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ORIGINAL RESEARCH

# Determination of the Median Effective Dose (ED50) of Ciprofol for Successful Sedation in Pediatric Patients During General Anesthesia Induction

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**Purpose:** To determine the median effective dose (ED50) and 90% effective dose (ED90) of ciprofol for successful sedation during general anesthesia induction in pediatric patients, optimize dosing regimens, and provide reference evidence for clinical practice.

**Patients and Methods:** We enrolled pediatric patients aged 3–12 years scheduled for elective surgery under general anesthesia with endotracheal intubation. The first patient received intravenous ciprofol 0.4 mg/kg. Using the modified Dixon's up-and-down sequential method, the ciprofol dose for each subsequent patient was determined based on the previous patient's sedation response. Sedation success was evaluated using two clinical endpoints: loss of eyelash reflex (LER) and acceptance of facemask (AFM). We calculated the ED50, ED90 and their 95% confidence intervals (CI) of ciprofol for successful induction sedation. Secondary outcomes included eyelash reflex disappearance time, vital sign changes during induction, and adverse events.

**Results:** The study achieved 7 transition points (from sedation success to failure) with a total enrollment of 36 pediatric cases. The ED50 and ED90 (with 95% CI) of ciprofol for successful induction sedation in pediatric general anesthesia were 0.618 (0.576~0.666) mg/kg and 0.708 (0.661~0.916) mg/kg, respectively. Eyelash reflex disappearance occurred at 31.04±8.19 seconds post-induction. During anesthesia induction, one case of hypoxemia was observed, while no patients experienced injection pain or hypotension.

**Conclusion:** Ciprofol demonstrates efficacy for anesthesia induction in pediatric patients aged 3–12 years. In the absence of premedication, the median effective dose (ED50) of ciprofol for successful sedation during general anesthesia induction in pediatric patients was 0.618 mg/kg. The recommended dose of ciprofol for induction of general anesthesia in children 3–12 years of age is 0.6–0.7 mg/kg to ensure smooth passage through the mask-assisted respiration phase during induction.

**Keywords:** ciprofol, effective dose, pediatric, anesthesia, general

## Introduction

Ciprofol is a novel intravenous anesthetic, similar to the traditional intravenous anesthetic propofol.[1] Compared with propofol, ciprofol offers significant advantages, including absence of injection pain, reduced cardiovascular and respiratory depression, minimal accumulation, and fewer adverse effects.[2,3] In terms of the above clinical characteristics, the use of ciprofol for general anesthesia in children has certain advantages. Previous studies have demonstrated that ciprofol at doses of 0.4–0.5 mg/kg exhibits good efficacy and safety for general anesthesia induction in adult patients,[4] However, there are currently no reported dosage recommendations for pediatric anesthesia induction. Moreover, since the induction dose of propofol is higher in pediatric patients than in adults,[5] we hypothesize that the induction dose of ciprofol would also be higher in children. This study employed the modified Dixon's up-and-down sequential method to determine the



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median effective dose (ED50) and 90% effective dose (ED90) of ciprofol for successful sedation during general anesthesia induction in pediatric patients, aiming to provide a reference for pediatric anesthesia induction.

# Materials and Methods

## Study Design and Patient Enrollment

This study was approved by the Medical Ethics Committee of Weifang People's Hospital and registered with the Chinese Clinical Trial Registry (ChiCTR2500099738). The clinical trial was conducted in compliance with the Declaration of Helsinki and other applicable regulations. Select pediatric patients scheduled to undergo elective surgery under general anesthesia at Weifang People's Hospital in April 2025. All pediatric participants' legal guardians were fully informed of the trial procedures and provided written informed consent. Inclusion criteria: ① American Society of Anesthesiologists (ASA) physical status I–II, ② Aged 3–12 years, ③ Scheduled for surgery under general anesthesia with endotracheal intubation. Exclusion Criteria: ① Body mass index (BMI) ≥28 kg/m², ② Inability to cooperate with intravenous induction, ③ Anticipated difficult airway, ④ Known or suspected allergy to study-related medications, ⑤ Neurodevelopmental delay, ⑥ Patients who received sedatives/anesthetics within 24 hours prior to induction.

