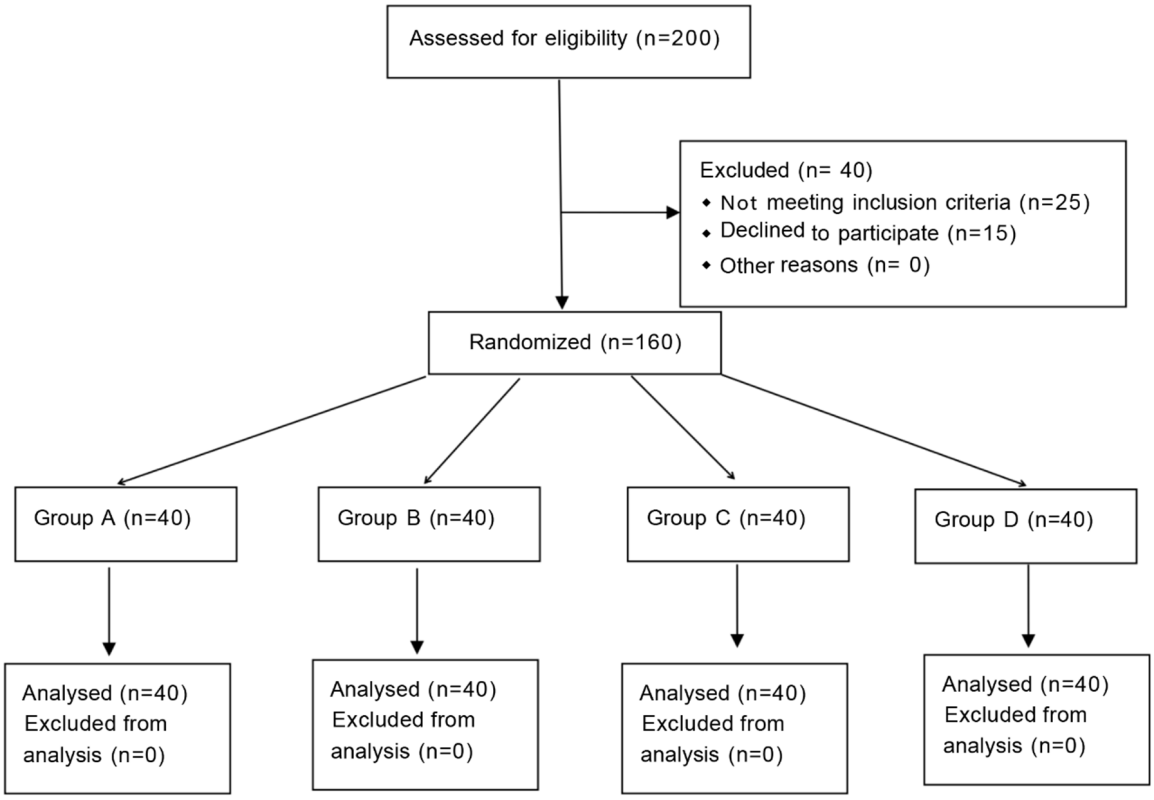

Figure 1. Flow diagram.

Table 1. Patient characteristics and clinical data

	Group A (n = 40)	Group B (n = 40)	Group C (n = 40)	Group D (n = 40)
Age (years)	5.55 ± 2.02	6.02 ± 2.35	5.77 ± 1.91	5.98 ± 1.67
Height (cm)	118.34 ± 14.21	120.60 ± 16.02	117.81 ± 13.65	120.49 ± 12.02
Weight (kg)	22.88 ± 7.60	23.57 ± 8.57	22.57 ± 6.65	25.03 ± 7.22
Body mass index (kg/m^2)	15.96 ± 2.65	15.75 ± 2.22	16.04 ± 2.27	16.97 ± 2.75
Sex (M/F)	21/19	22/18	24/16	24/16
ASA physical status (I/II)	40/0	40/0	40/0	40/0
Duration of surgery (minutes)	29.74 ± 11.14	29.40 ± 11.10	29.43 ± 13.68	27.34 ± 11.95
Time of extubation (minutes)	11.55 ± 3.32	13.72 ± 3.30*	13.70 ± 3.59*	13.68 ± 3.58*
Incidence of laryngospasm	0	0	0	0
Incidence of bronchospasm	0	0	0	0
Incidence of perioperative stridor	0	0	0	0
Tonsillectomy with or without adenoidectomy	38/2	40/0	40/0	39/1

Data expressed as n or mean ± SD. Group A = lidocaine (0.0 mg/kg) intravenously; Group B = lidocaine (1.0 mg/kg) intravenously; Group C = lidocaine (1.5 mg/kg) intravenously; Group D = lidocaine (2.0 mg/kg) intravenously. *P < 0.05 (compared with Group A). Abbreviations: ASA = American Society of Anesthesiologists, F = female, M = male.

