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ORIGINAL ARTICLE

# Clinical effect of different doses of ciprofol for induction of general anesthesia in elderly patients: A randomized, controlled trial

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## Abstract

Ciprofol is a newly developed intravenous anesthetic agent with improved pharmacokinetic properties. Compared to propofol, ciprofol exhibits stronger binding to the GABAA receptor and elicits a greater enhancement of GABAA receptor-mediated neuronal currents in vitro. The aims of the present clinical trials were to examine the safety and efficacy of different doses of ciprofol for induction of general anesthesia in elderly patients. A total of 105 elderly patients undergoing elective surgery were randomized, in a 1:1:1 ratio, to receive one of three sedation regimens: (1) the C1 group (0.2 mg/kg ciprofol), (2) the C2 group (0.3 mg/kg ciprofol), (3) the C3 group (0.4 mg/kg ciprofol). The primary outcome was the incidence of various adverse events, including hypotension, hypertension, bradycardia, tachycardia, hypoxemia, and injection pain. The secondary outcomes of efficacy were the success rate of general anesthesia induction, the time to anesthesia induction, and the frequency of remedial sedation was recorded in each group. Adverse events occurred in 13 patients (37%) in group C1, 8 patients (22%) in group C2, and 24 patients (68%) in group C3. Compared with group C2, the total incidence of adverse events was significantly higher in group C1 and group C3 ($p < .001$).The success rate of general anesthesia induction in the three groups was 100%. Compared with group C1, the frequency of remedial sedation was significantly lower in group C2 and group C3. The outcomes demonstrated that ciprofol at a dose of 0.3 mg/kg has good safety and efficacy in the induction of general anesthesia in elderly patients. Overall, ciprofol is a new and viable option for the induction of general anesthesia in elderly patients undergoing elective surgery.

**KEYWORDS**
ciprofol, different doses, elderly patients, hemodynamics, induction of general anesthesia

## 1 | INTRODUCTION AND BACKGROUND

Life expectancy is increasing, leading to widespread population aging. Elderly people have different degrees of multiorgan degenerative changes, which are often combined with hypertension, diabetes mellitus, and other underlying diseases. In these patients, it becomes difficult to avoid injurious stimuli during the perioperative period of surgical treatment.[1] One such example of an injurious stimulus is endotracheal intubation during induction of anesthesia, which can cause huge fluctuations in hemodynamics and even induce serious cardiovascular and cerebrovascular accidents, which threaten the safety of patients. Therefore, the level of inhibition of adverse reactions during endotracheal intubation is a common clinical indicator used to evaluate intravenous anesthetic induction.[2,3]

Ciprofol is a novel intravenous anesthetic with obvious sedative effects, with a potency that is four to five times that of propofol. Clinical studies have proven that ciprofol can be safely used for sedation in gastrointestinal endoscopy and induction of general anesthesia.[4,5] However, different doses of ciprofol have different effects on elderly patients. In this study, we analyzed the effects of different doses of ciprofol on hemodynamics and the adverse events induced by general anesthesia in elderly patients to provide a reference for the optimal dose of ciprofol that can effectively suppress the intubation response with few side effects.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and patient selection

This study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[6] The trial was conducted in accordance with the Declaration of Helsinki and the Chinese Clinical Trial Specification, and is registered in the Chinese Clinical Trial Registry (www.chictr.org.cn, registration number: ChiCTR2200062838). The study was approved by the medical ethics committee of Lishui People's Hospital (approval no. LLW-FO-403), and all enrolled patients provided written informed consent.

Overall, 105 elderly patients who were admitted to Lishui People's Hospital for elective surgery from December 2021 to March 2022 were selected for the study. The inclusion criteria were as follows: (i) aged 65–85 years; (ii) American Society of Anesthesiologists (ASA) grade I–II; and (iii) patients and their families were aware of the purpose of the study and voluntarily provided written informed consent. The exclusion criteria were as follows: (i) previous adverse reaction to anesthesia, such as the anesthetic allergy or a family history of malignant hyperthermia; (ii) bradycardia or other serious cardiovascular diseases; (iii) serious injuries or disorders of important organs, such as the lung, brain, liver, or kidney; (iv) serious psychiatric diseases; and (v) a history of drug addiction or other drug abuse.

### 2.2 | Randomization and grouping

Patients were randomly divided into three groups (group C1, group C2, and group C3) by computer-generated randomization, with 35 patients in each group. Randomization was done by an external statistician. The investigators were clearly know the situation of experimental groups, except for patients.

