

Exploring the Median Effective Dose of Ciprofol for Anesthesia Induction in Elderly Patients: Impact of Frailty on ED₅₀

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Purpose: Explore the median effective dose of ciprofol for inducing loss of consciousness in elderly patients and investigate how frailty influences the ED₅₀ of ciprofol in elderly patients.

Patients and Methods: A total of 26 non-frail patients and 28 frail patients aged 65–78 years, with BMI ranging from 15 to 28 kg/m², and classified as ASA grade II or III were selected. Patients were divided into two groups according to frailty: non-frail patients (CFS<4), frail patients (CFS≥4). With an initial dose of 0.3 mg/kg for elderly non-frail patients and 0.25 mg/kg for elderly frail patients, using the up-and-down Dixon method, and the next patient's dose was dependent on the previous patient's response. Demographic information, heart rate (HR), oxygen saturation (SpO₂), mean blood pressure (MBP), and bispectral index (BIS) were recorded every 30 seconds, starting from the initiation of drug administration and continuing up to 3 minutes post-administration. Additionally, the total ciprofol dosage during induction, occurrences of hypotension, bradycardia, respiratory depression, and injection pain were recorded.

Results: The calculated ED₅₀ (95% confidence interval [CI]) and ED₉₅ (95% CI) values for ciprofol-induced loss of consciousness were as follows: 0.267 mg/kg (95% CI 0.250–0.284) and 0.301 mg/kg (95% CI 0.284–0.397) for elderly non-frail patients; and 0.263 mg/kg (95% CI 0.244–0.281) and 0.302 mg/kg (95% CI 0.283–0.412) for elderly frail patients. Importantly, no patients reported intravenous injection pain, required treatment for hypotension, or experienced significant bradycardia.

Conclusion: Frailty among elderly patients does not exert a notable impact on the median effective dose of ciprofol for anesthesia induction. Our findings suggest that anesthesiologists may forego the necessity of dosage adjustments when administering ciprofol for anesthesia induction in elderly frail patients.

Keywords: ciprofol, median effective dose, elderly patients, frailty, loss of consciousness

Introduction

With the continuous growth of the global population and improvements in living standards, an increasing number of elderly individuals are opting for surgical interventions. However, due to age-related physiological changes, elderly patients exhibit higher sensitivity to anesthesia drugs.¹ Consequently, during general anesthesia, elderly patients typically receive lower doses of anesthesia drugs compared to their younger counterparts to minimize the occurrence of potential side effects such as respiratory arrest and bradycardia.²

Simultaneously, surgical frailty, as a multidimensional state accumulating age and disease-related deficits in elderly patients, leads to a reduction in their physiological reserves. Frail patients often demonstrate decreased tolerance to stressors, resulting in a diminished ability to adapt to adverse outcomes.³ Changes in pharmacokinetic and pharmacodynamics, such as decreased albumin levels and altered activity of ATP-gated potassium channels, may impact the sensitivity of frail patients to anesthetic drugs.^{4,5}

In the process of anesthesia induction, propofol typically plays a crucial role. Propofol, acting as a modulator and agonist of γ -aminobutyric acid (GABA) receptors,^{6,7} exerts its sedative and general anesthetic effects by enhancing central inhibitory GABA neurotransmission. However, propofol has known limitations, including significant inhibition of the circulatory system, the tendency to cause hypotension and hemodynamic fluctuations^{8,9} during anesthesia induction, dose-dependent respiratory depression, and injection pain.^{7,10}

To overcome these limitations, ciprofol (HSK3486) emerges as a new intravenous anesthetic agent with a chemical structure closely related to propofol. It demonstrates similar potency and advantages requires lower dosage. Moreover, it has been proven to have a noninferior efficacy profile compared to propofol, showcasing excellent tolerance.^{11–14}

Although there have been studies comparing single intravenous infusion of ciprofol between elderly and non-elderly patients, finding similarities in the pharmacokinetics and pharmacodynamics when elderly patients were given 0.3mg/kg and non-elderly patients were given 0.4mg/kg,² there is currently no research on the median effective dose of ciprofol required to induce loss of consciousness during general anesthesia in elderly patients. Additionally, there is a lack of research on the median effective dose of ciprofol required to induce loss of consciousness during general anesthesia in elderly frail patients. Therefore, this study aims to discuss the median effective dose of ciprofol induction for loss of consciousness in elderly patients and further explore the impact of frailty on the ED₅₀ of ciprofol for loss of consciousness in older patients.

Materials and Methods

This trial was conducted in accordance with the ethical standards of the Declaration of Helsinki¹⁵ and was approved by the institutional review board of the First Affiliated Hospital of Zhengzhou University (2023-KY-0407-002) and was registered in the Chinese Clinical Trial Registry (ChiCTR2300075692). It was conducted between September 2023 and November 2023 at the Department of Anesthesiology, Pain and Perioperative Medicine, the First Affiliated Hospital of Zhengzhou University, the research adhered to ethical standards. All subjects have signed the informed consent for this study. Eligible participants included elderly patients undergoing elective abdominal surgery under total intravenous anesthesia, aged between 65 and 78 years, with a BMI range from 15 to 28 kg/m² and an ASA physical status classification of II or III. Frailty classification was based on a CFS score equal to or greater than 4.^{16,17}

Exclusion criteria encompassed the following: Known allergies to eggs, soy products, or the study drugs (ciprofol, remifentanyl, rocuronium, neostigmine, atropine); Concurrent central nervous system diseases; Severe hypertension, diabetes mellitus, hepatic and renal dysfunction, and heart failure; Patients with difficult airways; and subjects exhibiting significant respiratory and cardiovascular dysfunction.

