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CLINICAL TRIAL REPORT

The ED_{90} of Oliceridine for Tracheal Intubation in Children: A Biased-Coin Up-and-Down Parallel Dose-Finding Study

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Background: Oliceridine as a novel biased μ-opioid receptors agonist that selectively activates G protein-mediated signaling, has been associated with a lower incidence of opioid-related adverse events (ORAEs). However, the effective dose of oliceridine for tracheal intubation in pediatric anesthesia was unknown.

Methods: In this prospective, double-blind, sequential allocation study, 100 children scheduled for general anesthesia were enrolled. An initial intravenous bolus of oliceridine and sufentanil was set at 70 μg/kg and 0.3 μg/kg. Subsequent doses were determined by the response of the previous participant using a biased coin up-and-down design (BCUD). Successful sedation was defined as the changes of hemodynamics was less than 20% of baseline. The 90% effective dose (ED_{90}) and its 95% confidence interval (CI) were estimated, using isotonic regression.

Results: For tracheal intubation in children aged 1–12 years, the ED_{90} of oliceridine was 74.3 μg/kg (95% CI: 73.6 to 77.4 μg/kg), while that of sufentanil was 0.34 μg/kg (95% CI: 0.32 to 0.42 μg/kg), yielding an equivalent dose ratio of approximately 220:1 (oliceridine: sufentanil). The incidences of hemodynamic changes were comparable between groups before and after tracheal intubation. No hypoxemia was observed after administration of oliceridine and sufentanil. All adverse events were self-limited and no intervention was required.

Conclusion: Oliceridine at an ED_{90} of 74.3 μg/kg can be effectively used for tracheal intubation during pediatric anesthesia.

Keywords: children, oliceridine, tracheal intubation, 90% effective dose

Background

Endotracheal intubation is essential for children undergoing general anesthesia. A balanced anesthesia regimen, combining fentanyl-family opioids with GABA receptor agonists (eg., propofol, sevoflurane), offers the benefits of potent analgesia against noxious stimuli and amnesia.[1] However, the activation of the β-arrestin pathway represents a key mechanistic drawback of μ-opioid receptor agonism, according to preclinical evidence.[2–4] This pathway is a key contributor to many opioid-related adverse events (ORAEs), such as respiratory depression, nausea, and hyperalgesia.[5] For pediatric patients, a higher risk of peri-procedural adverse events, most commonly including respiratory complications (eg., hypoxia, apnea), hemodynamic instability (eg., hypotension, bradycardia) and gastrointestinal adverse events.[6,7]

In contrast to traditional opioids, oliceridine is a novel G protein-biased modulator at the μ-opioid receptor.[8] It is designed to elicit analgesia primarily through G-protein coupling while minimizing activation of the β-arrestin pathway, the latter being considered a major contributor to ORAEs.[9] This potentially improved therapeutic profile positions

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oliceridine as not only a preferable option for postoperative analgesia due to fewer adverse events, but also as a promising alternative to fentanyl for ambulatory minor surgery (eg., wound debridement and primary closure) and procedural sedation in endoscopy—especially in pediatric patients.[10–12] Nevertheless, the optimal dosing regimen for oliceridine to manage the intense stimulus and hemodynamic consequences of endotracheal intubation has not been established, given that this stimulus intensity far exceeds that of many surgical procedures and frequently triggers significant hemodynamic fluctuations.

Therefore, the primary endpoint of this study was to estimate the 90% effective dose (ED_{90}) of oliceridine for tracheal intubation in children undergoing general anesthesia. Accordingly, we conducted a randomized, parallel-group dose-finding study using biased-coin up-and-down (BCUD) sequential allocation to estimate the ED_{90} of oliceridine and sufentanil for successful tracheal intubation.

Materials and Methods

Pediatric Patients

This prospective, double-blind, dose-finding study was approved by the Institutional Review Board of Shanghai Children's Medical Centre (No. SCMCIRB-K2025089-1) and registered with the Chinese Clinical Trial Registry (Registration No. ChiCTR2500115753). This study conformed to all the guidelines of the Declaration of Helsinki. Written informed consent was obtained from the parents or guardians of all children prior to enrollment.