## Interventions

The study utilized the modified Dixon's up-and-down sequential method,[6,7] with an initial ciprofol dose of 0.4 mg/kg (dose increment: 0.05 mg/kg). The dosage for each subsequent pediatric patient was determined by the sedation efficacy observed in the previous case. If sedation was judged successful after drug administration, the dose for the next patient was decreased by one step. Conversely, if sedation was deemed unsuccessful, the dose was increased by one step. The study was terminated after observing seven crossover points. For pediatric patients with failed sedation, rescue sedation was achieved by intravenous administration of propofol (1–2 mg/kg). Sedation success was evaluated using two clinical endpoints: loss of eyelash reflex (LER) and acceptance of facemask (AFM).

## Anesthesia Management

All pediatric patients followed routine preoperative fasting protocols and received no premedication. Upon entering the operating room, peripheral intravenous access was established, followed by standard monitoring including: non-invasive blood pressure (NIBP), heart rate (HR), electrocardiography (ECG), pulse oximetry ($SpO_2$), bispectral index (BIS). Baseline values were recorded prior to induction.

The pediatric patient was placed in the supine position and administered 100% oxygen via a non-sealed face mask at a flow rate of 5 L/min for 5 minutes prior to anesthesia induction. The first patient received an initial dose of ciprofol 0.4 mg/kg (the recommended induction dose for adult general anesthesia). The induction dose will be administered as a slow intravenous bolus over 1 minute, followed by a 1-minute observation period to assess for LER. Sedation will be considered failed if the eyelash reflex persists at 1 minute post-administration, necessitating rescue sedation. If the eyelash reflex disappears within 1 minute after drug administration, the patient's acceptance of the facemask will then be assessed. This will be accomplished by gently lifting the jaw to a sniffing position and applying the facemask to the face while avoiding painful stimuli. The absence of significant movement or coughing will be considered successful sedation. The occurrence of coughing or movement will be deemed sedation failure. Upon completion of all observations, the study personnel will administer analgesic and neuromuscular blocking agents as clinically indicated to facilitate surgical procedures. The induction dose for subsequent pediatric patients will be calculated based on the observed outcomes from the preceding case.

If bradycardia or hypotension occurs during the study, symptomatic treatment with atropine or ephedrine will be administered. For respiratory depression ($SpO_2$ <95%), ventilator settings will be adjusted to provide mask-assisted controlled ventilation. Following neuromuscular blocking agent administration, a endotracheal tube will be inserted. All anesthetic procedures were performed by the same dedicated anesthesiology team.

The study drug was prepared by an anesthesia nurse who had received detailed protocol training and was aware of patient allocation. Prior to anesthesia induction, the nurse calculated the ciprofol induction dose based on the child's weight, drew up the corresponding dose into a syringe, and sealed it in a sterile bag. The sealed bag was then handed to the anesthesiologist after the child entered the operating room. An independent researcher assessed sedation success after the anesthesiologist administered the ciprofol induction dose.

The primary observation: The ED50 of ciprofol for successful sedation during general anesthesia induction in pediatric patients. The success of sedation will be assessed using two indicators: LER and AFM.[8] Sedation will be deemed a failure if the child exhibits body movement during the assessment, and successful if no such movement occurs. LER will be assessed 10 seconds after the administration of ciprofol, repeated every 10 seconds for 1 minute, while the time of LER is recorded. AFM will be observed 1 minute after the completion of induction.

The Secondary observation: 1. To evaluate the changes in hemodynamics and other vital signs in pediatric patients 1 minute after induction of anesthesia, including blood pressure, HR, $SpO_2$ and BIS. 2. To observe adverse reactions during ciprofol induction, including Body movement (defined as movement induced by gently lifting the chin to place the facemask or spontaneous involuntary movement without stimulation, classified as slight or vigorous based on whether it subjectively interferes with mask placement), Respiratory depression (defined as $SpO_2$<95%), Injection pain (defined as limb withdrawal or movement response during ciprofol administration), Hypotension (defined as systolic blood pressure (SBP) < 70 mmHg + [2×age]).