Withdrawal criteria included: The occurrence of serious adverse events (SAEs) rendering it inappropriate for the subject to continue the trial; The investigator's decision to withdraw the subject from the trial for their well-being; and the subject's voluntary decision to withdraw from the trial.

Study Protocol

All patients received standardized surgery and anesthesia care, and no premedication was given for anesthesia. After admission to the operating room, routine monitoring was performed including electrocardiogram (ECG), oxygen saturation (SpO₂), non-invasive blood pressure (NIBP), and bispectral index (BIS). An intravenous line was opened, and radial artery catheterization under local anesthesia was performed to monitor invasive blood pressure (IBP). All patients were given pure oxygen at a flow rate of 5–8 L/min by mask for 3 minutes before induction. The modified observer's assessment of alertness and sedation (MOAA/S) score for pre-anesthetic evaluation of the patient was adopted for Anesthesia induction. To ensure relative blinding, administration of medication and evaluation were performed independently by two anesthesiologists. Beginning with the study, one anesthesiologist administered medication to the patient intravenously. The patient received an intravenous injection of a corresponding dose of ciprofol with 30 seconds, followed by an additional 1mL of 0.9% normal

saline to ensure complete absorption into the body. Another anesthesiologist judges whether the induction is successful (consciousness disappears) using two evaluation methods: MOAA/S \leq 1 and BIS value <60 indicates successful induction. The dose of ciprofol was determined using up and down sequential method, with an adjacent-dose ratio of 1:1.1. The initial dose for the non-frail group was 0.3mg/kg (based on previous literature²) and the initial dose for the frail group was 0.25mg/kg (based on pilot study results). If consciousness disappeared in a patient, the next patient's ciprofol dose was decreased by one dose gradient. Conversely, if consciousness did not disappear, the next patient's ciprofol dose was increased by one dose gradient, until there were seven crossovers from positive to negative or from negative to positive reactions. The experiment was stopped at this point. Patient vital signs, including heart rate (HR), SpO₂, MAP, BIS, and MOAA/S, were monitored at 30 seconds intervals from the initiation of drug administration until three minutes thereafter. The total dosage of ciprofol administered during the induction phase was also documented. In the event of hypotension during the induction phase, defined as a mean arterial pressure (MAP) dropping below 65mmHg or by 20% relative to baseline and persisting for over one minute, a proactive intervention protocol which involves the intravenous administration of norepinephrine at a dose 4–8 μ g or ephedrine at a dose 5–10 mg is activated. Additionally, for instances of bradycardia, indicated by HR falling below 45 beats per minute with a duration exceeding one minute, anesthesiologists may administer atropine intravenously, with the dose ranging from 0.2 to 0.5 mg, depending on their clinical judgment. In cases of respiratory depression, characterized by a breathing rate decrease of less than 10 times per minute or a determination by the anesthetic practitioner that the patient's tidal volume is insufficient (decreases to 40% of the pre-induction level), providing assistive ventilation through pressure mask ventilation to prevent the onset of hypoxemia in the patient should be taken.

Study Outcomes

The primary outcome of the study was the comparison of the ED₅₀ and the efficacy ratio with 95% CI of ciprofol for making elderly patients loss of consciousness between the two groups.

The secondary outcome: HR, MAP, and SpO₂ were measured at the following time points: initiation of anesthesia induction (T0), 30 seconds after induction (T1), 60 seconds after induction (T2), 90 seconds after induction (T3), 120 seconds after induction (T4), 150 seconds after induction (T5), 180 seconds after induction (T6). Record the occurrence of hypotension, bradycardia, respiratory depression, and injection pain. Demographic data, including gender, age, weight, BMI, and ASA classification and the use of vasoactive drugs during anesthesia induction period were recorded.

Statistical Analysis

The total number of participants depends on Dixon's up-and-down method.¹⁸ This method requires at least six crossover points (non-responsive to responsive) for statistical analysis. Additionally, according to prior studies, the sample size was regarded as sufficient when six pairs of reversals of sequence were obtained when the up-and-down method was applied to evaluate the ED₅₀.¹⁹ After 30 participants were allocated per group, we also obtained more than six pairs of reversals of sequence. Thus, the sample size in the current study was sufficient to calculate the ED₅₀.

All data were presented as mean (SD), median (interquartile range, IQR), or number (percentage) as appropriate. Comparison of normally distributed quantitative variables between groups was performed with student's *t*-test, and asymmetric distributed quantitative data was analyzed with Mann–Whitney *U*-test. Qualitative variables between groups were compared with Chi-square test or Fisher exact test as needed. Using Two-way ANOVA to analyze the data collected at various time points within the group. The ED₅₀ and ED₉₅ of ciprofol and their corresponding CI were analyzed using the probit regression test. SPSS 25.0 (SPSS, Inc., Chicago, IL, USA) was used for data analysis. $p < 0.05$ indicates a statistically significant difference. GraphPad Prism version 9.5.1 (GraphPad Software Inc. San Diego, CA, USA) was used to draw sequential graphs and dose–response curves.

Results

General Data

From September 2023 to November 2023, fifty-six patients were assessed for eligibility, and two patients were excluded due to changing the surgery plan. Fifty-four patients were finally analyzed. When 26 patients were included in the group

N and 28 patients in the group F, the seven crossovers of each group occurred (shown in Figure 1). The patient characteristics and induction data between the two groups are shown in Table 1. Compared to the Group N, the age of patients in Group F was significantly older (74.6 ± 6.8 vs 69.5 ± 3.8 years, $p < 0.001$). The proportion of ASA physical status II was significantly higher in Group N [15/26 (58%) vs 4/28 (14%), $p = 0.001$]. The proportion of ASA physical status III was significantly higher in Group F [24/28 (86%) vs. 11/26 (42%), $p = 0.001$]. There were no significant differences in the gender, height, weight, BMI, or dose between the two groups ($p > 0.05$).