Pediatric patients aged 1 to 12 years, with American Society of Anesthesiologists-Physical Status (ASA-PS) I to II and scheduled for elective surgery under general anesthesia were included.

Children were excluded from this study if the following criteria were met: 1) suspected or confirmed allergy to opioids; 2) history of chronic pain or recent opioid use within 24 h before surgery; 3) receiving general anesthesia within 7 days; 4) malnutrition; 5) obesity, defined as body mass index greater than 30 kg/m^2; 6) preoperative use of oral sedatives; 7) anticipated difficult airway (eg., difficulty in mask ventilation or tracheal intubation); 8) severe cardiopulmonary, hepatic or renal dysfunction; 9) parents or child refusal to participate.

Anesthetic Procedures

All children fasted for a minimum of 6 hours prior to the procedure. Upon arrival in the preoperative area, a topical local anesthetic (tetracaine hydrochloride gel) was applied to the dorsum of both hands, followed by placement of a peripheral intravenous catheter. Intravenous crystalloid fluid was administered according to the 4-2-1 rule. Standard monitoring was established, including electrocardiography, pulse oximetry, bispectral index (BIS), and non-invasive blood pressure (NiBP).

Supplemental oxygen was delivered at 6 L/min via a facemask. Sevoflurane was inhaled to maintain an age-adjusted end-tidal concentration of 1.0 minimum alveolar concentration (MAC). An intravenous bolus of oliceridine was then administered according to the biased coin up-and-down design (BCUD). Two minutes later, 0.6 mg/kg of rocuronium was given. Endotracheal intubation was performed by a senior anesthesiologist 90 seconds after rocuronium administration.

Successful intubation was defined as smooth tube insertion without any adverse response, including hemodynamic changes (an increase of >20% from baseline in either NIBP or heart rate), limb movement, or coughing. If intubation was considered a failure, a rescue bolus of sufentanil (0.1–0.2 μg/kg) was administered.

Anesthesia was maintained with sevoflurane and remifentanil. After surgery, patients were transferred to the post-anesthesia care unit (PACU) for continuous vital sign monitoring. Discharge criteria from the PACU included full awakening and stable vital signs within normal ranges. Complications were recorded for 24 hours postoperatively.

Dosage Determination

The initial doses of oliceridine and sufentanil were set at 70 μg/kg and 0.3 μg/kg, respectively. This was determined based on a pilot study and a morphine milligram equivalent (MME) conversion, where 1 mg of oliceridine is approximately equivalent to 4–5 mg of morphine.[13] Subsequent dosing followed the BCUD method: if tracheal

intubation was successful, the next patient was randomly assigned to either a reduced dose (decreased by 3 μg/kg) with a probability of 1/9 or the same dose with a probability of 8/9; if tracheal intubation failed, the dose was increased by 3 μg/kg for the next patient. The dose range was confined between a lower limit of 3 μg/kg and an upper limit of 80 μg/kg.

The BCUD dosing sequence was generated by the study statistician using Microsoft Excel 2016. An independent research assistant, who was the only individual unblinded to the allocation sequence, prepared the study drugs. All other study personnel remained blind to the administered doses.

Assessment of the Adverse Events

The following adverse events were recorded: hypoxia (SpO_2 < 92% and lasted more than 10s), hypoventilation (requirement for emergency assisted ventilation), cardiovascular response (eg., hypotension, hypertension, bradycardia or tachycardia, defined as a deviation of more than 20% from baseline values), other adverse events (nausea, vomiting, regurgitation, headache, dizziness, etc.) were recorded.

Vital signs were obtained at the following seven time points, designated as T0 through T6: baseline (pre-anesthesia); pre-opioid administration; 3 min post-opioid; pre-intubation; and 1, 3, and 5 min post-intubation.

Sample Size and Estimation of ED_{90}

In accordance with the recommendation by Pace and Stylianou, a sample size of 20 to 40 patients was targeted for this sequential design to ensure stable estimation of the target dose.[14] The ED_{90} was defined as the dose at which 90% of children achieved successful intubation. It was estimated to be using the isotonic regression method. A bias-corrected percentile method with 2,000 bootstrap replications was applied to calculate the 95% confidence interval (CI).[15] These analyses were performed by the study statistician using R version 3.4.4. (R Foundation for Statistical Computing, Vienna, Austria).