## Statistical Analysis

In this study, the sample size was not predetermined but determined by enrolling sufficient subjects to achieve 7 crossover transition points. The study has been terminated upon reaching the 7th transition point (indicating a shift from sedation success to failure).

Probit regression analysis was used to calculate the ED50 and ED90 values (with corresponding 95% confidence intervals) for successful sedation induction with ciprofol during general anesthesia in pediatric patients. The sequential trial diagram of ciprofol and the fitted dose-response curve were generated using GraphPad Prism 5 software (GraphPad Software, San Diego, CA). The remaining data were processed using SPSS 25.0 (IBM Corp., Armonk, NY, USA). Normally distributed continuous variables were expressed as mean ± standard deviation ($\bar{x}$ ± SD), with between-group comparisons of baseline characteristics analyzed by independent samples *t*-test and within-group hemodynamic comparisons by paired samples *t*-test. Non-normally distributed continuous variables were presented as median (interquartile range) [M (Q1, Q3)] and analyzed using Wilcoxon signed-rank test. Categorical data were summarized as frequencies (percentages). The significance level was set at α = 0.05 (two-tailed).

# Results

The study achieved 7 transition points (from sedation success to failure) with a total enrollment of 36 pediatric cases, comprising 16 positive responses and 20 negative responses. The baseline characteristics of the pediatric patients are presented in Table 1. Figure 1 illustrates the modified Dixon's up-and-down sequence plot for ciprofol used in general anesthesia induction in children.

For pediatric general anesthesia induction with ciprofol, the ED50 and ED90 values (with 95% confidence intervals) for successful sedation were 0.618 (0.576–0.666) mg/kg and 0.708 (0.661–0.916) mg/kg, respectively. The dose-response curve for ciprofol-induced sedation is presented in Figure 2.

**Table 1** Characteristics of Patients

| | Positive Group (n = 16) | Negative Group (n = 20) | *P* |
|---|---|---|---|
| Age (year) | 7.45±1.89 | 7.13±1.58 | 0.586 |
| Weight (kg) | 26.30±9.02 | 29.31±8.89 | 0.324 |
| Height (cm) | 129.13±15.30 | 128.93±12.35 | 0.966 |