Dose–Response to Ciprofol for Anesthesia Induction

In the effective dose experiment, ED_{50} of ciprofol-induced loss of consciousness for anesthesia induction was 0.267 mg/kg (95% CI 0.250–0.284) and 0.263 mg/kg (95% CI 0.2440–0.281) in groups N and F, respectively, using the probit regression model. No significant statistical difference was found between the two groups ($p = 0.063$) (Table 2). The ED_{95} was 0.301 mg/kg (95% CI 0.284–0.397) and 0.302 mg/kg (95% CI 0.283–0.412 mg/kg) in groups N and F, respectively, shown in Table 2. The Dixon up-and-down plot for each group is shown in Figure 2A and B. The dose–response curve of ciprofol induction in each group is shown in Figure 2C and D.

Hemodynamics

Figure 3 includes hemodynamic changes and BIS values in the two groups. Both Group N and Group F patients experienced significant decreases in BIS and MAP at all time points from T1 to T6 compared to their pre-induction levels ($p < 0.001$). The BIS value of patients in both groups decreased to approximately 60 from T3, and the MAP also decreased a little bit and stabilized from T3. The HR of patients in both groups did not change significantly throughout the induction phase. There was no significant difference in MAP and BIS between the two groups at each time point.

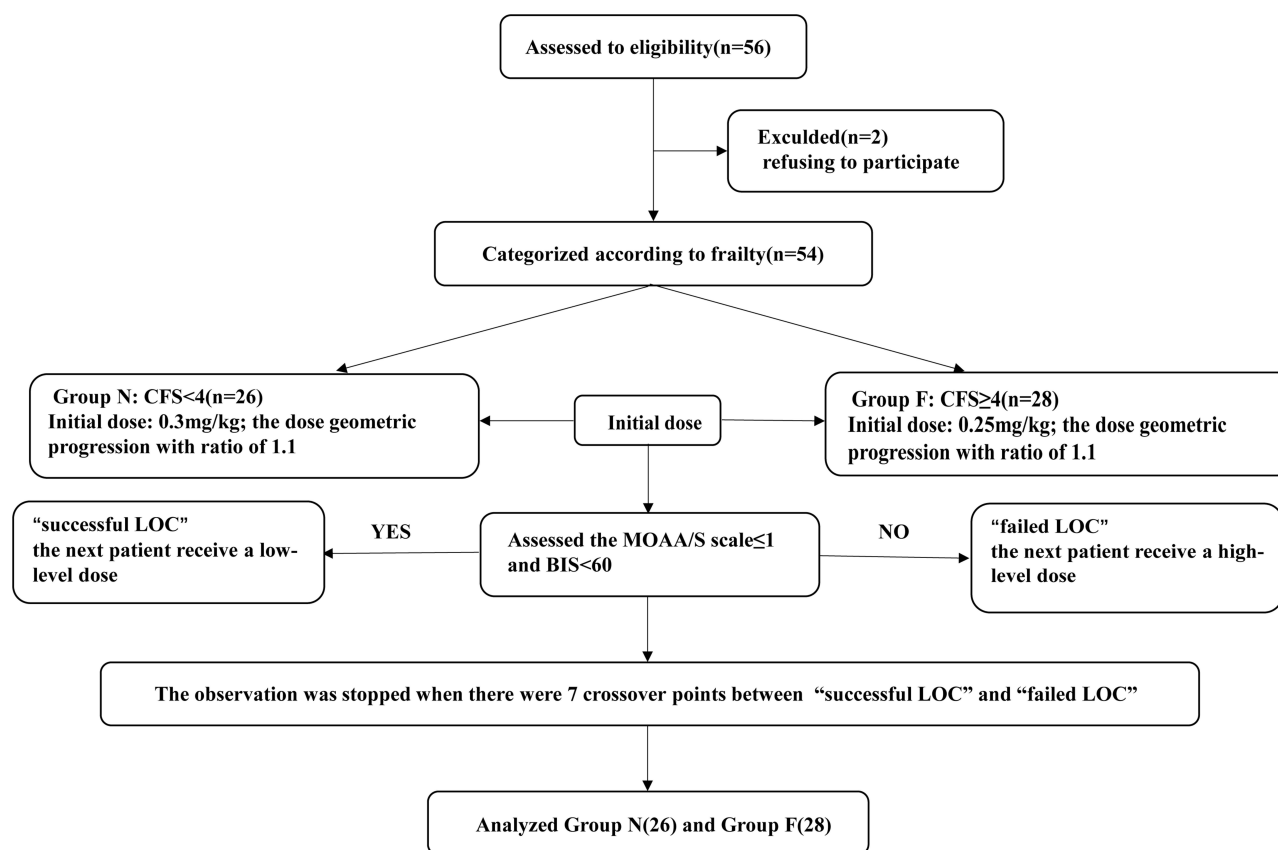


Figure 1 Flow diagram of included participants.

Table 1 Patient Characteristics and Induction Data in the Groups

Variable	Group N (n=26)	Group F (n=28)	P value
Female, n (%)	7/26(27%)	11/28(39%)	0.395
Age (yr)	69.5±3.8	74.6±6.8	<0.001
Height (cm)	163.6±6.9	163.1±6.9	0.790
Weight (kg)	64.4±9.9	60.7±9.9	0.154
BMI (mg kg ⁻²)	23.9±2.7	22.5±2.7	0.060
ASA physical status, n (%)			
II	15/26(58%)	4/28(14%)	0.001
III	11/26(42%)	24/28(86%)	0.001
Comorbidities			
MMSE (score)	21.2±2.3	20.5±2.1	0.256
HBP history, n (%)	8/26(31%)	11/28(39%)	0.513
DM, n (%)	5/26(19%)	7/28(25%)	0.610
Cardiac disease history, n (%)	6/26(23%)	8/28(29%)	0.645
Dose (mg/kg)	0.27±0.2	0.26±0.2	0.512
Respiratory depression, n (%)	10/26(39%)	16/28(57%)	0.187

Notes: Data are expressed as mean (standard deviation), n (%), or median (interquartile range). Group N: the non-frail group; Group F: the frail group.