Data Analysis

Data normality was assessed using the Shapiro–Wilk test. Continuous variables are presented as the mean ± standard deviation (SD) or median [interquartile ranges, IQR] according to the distribution of data, while categorical variables are summarized as count and percentages (n, %). Continuous variables between the groups were analyzed using repeated measures analysis of variance (ANOVA), and 1-way ANOVA was performed for all continuous variables within groups. When a significant difference was noted, a Bonferroni test was conducted for post hoc comparison. Nonparametric variables were analyzed using Mann–Whitney *U*-test. All statistical analyses were conducted using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, United States) and GraphPad Prism 8 (GraphPad Software, San Diego, California, USA).

Results

A total of 100 patients were initially enrolled. Among them, 20 were excluded for the following reasons: three did not meet the fasting requirements, five had recent respiratory infections, and seven were lost to follow-up. Additionally, five parents declined to participate. Consequently, data from 80 children were included in the final analysis. The patient flow is summarized in Figure 1, and demographic characteristics are presented in Table 1.

Among the 80 children who completed the study, 77.5% (31/40) children in oliceridine group as well as 87.5% (35/40) in sufentanil group achieved successful tracheal intubation without requiring rescue medication. The response sequences of the 40 participants in each group are illustrated in Figure 2. The ED_{90} was 74.3 μg/kg (95% CI, 73.6 to 77.4 μg/kg) for oliceridine and 0.34 μg/kg (95% CI, 0.32 to 0.42 μg/kg) for sufentanil, as estimated by isotonic regression.

The incidences of hemodynamic changes (hypertension, hypotension, tachycardia and bradycardia) were similar between groups before and after tracheal intubation, as shown in Table 2. No hypoxemia was observed after administration of oliceridine and sufentanil. The median time for extubation was 9 min [IQR, 6–10 min] in oliceridine group, which was comparable to that in sufentanil group (vs. 8 min [6–9 min], $p = 0.393$). Under this anesthesia regimen, the