### 2.3 | Anesthesia induction and maintenance

Patients in each of the three groups were routinely administered 10 mL/kg/h lactated Ringer's solution in an open hand vein upon admission, and the mean arterial pressure (MAP), electrocardiogram, pulse oxygen saturation ($SpO_2$), and bispectral index (BIS) value (ConView YY-106, Pearl Care) were continuously monitored with a multifunctional monitor. After the monitoring was completed, all patients underwent radial artery puncture and catheterization under local anesthesia to monitor the real-time invasive arterial blood pressure, and efforts were made to relieve any nervousness. After lying down for 10 min, anesthesia was induced after the patient was quiet and the vital signs were stable. All patients underwent nitrogen removal and were given oxygen for 3 min (flow rate of 5 L/min), and 0.4 μg/kg sufentanil (Hubei, Yichang Humanwell Pharmaceutical Co., Ltd.) was administered by slow intravenous infusion. After 2 min, patients in group C1, group C2, and group C3 were slowly injected with 0.2, 0.3, and 0.4 mg/kg ciprofol (Liaoning HISCO Pharmaceutical Co., Ltd.), respectively, for 30 s. A dose of 0.2 mg/kg cis-atracurium (Jiangsu Hengrui Pharmaceutical Co., Ltd.) was then administered. After all of the drugs had been injected after approximately 2–3 min, muscle relaxation was achieved and tracheal intubation was performed. Endotracheal intubation was required to be successful in one attempt. After successful intubation, mechanical ventilation was connected to the anesthesia machine, and respiratory parameters were adjusted. Continuous inhalation of 1.5% sevoflurane (Shanghai Hengrui Pharmaceutical Co., Ltd.) was administered to maintain anesthesia. During induction of anesthesia, if the BIS value continued to be greater than 60, 0.1 mg/kg ciprofol was administered each time for remedial sedation. The duration of administration was 10 s, and each additional interval was >1 min until the BIS value stabilized below 60.

The following evaluation time points were defined: T0: Admission (basal); T1: Before endotracheal intubation; T2: 10 s after endotracheal intubation; T3: 3 min after endotracheal intubation; T4: 5 min after endotracheal intubation.

### 2.4 | Primary outcomes

The primary outcomes of this study were the incidence of various adverse events, including hypotension, hypertension, bradycardia, tachycardia, hypoxemia, and injection pain. These events were

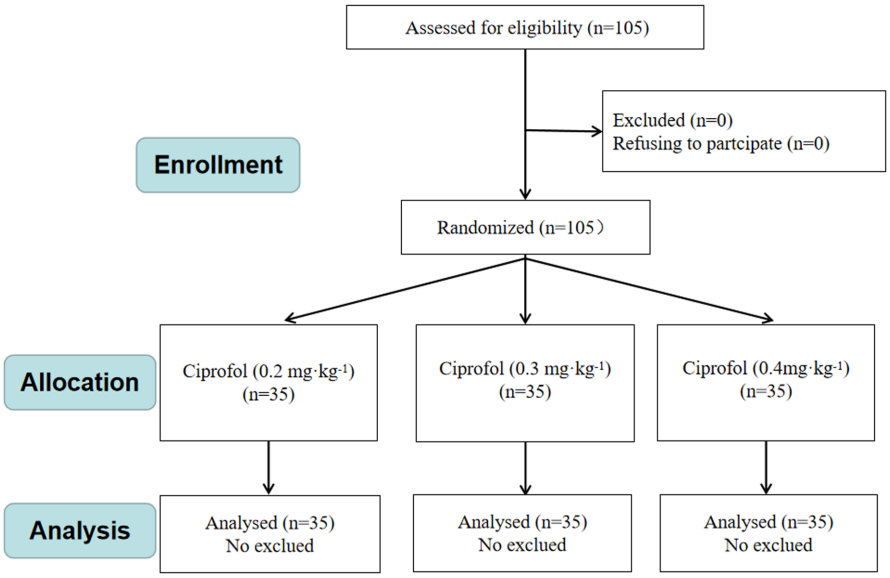


**FIGURE 1** Flow diagram of patient enrollment, allocation, and analysis.

treated by intravenous injection of ephedrine, urapidil, or atropine, or by mask ventilation.