Abbreviations: ASA physical status, American Society of Anesthesiologists Physical Status classification; SD, standard deviation; BMI, body mass index; MMSE, Mini-mental state examination; HBP, high blood pressure; DM, diabetes mellitus.

Table 2 ED₅₀ and ED₉₅ of Ciprofol for Anesthesia Induction

	Group N(n=26)	Group F(n=28)	P value
ED ₅₀	0.267 (0.250–0.284)	0.263 (0.244–0.281)	0.512
ED ₉₅	0.301 (0.284–0.397)	0.302 (0.283–0.412)	–

Note: The ED₅₀ and ED₉₅ with their 95% confidence interval.

No rescue boluses of norepinephrine or ephedrine were required during the study period, as the blood pressure was stable enough during the study period. Neither group experienced bradycardia and injection pain. The incidence of respiratory depression was 39% in group N and 57% in group F, both of which were relatively high. Elderly patients often suffer from comorbidities and have poor tolerance to hypoxia, making them a high-risk group for respiratory depression. Additionally, the definition of respiratory depression in this study is more rigorous, resulting in a higher incidence of respiratory depression. Most respiratory depressions during the observation process were transient, and once the patient experienced respiratory depression, the anesthesiologist promptly provided ventilation assistance by holding the mandible or using a face mask. Therefore, the SpO₂ values were almost 100% at the fixed time points during observation.

Discussion

Due to the degeneration of various organ functions and changes in the distribution and metabolism of anesthetic drugs in the body, the risk of undergoing anesthesia and surgery in elderly patients is significantly higher than that of adults, and the induction phase of anesthesia is the highest anesthesia risk.²⁰ Therefore, there is an urgent need to further evaluate the dosage and safety of the use of ciprofol.

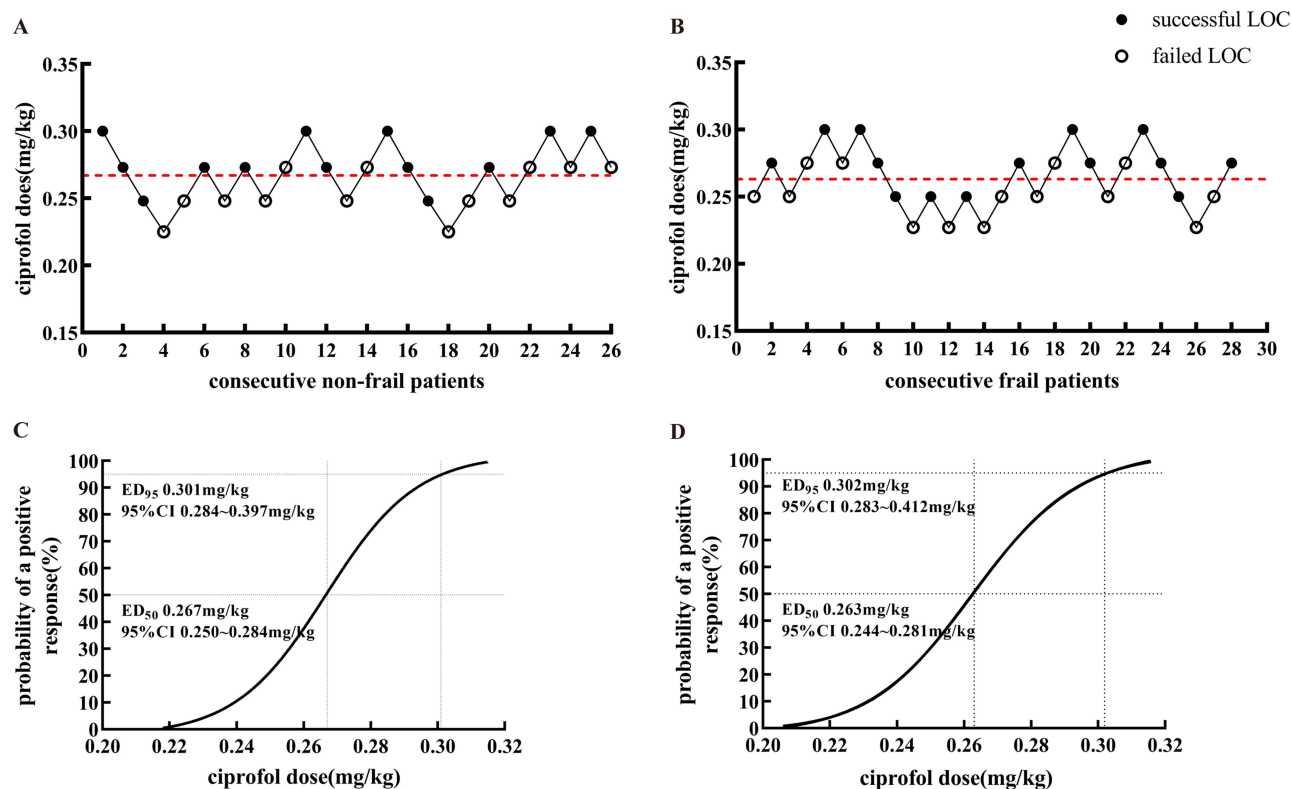


Figure 2 (A) The up-and-down sequence of ciprofol dose for loss of consciousness in Group N. The black dot represents “successful loc” and the white dot represents “failed loc”. (B) The up-and-down sequence of ciprofol dose for loss of consciousness in Group F. (C) Dose–response curve fitted to the Saidman and Eger data and used to generate the simulation data in Group N. Here a positive response is defined as the MOAA/S \leq 1 and BIS value $<$ 60. (D) Dose–response curve fitted to the Saidman and Eger data and used to generate the simulation data in Group F.