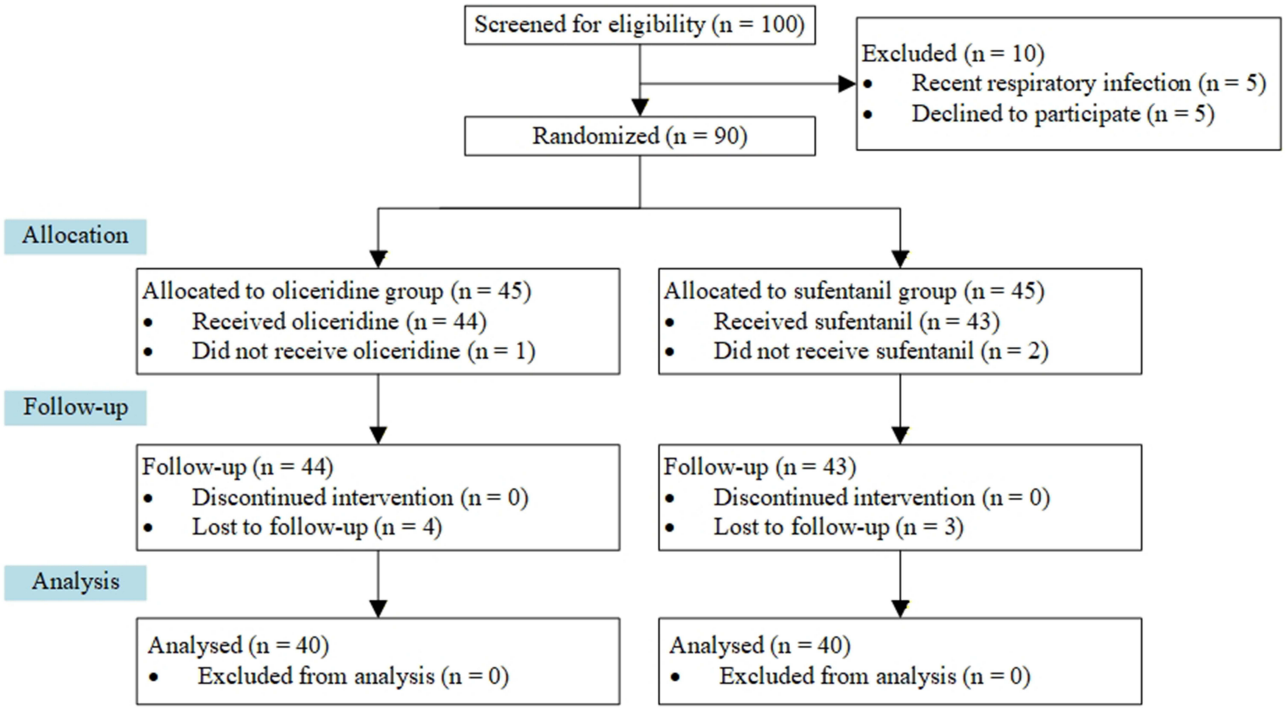

Figure 1 The flow diagram.

incidences of adverse events in PACU including desaturation, pain needed for intervention and bronchospasm were similar between groups. A summary of all adverse events is provided in Table 3.

Discussion

In this dose-finding study using BCUD sequential allocation, we estimated the ED_{90} of oliceridine for endotracheal intubation in children undergoing general anesthesia.

The ED_{90} of oliceridine for pediatric endotracheal intubation was 74.3 μg/kg (equivalent to 300 μg/kg MME). In contrast, the required dose was significantly lower in adults and elderly patients, with ED_{95} values of 55.4 μg/kg for those aged 18–65 years and 50.11 μg/kg for those ≥65 years.[16] When used to suppress the response to laryngeal mask airway insertion, the effective dose of oliceridine was further reduced, with ED_{90} values of 24.6 μg/kg in adults and 22.9 μg/kg

Table 1 Pediatric Characteristics Receiving Oliceridine

	Oliceridine (n = 40)	Sufentanil (n = 40)	*p* value
Age, years	5.5 [3.3, 7.0]	6.5 [3.1, 8.8]	0.224
Gender, male/female, n (%)	31 (77.5%)/9 (22.5%)	29 (72.5%)/11 (27.5%)	0.606
Weight, kg	20.9 [15.6, 24.8]	20.8 [15.4, 28.0]	0.544
Height, cm	115.0 [99.3, 125]	116.5 [98.5, 135.0]	0.124
ASA-PS, I/II, n (%)	25 (62.5%)/15 (37.5%)	24 (60%)/16 (40%)	0.818
Surgery, n (%)			0.447
ENT surgery	11 (27.5%)	10 (25%)	
General surgery	10 (25%)	9 (22.5%)	
Urinary/Orthopedic surgery	5 (12.5%)	10 (25%)	
Others	14 (35%)	11 (27.5%)	
History of surgery, n (%)	1 (2.5%)	0 (0%)	NA
History of allergy, n (%)	4 (10%)	4 (10%)	0.644

Notes: Numerical data are presented as median [interquartile ranges], and categorical data as number (%).
Abbrevation: ENT, eye, nose and throat.