The ED_{50} of intravenous lidocaine for pain on awakening was 1.75 mg/kg (1.14-2.13 mg/kg) (**Figure 2A**). All 40 patients in each group were assessed for the primary outcome. ANOVA revealed a significant difference between lidocaine dose and postoperative pain score (P < 0.0001), prompting multiple post hoc comparisons using the Bonferroni method to correct the P-value. The results showed that all 40 patients in each group completed the primary outcome assessment. The pain score on awakening was significantly different between the

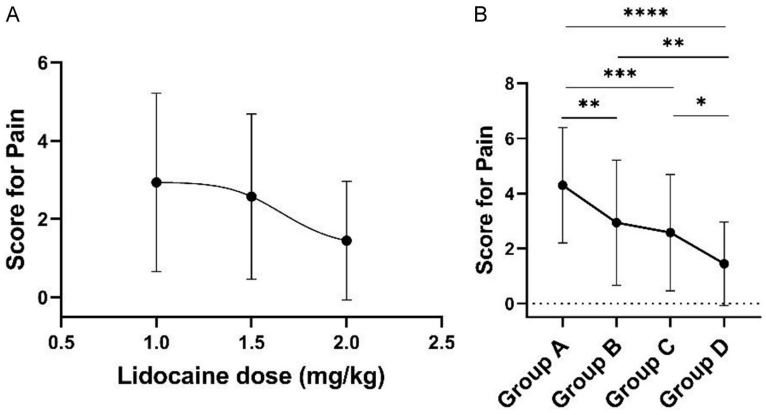

Figure 2. Intravenous lidocaine for pain on awakening. A. Concentration-response curve; B. Pain on awakening scores. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001. ED_{50} = median effective dose.

groups, in a dose-dependent manner, with significant differences between Groups A and B (P = 0.007), B and D (P = 0.003), and A and C ($P \leq$ 0.001) (**Table 2**; **Figure 2B**).

Pain scores at 1 hour after awakening were significantly different between Groups A and B ($P \leq 0.001$); A, C, and D ($P \leq 0.001$); and B and D (P = 0.010). Pain scores at 4 hours after awakening were significantly different between Groups A and B ($P \leq 0.001$) and A, C, and D ($P \leq$ 0.001); however, there were no significant differences in the pain scores at 12 and 24 hours after awakening (**Table 3**). No laryngospasm, bronchospasm, perioperative stridor, perioral numbness, or muscle tremors were observed in any group. No severe complications, such as arrhythmia, were observed in any group.

Discussion

Tonsillectomy is widely recognized as one of the most painful surgical procedures in children, and achieving effective postoperative pain relief remains challenging and controversial. Pain management impacts morbidity, quality of life, and hospitalization costs. In children, inadequate pain control impacts not only the patient but also the entire family [11]. Several interventions have been recommended to manage pain after tonsillectomy in children [12]. Opioids remain an important treatment strategy for postoperative analgesia; however, their use is often limited due to concerns about respiratory depression in pediatric patients. Large studies using non-steroidal anti-inflammatory drugs have demonstrated effective pain management [12]; however, their association with increased risk of post-tonsillectomy bleeding continues to be debated.