Abbreviations: LOC, loss of consciousness; ED₅₀, median effective dose; CI, confidence interval.

In this study, the sequential method was used to determine the quantity–effect relationship of ciprofol-induced loss of consciousness in elderly patients. According to the results of previous studies, the initial dosage of the non-frail group was set at 0.3 mg/kg in this study, and considering the pharmacokinetics and pharmacodynamics of frail patients, we set the initial dosage of the frail group at 0.25 mg/kg, and the ratio of neighboring measures in both groups was 1:1.1. The study was stopped when at least seven consecutive transitions occurred.

The reduction in brain and blood volume, the decreased number of anesthetic drug-binding sites (eg, GABA receptors, NMDA receptors) and the decreased number and function of neuronal synapses, and the reduced cortical volume in frail patients all contribute to the higher sensitivity of frail elderly patients to anesthetic drugs compared to non-frail patients.^{21–24} The above causes that the superimposition of multiple organ system defects in frail elderly patients lead to physiological decline, which change pharmacokinetics and pharmacodynamics, and often reduce the use of anesthetic drugs in clinical practice.²⁵ Pharmacokinetic factors in frail patients may increase the concentration of drugs at the effect site, and lower plasma proteins (mainly albumin) in frail patients may lead to a relative increase in unbound ciprofol, resulting in higher “active” ciprofol concentrations in the biological phase, making the effect of ciprofol greater.^{26,27} In addition, the reduction in GABA receptor subunits and the decrease in the threshold for the binding of ciprofol to achieve the corresponding pharmacodynamic effect lead to a lower in the dose of ciprofol required to induce unconsciousness in frail elderly patients. It has shown that the ED₅₀ of ciprofol for loss of consciousness is not significantly lower in frail elderly patients than in non-frail elderly patients [0.263 mg/kg (95% CI 0.244–0.281 vs 0.267 mg/kg) (95% CI 0.250–0.284), $p=0.063$]. The clinical implication of this finding is that an approximately ciprofol dose of 0.301 mg/kg should be administered for induction of anesthesia in non-frail elderly patients, which is consistent with the recommended dose in previous studies on the induction of elderly patients.² Simultaneously, frail elderly patients will require an approximately same dose of 0.302 mg/kg. Our results do not suggest that frail elderly patients require a reduced induction dose during the induction process, which implies that the safety range for utilizing ciprofol in the elderly and those with frailty may be substantial.