**Note**: Data are expressed as mean±SD.

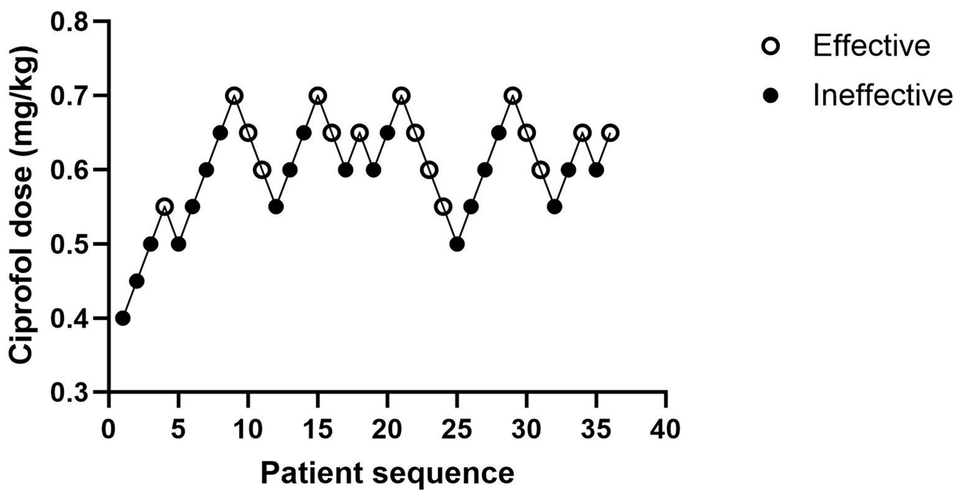


**Figure 1** Sequential diagram of ciprofol for anesthesia induction in pediatric patients.

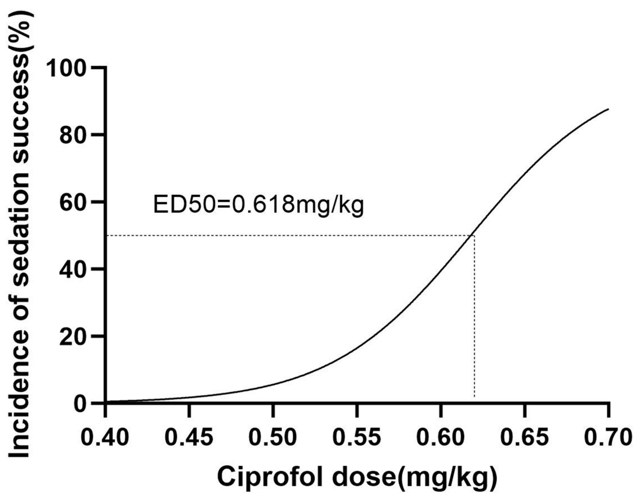


**Figure 2** The dose–effect curve of ciprofol for general anesthesia induction in pediatric patients.

The changes in vital signs during the induction period for all pediatric patients are shown in Table 2: Both blood pressure and BIS values decreased from baseline after induction ($P < 0.05$), while heart rate increased compared to baseline values ($P = 0.007$).

**Table 2** Changes of Vital Signs During Anesthesia Induction

| | Baseline | After Induction 1 min | *P* |
|---|---|---|---|
| SBP | 110.87±12.81 | 105.48±12.53 | 0.005 |
| DBP | 69.61±9.03 | 61.55±14.41 | 0.001 |
| MAP | 80.65±9.60 | 75.97±12.40 | 0.020 |
| HR | 92.74±15.14 | 103.13±11.82 | 0.007 |
| BIS | 92.06±4.32 | 42.84±8.24 | 0.001 |
| $SpO_2$ | 100 (99–100) | 99 (99–100) | 0.167 |

**Notes**: Data are expressed as mean±SD or median (interquartile range).

**Table 3** Correlation Between Ciprofol Induction Dose and Adverse Reactions

| Induction dose (mg/kg) | 0.4 | 0.45 | 0.5 | 0.55 | 0.6 | 0.65 | 0.7 |
|---|---|---|---|---|---|---|---|
| Movement of the limbs | | | | | | | |
| None/slight/vigorous (n) | 0/0/1 | 0/0/1 | 0/0/3 | 2/1/3 | 3/5/2 | 7/4/0 | 4/0/0 |
| Apnea (%) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (25.0) |
| Injection pain (%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypotension (%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Table 3 summarizes the adverse events observed during ciprofol induction. During anesthesia induction, one patient developed hypoxemia, while no cases of injection pain or hypotension were recorded. Among the 20 patients exhibiting body movements, these were triggered by facemask ventilation in 19 cases, with only 1 patient showing spontaneous involuntary movements in the absence of stimulation following induction.

## Discussion

This study is a prospective, interventional dose-exploration study, with the primary study subjects being pediatric patients aged 3–12 years. None of the children received premedication prior to induction. Our study found that the ED50 and ED90 of ciprofol for successful sedation induction in pediatric patients were 0.618 mg/kg and 0.708 mg/kg, respectively. Given that the potency ratio of ciprofol to propofol for anesthesia induction is approximately 1:4,[9,10] these doses correspond to propofol equivalents of 2.47 mg/kg and 2.83 mg/kg, which align with the currently recommended propofol induction doses for children.

There are many methods for assessing the depth of sedation for anesthesia induction, and LER as well as Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores are common evaluations for anesthesia induction in adults.[11,12] However, these methods may not be applicable to pediatric patients. During the experimental design phase of this study, we initially set MOAA/S ≤1 and LER as the study endpoints. But, the results revealed a high incidence of body movement in pediatric patients after induction. Even with the administration of opioids and neuromuscular blocking agents, body movements still occurred during mask-assisted mechanical ventilation. Therefore, the ciprofol induction doses determined by this method may not be suitable for general anesthesia with endotracheal intubation in children. Therefore, we ultimately adopted the conventional propofol dose-determination method for pediatric induction, using loss of eyelash reflex and mask acceptance as the criteria for successful sedation.[5,8,13] This approach may facilitate a more stable transition during the mask-assisted ventilation phase. Hannallah also mentioned that in clinical practice, after a pediatric patient receives intravenous induction of anesthesia, healthcare professionals often use the smoothness of the transition of the anesthesia phase as a key indicator to assess the success of intravenous induction of anesthesia, which is usually accompanied by the use of a mask device to maintain airway management, so the evaluation of the child's acceptance of the facemask is a more important indicator.[14]