Lidocaine is recommended for its analgesic effects and ability to improve pain management with high patient satisfaction [13]. The guideline recommends an initial bolus of 1-2 mg/kg followed by a continuous infusion of 1-2 mg/kg/h [8]. We strictly followed the guideline when selecting the injection rate and concentration of lidocaine; therefore, no blood concentration testing of lidocaine was performed. However, the ED_{50} of intravenous lidocaine for pain on awakening has not been previously established. In this study, intravenous lidocaine resulted in a dose-dependent reduction in pain on awakening, with an ED_{50} of 1.75 mg/kg. Pain scores were significantly lower at 1 and 4 hours postoperatively in patients who received lidocaine compared with controls, whereas no significant differences were observed at 12 hours. This is consistent with the short duration of surgery (< 1 hour) and the approximate 2-hour half-life of intravenous lidocaine [14], supporting the use of a single bolus without continuous infusion. The exact inhibitory mechanism of lidocaine is unclear, although it may involve a combination of analgesic, anti-hyperalgesic/inflammatory, and immunomodulatory properties related to stress modulation [10, 15, 16].

No cases of laryngospasm, bronchospasm, perioperative stridor, or other serious complications were observed during anesthesia. Lidocaine is an antiarrhythmic drug, and its main mechanism of action involves blocking voltage-gated Na^+ channels, which inhibits the activity of the upper laryngeal nerve and reduces prolonged glottic reflexes [17]. Extubation times were longer in the lidocaine groups (B, C, and D) compared to the control group (A), requiring an additional 2 minutes. This may be because intravenous lidocaine can enhance the effects of anesthetics [18-20]. Prolonged extubation following general anesthesia is defined as a time of ≥ 15 minutes [21]. The mean extubation time was < 15 minutes in all three study groups,

Table 2. Pain on awakening scores

	Group A (*n* = 40)	Group B (*n* = 40)	Group C (*n* = 40)	Group D (*n* = 40)	*P*-value
Score	4.30 ± 2.09*	2.90 ± 2.28*,†	2.57 ± 2.11*	1.45 ± 1.52*	< 0.001

Data expressed as mean ± SD. Group A = lidocaine (0.0 mg/kg) intravenously; Group B = lidocaine (1.0 mg/kg) intravenously; Group C = lidocaine (1.5 mg/kg) intravenously; Group D = lidocaine (2.0 mg/kg) intravenously. *P < 0.001 (compared with Group A); †P < 0.001 (compared with Group D).

Table 3. Pain on awakening scores at different time points

Score at different time points (h)	Group A (*n* = 40)	Group B (*n* = 40)	Group C (*n* = 40)	Group D (*n* = 40)	*P*-value‡
1	2.34 ± 0.79	1.66 ± 0.96*	1.45 ± 0.95*	1.15 ± 0.72*,†	< 0.001
4	2.19 ± 0.77	1.55 ± 0.75*	1.34 ± 0.87*	1.06 ± 0.92*,†	< 0.001
12	1.89 ± 0.70	1.89 ± 0.79	1.85 ± 1.00	1.51 ± 0.75	> 0.05
24	1.49 ± 0.55	1.23 ± 0.63	1.13 ± 0.74	1.09 ± 0.62	> 0.05

Data expressed as mean ± SD. Group A = lidocaine (0.0 mg/kg) intravenously; Group B = lidocaine (1.0 mg/kg) intravenously; Group C = lidocaine (1.5 mg/kg) intravenously; Group D = lidocaine (2.0 mg/kg) intravenously. *P < 0.05 (compared with Group A); †P < 0.05 (compared with Group B); ‡P-values of Group A compared with Groups B, C, and D.

which is considered safe and clinically insignificant. The ED_{50} of intravenous lidocaine was 1.75 mg/kg, which falls within the recommended concentration range according to the guideline. Overall, these findings suggest that intravenous lidocaine is safe in children and does not result in serious adverse events.

This study does have some limitations. First, it was a single-center study, which may limit the generalizability and robustness of the findings. Future multi-center studies are required to confirm the effect of lidocaine on pain on awakening. Additionally, sevoflurane concentration in end-expiratory gas was used to monitor anesthesia depth, which may have influenced the calculated ED_{50}. Given the limited data on potential synergistic effects, further research is warranted to explore interactions between lidocaine and other anesthetic agents.

In conclusion, the ED_{50} of intravenous lidocaine for pain on awakening was 1.75 mg/kg. Intravenous lidocaine reduced pain on awakening in children undergoing tonsillectomy with or without adenoidectomy, in a dose-dependent manner, without causing serious adverse events, supporting its potential role in pediatric perioperative pain management.

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Disclosure of conflict of interest

None.

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