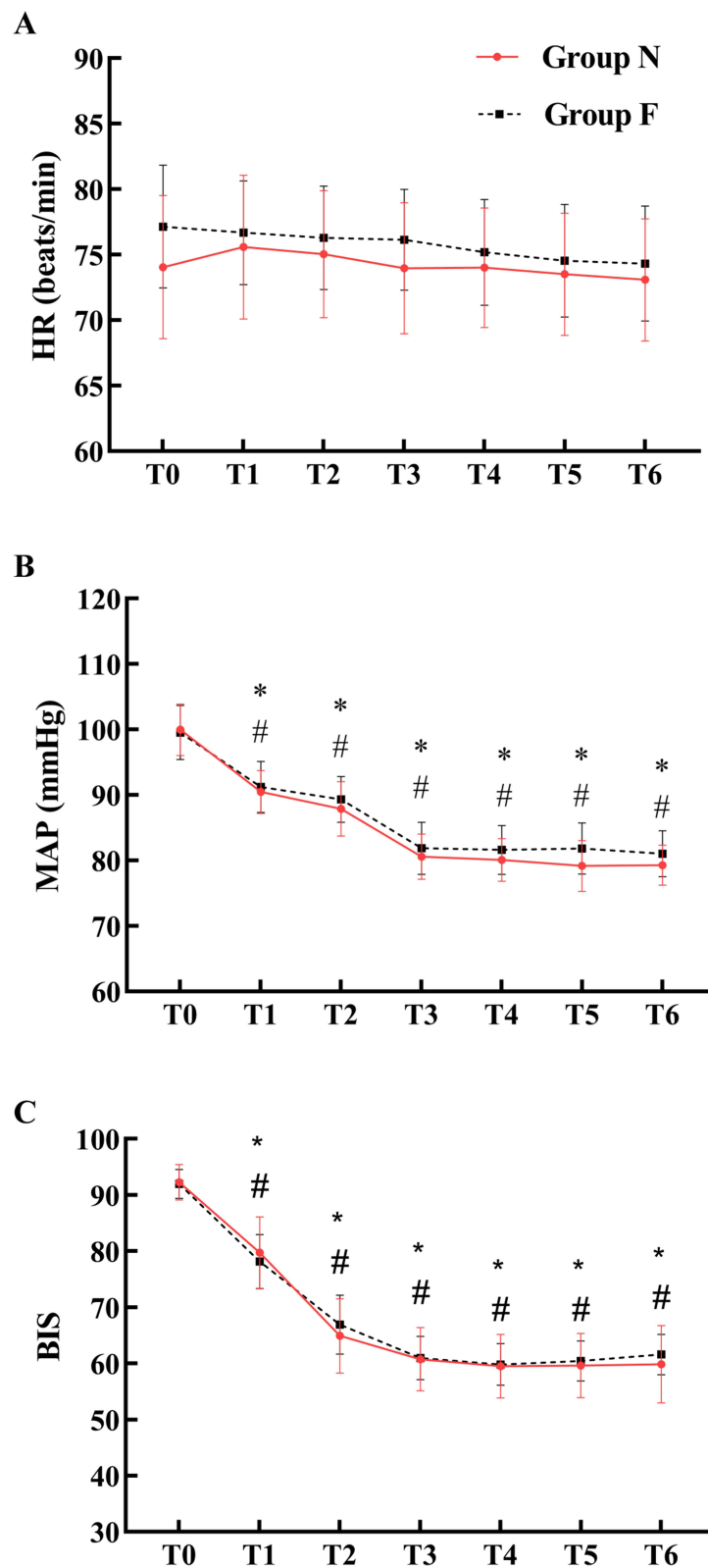


Figure 3 Hemodynamic parameters and BIS values during anesthesia induction. HR didn't decrease (A), MAP decreased (B), BIS decreased (C) after bolus administration of ciprofol in the groups. Error bars represent 95% confidence interval.

Notes: * $p < 0.001$ compared to T_0 in the Group N. # $p < 0.001$ compared to T_0 in the Group F. T_0 - initiation of anesthesia induction; T_1 - 30 seconds after induction; T_2 - 60 seconds after induction; T_3 - 90 seconds after induction; T_4 - 120 seconds after induction; T_5 - 150 seconds after induction; T_6 - 180 seconds after induction.

Abbreviations: BIS, bispectral index; MAP, Mean arterial pressure; HR, heart rate.

Direct comparisons of the induction dose of ciprofol from our study and previously published studies are difficult because of differences in endpoints used for loss of consciousness and the statistical methods for determining the ED₅₀. In our study, we defined the loss of consciousness as follows: within 30 seconds of intravenous drug administration, the patient's MOAA/S score ≤ 1 ²⁸ and BIS value < 60 within 3 minutes. Naguib et al²⁹ noted that the dose–response curves for propofol for loss of consciousness differed and concluded that doses reflecting different endpoints of anesthesia were not comparable. In the present study, the duration until the onset of loss of consciousness is observed to be approximately 1.5 minutes across both groups, as depicted in Figure 3. This duration appears to exceed that reported in prior studies, such as those referenced in literature,³⁰ where the recorded time to loss of consciousness was approximately 1 minute. The protracted onset duration in our study may be attributed to age-related alterations in cardiovascular parameters among the elderly, including diminished cardiovascular function, myocardial contractility, and cardiac output. These physiological changes collectively contribute to a decelerated circulatory response, thereby providing a plausible explanation for the observed delay in drug action compared to findings in earlier investigations. Probit regression analysis was used in this study, the ED₉₅ value is extrapolated from the dose–response curve, and the 95% CI of ED₉₅ values are dependent on the steepness of the curve. ED₅₀ is a commonly used index for studying the quantity–effect relationship of a drug, which is usually regarded as the initial dosage of a drug for clinical trials. The sequential test is a commonly used method to determine the ED₅₀ of a drug, which can fully utilize the information provided by the clinic with a small sample size. Using probit regression, the 95% CI of the ED₅₀ is usually narrower, permitting more reliable comparisons of drug potency.^{19,31,32}

In recent years, frailty has gained recognition as a significant comorbidity and determinant of surgical outcomes.^{33,34} While frailty is referenced as a complement to the ASA Physical Status classification system in the ASA's preamble, it remains absent from the official definitions and examples. Consequently, there is currently no formal guidance for integrating frailty into the ASA Physical Status.^{35,36} However, an objective assessment of frailty could potentially equate to a serious systemic disease (ASA Physical Status III) and may pose a life-threatening risk (ASA Physical Status IV).^{36,37} Therefore, frailty should be included as a standard component of preoperative evaluations and considered for inclusion in future updates to the ASA Physical Status system.³⁸ This study is an observational one that excludes patients with ASA grades IV and above due to their higher clinical anesthesia risk and subsequent patient safety concerns. During case inclusion, it was overlooked that the frail patients in this study exhibited higher ASA grades. Future research may explore similar comparisons among patients within the same ASA grade.

This study also evaluated the hemodynamic stability after ciprofol induction. Hypotension frequently occurs during and after anesthetic induction and can threaten patient safety.³⁹ For this reason, anesthesiologists try to minimize hemodynamic changes during and after the induction of anesthesia. Ciprofol is known to preserve the hemodynamics of a noninferior efficacy profile compared to propofol, exhibiting excellent tolerance.^{11,40} Propofol acts through GABA receptor-mediated autonomic control of the brainstem to decrease heart rate and blood pressure,⁴¹ and hemodynamics appeared to be consistently stable in the present study, indicating that the circulatory effects of ciprofol may be less than those of propofol. The absence of injection pain in the present study may be related to the fact that the lipid content of ciprofol is lower than that of propofol and the triglyceride solvent has a medium to long chain, with a lower concentration of free drug in the aqueous phase.⁴²

The present study has some limitations. First, this study only explored the ED₅₀ of ciprofol for the loss of consciousness in elderly non-frail and frail patients, and did not conduct a randomized controlled trial based on age stratification to explore the influence of different age groups on the loss of consciousness during induction with ciprofol in elderly non-frail and frail patients. In addition, when recruiting elderly frail patients, we did not stratify them based on their degree of frailty to explore the influence of degree of frailty on the loss of consciousness. Second, we used a classical up-and-down design and probit regression with a relatively small sample size. Although it is reasonable to estimate a 50% effective dose, a fixed-staircase or biased-coin up-and-down design including more samples could be appropriate to estimate a highly effective dose, such as a 95% effective dose.^{19,32} Third, the study was designed to evaluate the success or failure of loss of consciousness within 3 min after ciprofol infusion as a sole anesthetic agent. Therefore, the appropriate dose or hemodynamic stability of ciprofol when administered in combination with other anesthetic agents, such as opioids and neuromuscular blockers, was not evaluated.