The effective induction dose of ciprofol for children has not been established, and appropriate dosing recommendations are still being explored. Chen et al's study established the safety profile of ciprofol for both induction and maintenance of general anesthesia in pediatric patients aged >2 years, although it did not conduct further investigation into dosing protocols specifically for children aged 2–11 years.[15] Pei et al[16] investigated varying ciprofol doses (0.4, 0.6, and 0.8 mg/kg) for anesthesia induction in children aged 3–12 years to evaluate intubation conditions. Their results demonstrated body movement occurrence rates of 51%, 19.5%, and 18.3% during tracheal intubation at these respective doses. Although Pei's observations are different from those of the present study, they also give us some indication that the recommended induction dose of 0.4 mg/kg for adults may not be applicable to pediatric patients. In addition, opioid drugs can also affect the dosage of ciprofol. Zhang et al found that a higher dose of remifentanil (0.5 µg/kg) significantly reduced the ED50 of ciprofol required for gastrointestinal endoscopy procedures.[17] Wang et al found that the ED50 of ciprofol for laryngeal mask insertion response in children was 1.81 mg/kg when not used in combination with opioid drugs.[18] Unlike this study, the two aforementioned studies employed different stimuli for the children due to variations in examination protocols. As a result, the derived ED50 values are only applicable to specific research conclusions and cannot be generalized to the anesthesia induction process.

This study also found that the application of ciprofol caused no injection pain in children, and no limb movements—such as arm retraction—occurred during its administration. After the injection of ciprofol, 35 pediatric patients lost their eyelash reflex within 1 minute, with an average disappearance time of 31.04 ± 8.19 seconds post-induction. Only one child exhibited involuntary, sustained limb movement after receiving 0.6 mg/kg of ciprofol, which we speculate might be related to insufficient anesthetic depth. After observing no signs of sedation for 1 minute, this patient was administered 20 mg of propofol as a rescue sedative. The remaining children who exhibited involuntary movements did so during facemask acceptance testing. We graded the severity of these movements: mild movements were within clinically acceptable limits, while severe cases often required physical restraint by nursing staff to prevent the child from falling off the operating table Additionally, during the study, one pediatric patient developed respiratory depression within 1 minute after ciprofol administration, with oxygen saturation dropping below 95%. We provided assisted ventilation in response.

Compared to the recommended dose for adult patients, pediatric patients typically require higher doses of ciprofol to achieve satisfactory anesthetic depth. Concurrently, clinical observations demonstrate substantial interpatient variability in pediatric responses to this agent, necessitating both anesthetic depth monitoring and implementation of individualized dosing protocols in clinical practice. Based on the ED50 and ED90 values of ciprofol in pediatric patients established in this study, we recommend an induction dose range of 0.6–0.7 mg/kg for children.

This study has several limitations. First, it only included relatively healthy children with ASA physical status I–II undergoing elective surgery, which limits its applicability to high-risk pediatric patients. Additionally, the study enrolled children aged 3–12 years with a relatively wide age range but did not conduct subgroup analyses by age.

## Conclusion

Ciprofol demonstrates efficacy for anesthesia induction in pediatric patients aged 3–12 years. In the absence of premedication, the median effective dose (ED50) of ciprofol for successful sedation during general anesthesia induction in pediatric patients was 0.618 mg/kg. The recommended dose of ciprofol for induction of general anesthesia in children 3–12 years of age is 0.6–0.7 mg/kg to ensure smooth passage through the mask-assisted respiration phase during induction.

## Data Sharing Statement

All data generated or analyzed during this study were included in the published article. Further inquiries about the datasets can be directed to the first author on reasonable request.

## Consent for Publication

All authors have agreed to submit and publish the manuscript.

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## Disclosure

The authors have no competing interests in this work.

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