The adverse events were defined as follows[7–10]: Hypotension: MAP of <60 mm Hg or a decrease of<30% from baseline; hypertension: MAP of >120 mm Hg or an increase of >30% from baseline; bradycardia: Heart rate (HR) of <55 bpm; tachycardia: HR of >100 bpm; hypoxemia: $SpO_2$ of <90%; injection pain[10]: The incidence of injection site pain as detected by a withdrawal response or a numeric rating scale value ≥3, subjects were asked "Do you feel pain in the hand where the drug was injected?" during the injection. If the answer was "yes," subjects were asked to describe the intensity of the pain (0–10 points indicated "no pain" to "unbearable pain"). Evaluation was performed at least once during the study drug injection until the successful induction.

## 2.5 | Secondary outcomes

One of the secondary outcomes was the success rate of induction of general anesthesia, which was defined according to the following criteria: BIS value of ≤60 after administration of a study drug (up to two top-up doses given) or no requirement for an alternative sedative. The time to successful induction of anesthesia (the time from the end of the injection of sedative drug to a BIS value of ≤60) and the frequency of remedial sedation were recorded in each group. As other secondary outcomes, hemodynamics (including MAP and HR) and BIS values were measured at five different time points: T0, T1, T2, T3, and T4.

## 2.6 | Sample size and statistical analysis

A total of 60 patients were enrolled and finished the pre-experiment. The patients were randomly divided into three groups: group C1 ($n = 20$), group C2 ($n = 20$), and group C3 ($n = 20$). The results of our small-sample pre-experiment indicated a clinically significant difference in the incidence of adverse events between the three groups (group C1: 30%, group C2: 15%, group C3: 60%). Assuming the significance level was 0.05 ($\alpha = 0.05$) and a power of 80% ($\beta = 0.20$), PASS 15 software was used to calculate the total sample size of the three groups, $N = 95$ cases. Given a 10% attrition rate, the total sample size should be 105, we required a minimum of 35 patients in each group.

SPSS 20.0 statistical software (IBM Corp.,) was used for data processing and analysis. The normality test in SPSS was used to determine whether the data conformed to a normal distribution. Normally distributed continuous variables are expressed as the mean ± standard deviation. If the assumption of homogeneity of variance was satisfied, the analysis of variance was used for comparisons between groups, and the least significant difference test was used for pairwise comparisons. If the assumption of homogeneity of variance was not satisfied, the Welch analysis of variance and the Games–Howell test were used for pairwise comparisons between groups. The data within group were compared using the repeated measures analysis of variance. Categorical variables are expressed as frequency (percentage) and were analyzed using Pearson's chi-square test, for multiple comparisons, we did Bonferroni corrections to determine the P value significance threshold. A $p$ value of <.05 was considered statistically significant.

# 3 | RESULTS

## 3.1 | Patients' baseline demographic and clinical characteristics

A total of 105 patients were enrolled and finished the experiment. The flow diagram of the study is shown in Figure 1. The patients were randomly divided into three groups: Group C1 ($n = 35$), group C2 ($n = 35$), and group C3 ($n = 35$).

**TABLE 1** Demographic characteristics of the three groups.

| | Group C1 ($n = 35$) | Group C2 ($n = 35$) | Group C3 ($n = 35$) | Statistic | $p$-value |
|---|---|---|---|---|---|
| Age (years) | 73 ± 5.4 | 72 ± 5.4 | 72 ± 4.4 | .489 | .614 |
| Height (cm) | 161 ± 7.3 | 161 ± 6.9 | 163 ± 6.9 | .608 | .546 |
| Weight (kg) | 61.4 ± 7.9 | 62.9 ± 8.6 | 63.8 ± 8.8 | .722 | .488 |
| Sex(male/female) (n) | 19/16 | 20/15 | 22/13 | .548 | .827 |
| ASA status(I/II) (n) | 10/25 | 14/21 | 9/26 | 1.856 | .502 |

*Note*: Data are presented as the mean ± standard deviation or n. Data of frequency (percentage) are analyzed using Pearson's chi-square test. The other data are analyzed using the analysis of variance was used for comparisons between groups, and the least significant difference test was used for pairwise comparisons. There were no significant differences in demographics among the three groups.Abbreviation: ASA, American Society of Anesthesiologists.