Conclusions

We have shown that the ED₅₀ of ciprofol-induced loss of consciousness for anesthesia induction was 0.267 mg/kg (95% CI 0.250–0.284) in elderly non-frail patients and 0.263 mg/kg (95% CI 0.244–0.281) in elderly frail patients, respectively, no significant differences were found between the two groups. Frailty among elderly patients does not exert

a notable impact on the median effective dose of ciprofol for anesthesia induction. Consequently, our findings suggest that anesthesiologists may forego the necessity of dosage adjustments when administering ciprofol for anesthesia induction in elderly frail patients. This underscores the robust and consistent efficacy of ciprofol across varying frailty statuses within the elderly population, providing valuable insights for clinical practice.

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 corresponding author on reasonable request.

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Disclosure

The authors declare no conflicts of interest in this work.

References

1. Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. *Anesthesiology*. 1999;90(6):1502–1516. doi:10.1097/0000542-199906000-00003
2. Li X, Yang D, Li Q, et al. Safety, pharmacokinetics, and pharmacodynamics of a single bolus of the γ -aminobutyric acid (GABA) receptor potentiator HSK3486 in healthy Chinese elderly and non-elderly. *Front Pharmacol*. 2021;12:735700. doi:10.3389/fphar.2021.735700
3. Gottesman D, McIsaac DI. Frailty and emergency surgery: identification and evidence-based care for vulnerable older adults. *Anaesthesia*. 2022;77(12):1430–1438. doi:10.1111/anae.15860
4. Ching S, Purdon PL, Vijayan S, Kopell NJ, Brown EN. A neurophysiological-metabolic model for burst suppression. *Proc Natl Acad Sci U S A*. 2012;109(8):3095–3100. doi:10.1073/pnas.1121461109
5. Protasi F, Pietrangelo L, Boncompagni S. Improper remodeling of organelles deputed to Ca²⁺ handling and aerobic ATP production underlies muscle dysfunction in ageing. *Int J Mol Sci*. 2021;22(12):6195. doi:10.3390/ijms22126195
6. Kreuzer M, Butovas S, García PS, et al. Propofol affects cortico-hippocampal interactions via β 3 subunit-containing GABA(A) receptors. *Int J Mol Sci*. 2020;21(16). doi:10.3390/ijms21165844.
7. Sahinovic MM, Struys M, Absalom AR. Clinical pharmacokinetics and pharmacodynamics of propofol. *Clin Pharmacokinet*. 2018;57(12):1539–1558. doi:10.1007/s40262-018-0672-3
8. Farhan M, Hoda MQ, Ullah H. Prevention of hypotension associated with the induction dose of propofol: a randomized controlled trial comparing equipotent doses of phenylephrine and ephedrine. *J Anaesthesiol Clin Pharmacol*. 2015;31(4):526–530. doi:10.4103/0970-9185.169083
9. Phillips AT, Deiner S, Mo Lin H, Andreopoulos E, Silverstein J, Levin MA. Propofol use in the elderly population: prevalence of overdose and association with 30-day mortality. *Clin Ther*. 2015;37(12):2676–2685. doi:10.1016/j.clinthera.2015.10.005
10. Tan CH, Onsiang MK. Pain on injection of propofol. *Anaesthesia*. 1998;53(5):468–476. doi:10.1046/j.1365-2044.1998.00405.x
11. Liang P, Dai M, Wang X, et al. Efficacy and safety of ciprofol vs. propofol for the induction and maintenance of general anaesthesia: a multicentre, single-blind, randomised, parallel-group, Phase 3 clinical trial. *Eur J Anaesthesiol*. 2023;40(6):399–406. doi:10.1097/EJA.0000000000001799
12. Liu Y, Yu X, Zhu D, et al. Safety and efficacy of ciprofol vs. propofol for sedation in intensive care unit patients with mechanical ventilation: a multi-center, open label, randomized, Phase 2 trial. *Chin Med J*. 2022;135(9):1043–1051. doi:10.1097/CM9.0000000000001912
13. Chen X, Guo P, Yang L, Liu Z, Yu D. Comparison and clinical value of ciprofol and propofol in intraoperative adverse reactions, operation, resuscitation, and satisfaction of patients under painless gastroenteroscopy anesthesia. *Contrast Media Mol Imaging*. 2022;2022:9541060. doi:10.1155/2022/9541060
14. Liu Y, Peng Z, Liu S, et al. Efficacy and safety of ciprofol sedation in ICU patients undergoing mechanical ventilation: a multicenter, single-blind, randomized, noninferiority trial. *Crit Care Med*. 2023;51(10):1318–1327. doi:10.1097/CCM.0000000000005920
15. World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191–2194. doi:10.1001/jama.2013.281053
16. Liang YD, Zhang YN, Li YM, et al. Identification of frailty and its risk factors in elderly hospitalized patients from different wards: a cross-sectional study in China. *Clin Interv Aging*. 2019;14:2249–2259. doi:10.2147/CIA.S225149
17. Chou YC, Tsou HH, Chan DD, et al. Validation of clinical frailty scale in Chinese translation. *BMC Geriatr*. 2022;22(1):604. doi:10.1186/s12877-022-03287-x
18. Dixon WJ. Staircase bioassay: the up-and-down method. *Neurosci Biobehav Rev*. 1991;15(1):47–50. doi:10.1016/S0149-7634(05)80090-9
19. Pace NL, Stylianou MP, Wartier DC. Advances in and limitations of up-and-down methodology: a précis of clinical use, study design, and dose estimation in anesthesia research. *Anesthesiology*. 2007;107(1):144–152. doi:10.1097/01.anes.0000267514.42592.2a