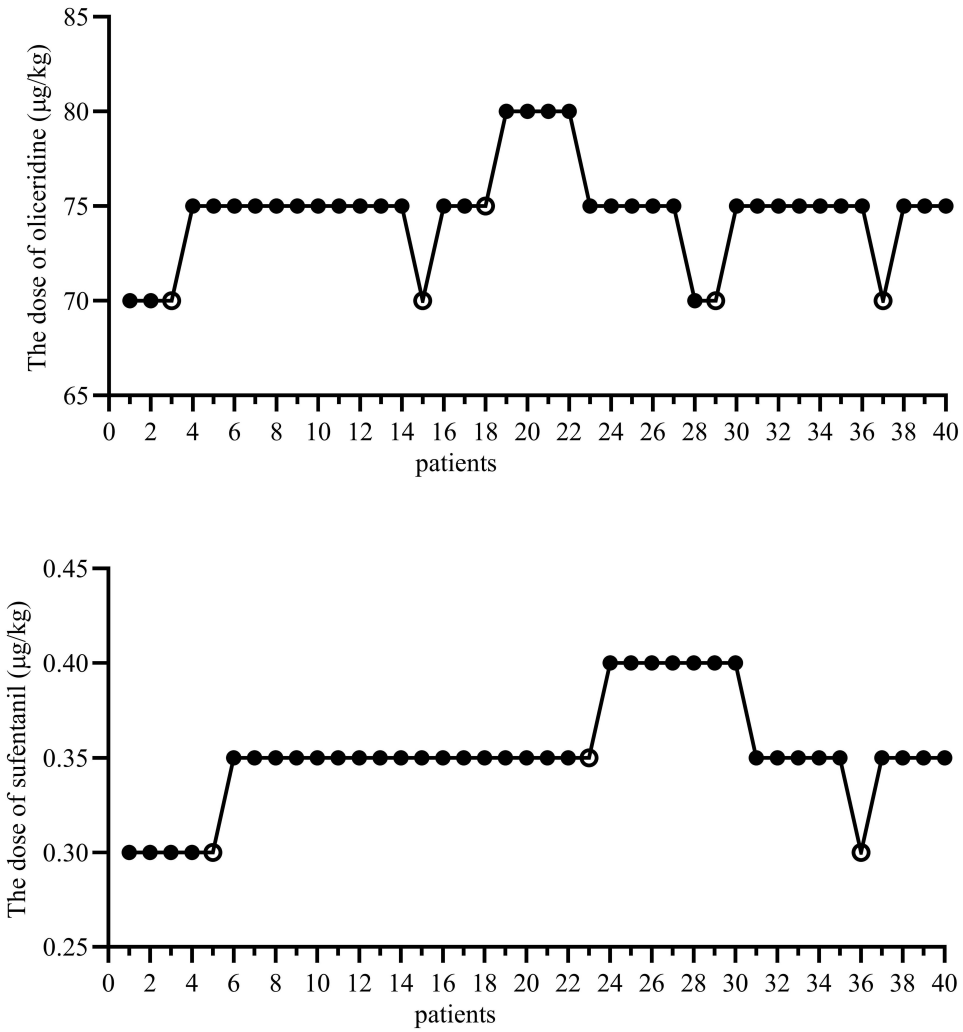

Figure 2 The children allocation sequence and the response to the assigned dose of oliceridine. The patient sequence number (X-axis) is the order of children exposures using the BCUD design. The assigned dose levels are presented on Y-axis. Circle represents failure, and Solid dot represents success.
Abbreviation: BCUD, biased coin up-and down.

in elderly patients, respectively.[17] Moreover, oliceridine has been reported for use in ambulatory endoscopic procedures in adults, including bronchoscopy, gastroscopy, and hysteroscopy, with ED_{90} or ED_{95} values ranging from 22.5 μg/kg to 45 μg/kg.[18–20] This relatively higher dose may be explained by the younger age of the population and the greater intensity of the stimulus.

Table 2 Intraoperative Vital Signs

	T0	T1	T2	T3	T4	T5	T6	*p* value
SBP (mmHg)	110±14	96±13	94±12	96±13	96±12	97±12	96±11	0.197
	117±16	98±11	96±11	96±11	99±12	98±14	95±12	
DBP (mmHg)	62±11	49±6	48±6	49±7	50±7	50±6	50±6	0.090
	68±12	52±5	51±6	51±6	53±7	51±7	51±6	
HR (bpm)	107±21	109±15	109±15	114±15	121±15	122±17	117±15	0.208
	108±28	108±18	110±20	115±19	122±21	119±20	115±21	

Notes: All vital signs were recorded at 7 timepoints: baseline prior to anesthesia (T0), before opioids (T1), 3 min after opioids (T2), before intubation (T3), 1 min after intubation (T4), 3 min after intubation (T5) and 5 min after intubation (T6). A *p*-value < 0.05 was considered significantly different.