**TABLE 2** Comparison of adverse reactions among the three groups.

| Adverse events | Group C1 ($n = 35$) | Group C2 ($n = 35$) | Group C3 ($n = 35$) | Statistic | $p$-value |
|---|---|---|---|---|---|
| Hypotension | 4 (11) | 8 (22) | 20 (57)[ab] | 18.699 | <.001 |
| Hypertension | 6 (17) | 0 (0)[a] | 0 (0)[a] | 9.953 | .003 |
| Bradycardia | 6 (17) | 6 (17) | 16 (45)[ab] | 9.740 | .008 |
| Tachycardia | 6 (17) | 0 (0)[a] | 0 (0)[a] | 9.953 | .003 |
| Hypoxemia | 0 (0) | 1 (2) | 4 (11) | 4.428 | .124 |
| Injection pains | 0 (0) | 0 (0) | 0 (0) | - | - |
| Total incidence of adverse events | 13 (37) | 8 (22) | 24 (68)[ab] | 15.633 | <.001 |

*Note*: Values are presented as *n* (%). Data are analyzed using Pearson's chi-square test, for multiple comparisons, we did Bonferroni corrections to determine the $p$ value significance threshold.

[a]$p < .05$ compared with group C1.

[b]$p < .05$ compared with group C2.

The demographic and surgical characteristics of the patients are shown in Table 1. There were no statistically significant differences in ASA grade, sex, age, height, or weight among the three groups (all $p > .05$).

## 3.2 | Primary outcomes

### 3.2.1 | Adverse events

Adverse events occurred in 13 patients (37%) in group C1, 8 patients (22%) in group C2, and 24 patients (68%) in group C3. Compared with group C2, the total incidence of adverse events was significantly higher in group C1 and group C3 ($p < .001$). Compared with group C3, the incidence of hypotension and bradycardia was significantly lower in group C1 and group C2 ($p < .05$). Compared with group C1, the incidence of tachycardia was significantly lower in group C2 and group C3 ($p < .05$). No cases of injection pain occurred in any of the three groups, and the incidence of hypertension and hypoxemia was not significantly different between the three groups ($p > .05$) (Table 2).

## 3.3 | Secondary outcomes

### 3.3.1 | Success rate of general anesthesia induction and sedation

The success rate of general anesthesia induction in the three groups was 100%. Compared with group C1, the frequency of remedial sedation was significantly lower in group C2 and group C3. There was no statistically significant difference in the time to anesthesia induction among the three groups ($p > .05$) (Table 3).

### 3.3.2 | Changes in hemodynamics and BIS values

Compared with T0, the MAP and BIS values at T1–T4 were reduced in all three groups ($p < .05$). The HR in group C1 significantly decreased after induction of general anesthesia and significantly increased after tracheal intubation ($p < 0.05$), indicating an insufficient depth of anesthesia (Tables 4–6). Compared with group C1 and group C3, group C2 showed less fluctuation in MAP and HR (Figures 2 and 3). The BIS value of all patients stabilized below 60 after induction of

**TABLE 3** Comparison of the success rate of general anesthesia induction and sedation.

| | GroupC1 ($n = 35$) | GroupC2 ($n = 35$) | GroupC3 ($n = 35$) | Statistic | $p$-value |
|---|---|---|---|---|---|
| The success rate of induction of general anesthesia | 35 (100) | 35 (100) | 35 (100) | - | - |
| The times to anesthesia induction success (s) | 45 ± 3.5 | 45 ± 3.1 | 45 ± 3.5 | .051 | .950 |
| Remedial sedation ($n$) | 8 (22) | 0 (0)[a] | 0 (0)[a] | 14.379 | <.001 |

*Note*: Data are presented as the mean ± standard deviation or n (%). Data of frequency (percentage) are analyzed using Pearson's chi-square test, for multiple comparisons, we did Bonferroni corrections to determine the $p$ value significance threshold. The other data are analyzed using the analysis of variance was used for comparisons between groups, and the least significant difference test was used for pairwise comparisons.

[a]$p < .05$ compared with group C1.