20. Dodds C. Anaesthetic drugs in the elderly. *Pharmacol Ther.* 1995;66(2):369–386. doi:10.1016/0163-7258(94)00070-J
21. Chen WT, Chou KH, Liu LK, et al. Reduced cerebellar gray matter is a neural signature of physical frailty. *Hum Brain Mapp.* 2015;36(9):3666–3676. doi:10.1002/hbm.22870
22. Beishon L, Clough RH, Kadicheeni M, et al. Vascular and haemodynamic issues of brain ageing. *Pflugers Arch.* 2021;473(5):735–751. doi:10.1007/s00424-020-02508-9
23. Kruijt Spanjer MR, Bakker NA, Absalom AR. Pharmacology in the elderly and newer anaesthesia drugs. *Best Pract Res Clin Anaesthesiol.* 2011;25(3):355–365. doi:10.1016/j.bpa.2011.06.002
24. Caspary DM, Hughes LF, Ling LL. Age-related GABAA receptor changes in rat auditory cortex. *Neurobiol Aging.* 2013;34(5):1486–1496. doi:10.1016/j.neurobiolaging.2012.11.009
25. Taylor JA, Greenhaff PL, Bartlett DB, Jackson TA, Duggal NA, Lord JM. Multisystem physiological perspective of human frailty and its modulation by physical activity. *Physiol Rev.* 2023;103(2):1137–1191. doi:10.1152/physrev.00037.2021
26. Kanto J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. *Clin Pharmacokinet.* 1989;17(5):308–326. doi:10.2165/00003088-198917050-00002
27. Coetzee E, Absalom AR. Pharmacokinetic and pharmacodynamic changes in the elderly: impact on anesthetics. *Anesthesiol Clin.* 2023;41(3):549–565. doi:10.1016/j.anclin.2023.02.006
28. Quan X, Yi J, Ye TH, et al. Propofol and memory: a study using a process dissociation procedure and functional magnetic resonance imaging. *Anaesthesia.* 2013;68(4):391–399. doi:10.1111/anae.12147
29. Naguib M, Sari-Kouzel A, Seraj M, el-Gammal M, Gomma M. Induction dose-responses studies with propofol and thiopentone. *Br J Anaesth.* 1992;68(3):308–310. doi:10.1093/bja/68.3.308
30. Ding YY, Long YQ, Yang HT, Zhuang K, Ji FH, Peng K. Efficacy and safety of ciprofol for general anaesthesia induction in elderly patients undergoing major noncardiac surgery: a randomised controlled pilot trial. *Eur J Anaesthesiol.* 2022;39(12):960–963. doi:10.1097/EJA.0000000000001759
31. Gorges M, Zhou G, Brant R, Ansermino JM. Sequential allocation trial design in anesthesia: an introduction to methods, modeling, and clinical applications. *Paediatr Anaesth.* 2017;27(3):240–247. doi:10.1111/pan.13088
32. Oron AP, Souter MJ, Flournoy N. Understanding research methods: up-and-down designs for dose-finding. *Anesthesiology.* 2022;137(2):137–150. doi:10.1097/ALN.0000000000004282
33. Choi JY, Kim KI, Choi Y, et al. Comparison of multidimensional frailty score, grip strength, and gait speed in older surgical patients. *J Cachexia Sarcopenia Muscle.* 2020;11(2):432–440. doi:10.1002/jcsm.12509
34. Varley PR, Buchanan D, Bilderback A, et al. Association of routine preoperative frailty assessment with 1-year postoperative mortality. *JAMA Surg.* 2023;158(5):475–483. doi:10.1001/jamasurg.2022.8341
35. Kopp VJ. Use of the American society of anesthesiologists physical status classification system in research. *Anesth Analg.* 2013;117(3):752. doi:10.1213/ANE.0b013e31829ec1bc
36. AmericanSocietyofAnesthesiologists. Statement on ASA physical status classification system. [EB/OL]. <http://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system>. Accessed March 27, 2024).
37. Mayhew D, Mendonca V, Murthy BVS. A review of ASA physical status - historical perspectives and modern developments. *Anaesthesia.* 2019;74(3):373–379. doi:10.1111/anae.14569
38. Horvath B, Kloesel B, Todd MM, Cole DJ, Prielipp RC. The evolution, current value, and future of the American society of anesthesiologists physical status classification system. *Anesthesiology.* 2021;135(5):904–919. doi:10.1097/ALN.0000000000003947
39. Aissaoui Y, Jozwiak M, Bahi M, et al. Prediction of post-induction hypotension by point-of-care echocardiography: a prospective observational study. *Anaesth Crit Care Pain Med.* 2022;41(4):101090. doi:10.1016/j.accpm.2022.101090
40. Lan H, Shan W, Wu Y, et al. Efficacy and safety of ciprofol for sedation/anesthesia in patients undergoing hysteroscopy: a randomized, parallel-group, controlled trial. *Drug Des Devel Ther.* 2023;17:1707–1717. doi:10.2147/DDDT.S414243
41. McDougall SJ, Bailey TW, Mendelowitz D, Andresen MC. Propofol enhances both tonic and phasic inhibitory currents in second-order neurons of the solitary tract nucleus (NTS). *Neuropharmacology.* 2008;54(3):552–563. doi:10.1016/j.neuropharm.2007.11.001
42. Zhong J, Zhang J, Fan Y, et al. Efficacy and safety of ciprofol for procedural sedation and anesthesia in non-operating room settings. *J Clin Anesth.* 2023;85:111047. doi:10.1016/j.jclinane.2022.111047

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