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Table 3 Adverse Events During the Procedure and Post-Procedure Emergence

	Oliceridine (n = 40)	Sufentanil (n = 40)	*p* value
Extubation time, min	9 [6, 10]	8 [6, 9]	0.393
FLACC/NRS	2 [1, 3]	2 [1, 3]	0.480
Analgesia rescue, n (%)	7 (17.5%)	2 (5.0%)	0.077
Desaturation, n (%)	0	0	NA
Bronchospasm, n (%)	1 (2.5%)	1 (2.5%)	0.753
PONV	0	3 (7.5%)	NA

Notes: Numerical data are presented as mean ± standard deviation, and categorical data as number (%).
Abbreviation: NA, not applicable.

Following sevoflurane induction, we also calculated the ED_{90} of sufentanil required to blunt cardiovascular responses to laryngoscopy and intubation as 0.34 μg/kg. This finding serves a dual purpose: it confirms that our model reproduces the clinically relevant sufentanil dose range (0.2–0.3 μg/kg) known from earlier work and it provides a robust pharmacokinetic anchor for subsequent comparisons.[21,22] From this anchor dose, the equivalent potency ratio between oliceridine and sufentanil was estimated at approximately 220:1. This ratio reaffirms prior adult data, in which 1 mg of oliceridine was equated to 4–5 MME.

Prior clinical trials have validated the analgesic profile of oliceridine in postoperative settings, demonstrating rapid onset and efficacy superior to morphine in adults.[23–25] However, evidence for its intraoperative use, particularly in pediatric airway management, is limited. It has been postulated that oliceridine's weaker μ-opioid receptor agonism might translate to a reduced risk of certain adverse effects; however, its practical efficacy in pediatric intubation remained unverified. Our dose-finding trial now demonstrates that oliceridine is effective in this context, thereby extending its potential utility to pediatric anesthetic induction.

In terms of safety, no cases of perioperative hypoxia were observed in either group, with comparable hemodynamic changes between them. A nonsignificant trend toward a lower incidence of postoperative nausea and vomiting was noted in the oliceridine group compared to the sufentanil group. Collectively, these findings—encompassing respiratory, hemodynamic, and gastrointestinal parameters—are consistent with the favorable safety profile of oliceridine reported in prior phase 1b and 2a/2b trials.[26–29]

This study has several limitations. First, the relatively wide pediatric age range may have introduced heterogeneity in the estimated dose–response relationship, as developmental differences may affect oliceridine dose requirements. Larger age-stratified studies are needed to establish age-adjusted dosing regimens. Second, although sevoflurane was maintained at an age-adjusted end-tidal concentration of 1.0 MAC to standardize the anesthetic background, BIS values were not recorded; therefore, hypnotic depth could not be directly compared among patients. Finally, the BCUD design may result in dose clustering around the target quantile, and the single-center setting may limit generalizability. Multicenter studies with larger samples, complementary dose–response designs, and pharmacokinetics-pharmacodynamics analyses are needed.

Conclusion

The administration of oliceridine at its ED_{90} (74.3 μg/kg) with 1.0 MAC sevoflurane is effective for endotracheal intubation, providing effective conditions for pediatric general anesthesia.

Clinical Trial Number and Registry URL

Chinese Clinical Trial Registry, No. ChiCTR2300074473 (https://www.chictr.org.cn/showproj.html?proj=227370)

Abbreviation

ANOVA, analysis of variance; ASA-PS, American society of anesthesiologists - physical status; BCUD, biased coin up-and-down design; BIS, bispectral index; CI, confidence interval; ED_{90}, 90% effective dose; IQR, interquartile ranges;

MME, morphine milligram equivalents; ORAEs, opioid-related adverse reactions; PACU, post-anesthesia recovery room; NiBP, non-invasive blood pressure; SD, standard deviation.

Data Sharing Statement

Deidentified individual participant data that underlie the results reported in this article may be made available from the corresponding author upon reasonable request, subject to approval by the institutional ethics committee and compliance with applicable privacy and data protection regulations. The data available for sharing may include anonymized demographic, clinical, perioperative, and outcome data relevant to the analyses presented in this study. Data requests should be directed to the corresponding author at drzhangkan@foxmail.com. Data will be available beginning 6 months after publication and for 3 years thereafter.

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Disclosure

The authors report no conflicts of interest in this work.

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