**TABLE 4** Comparison of MAP at each time point among the three groups.

| | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|
| Group C1 ($n = 35$) | 102 ± 10.6 | 84 ± 9.7[a] | 103 ± 13.5[b] | 87 ± 7.7[a] | 87 ± 9.7[a] |
| Group C2 ($n = 35$) | 101 ± 11.2 | 81 ± 13.0[a] | 88 ± 12.1[ab] | 84 ± 10.3[a] | 82 ± 11.0[a] |
| Group C3 ($n = 35$) | 101 ± 10.6 | 69 ± 12.8[ab] | 75 ± 9.8[ab] | 73 ± 8.0[ab] | 71 ± 7.8[ab] |
| Statistic | .224 | 16.179 | 47.927 | 23.472 | 25.170 |
| $p$-value | .799 | <.001 | <.001 | <.001 | <.001 |

*Note*: Data are presented as the mean ± standard deviation (mm Hg). Data are analyzed using the analysis of variance was used for comparisons between groups, and the least significant difference test was used for pairwise comparisons. If the assumption of homogeneity of variance was not satisfied, the Welch analysis of variance and the Games–Howell test were used for pairwise comparisons between groups. The data within group were compared using the repeated measures analysis of variance.Each time point is defined as follows: T0: Admission (basal); T1: Before endotracheal intubation; T2: 10 s after endotracheal intubation; T3: 3 min after endotracheal intubation; T4: 5 min after endotracheal intubation.

Abbreviations: MAP, mean arterial pressure.

[a]$p < .05$ compared with T0.

[b]$p < .05$ compared with group C1.

**TABLE 5** Comparison of HR at each time point among the three groups.

| | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|
| Group C1 ($n = 35$) | 72 ± 7.1 | 66 ± 9.8[a] | 84 ± 10.4[a] | 70 ± 10.5 | 70 ± 10.0 |
| Group C2 ($n = 35$) | 71 ± 6.6 | 62 ± 6.2[a] | 72 ± 6.5[b] | 67 ± 5.5 | 70 ± 6.7 |
| Group C3 ($n = 35$) | 71 ± 6.2 | 58 ± 6.5[ab] | 70 ± 12.6[b] | 62 ± 6.6[ab] | 60 ± 5.2[ab] |
| Statistic | .831 | 9.422 | 19.383 | 10.613 | 25.444 |
| $p$-value | .439 | <.001 | <.001 | <.001 | <.001 |

*Note*: Data are presented as the mean ± standard deviation (bpm). Data were analyzed using the analysis of variance for comparisons between groups, and the least significant difference test was used for pairwise comparisons. If the assumption of homogeneity of variance was not satisfied, the Welch analysis of variance and the Games–Howell test were used for pairwise comparisons between groups. The data within group were compared using the repeated measures analysis of variance.Each time point is defined as follows: T0: Admission (basal); T1: Before endotracheal intubation; T2: 10 s after endotracheal intubation; T3: 3 min after endotracheal intubation; T4: 5 min after endotracheal intubation.

Abbreviation: HR, heart rate.

[a]$p < .05$ compared with T0.

[b]$p < .05$ compared with group C1.

anesthesia, and there were no statistically significant differences in BIS values at T0–T4 among the three groups ($p > .05$) (Figure 4).

## 4 | DISCUSSION

Many elderly patients have poor cardiac reserve and often have a variety of chronic diseases. Various stimuli during the perioperative period can lead to severe fluctuations in hemodynamics. Adverse cardiovascular events can be triggered during the induction of general anesthesia, such as hypotension, hypertension, bradycardia, and arrhythmia.[11,12] As one of the strongest stimuli during the induction of general anesthesia, the stimulation intensity of endotracheal intubation is approximately 1.5 times that of a skin incision. The stress reaction caused by endotracheal intubation can increase blood pressure, HR, and myocardial oxygen consumption.

**TABLE 6** Comparison of BIS values at each time point among the three groups.

| | T0 | T1 | T2 | T3 | T4 |
|---|---|---|---|---|---|
| Group C1 ($n = 35$) | 92 ± 2.7 | 47 ± 4.0[a] | 46 ± 5.0[a] | 45 ± 3.2[a] | 48 ± 3.8[a] |
| Group C2 ($n = 35$) | 93 ± 2.7 | 48 ± 3.5[a] | 46 ± 4.2[a] | 46 ± 4.4[a] | 47 ± 4.2[a] |
| Group C3 ($n = 35$) | 93 ± 3.0 | 48 ± 4.5[a] | 45 ± 5.2[a] | 47 ± 4.8[a] | 46 ± 6.5[a] |
| Statistic | 1.180 | 1.514 | .516 | 2.016 | .961 |
| *p*-value | .312 | .225 | .598 | .138 | .386 |

*Note*: Data are presented as the mean ± standard deviation. Data are analyzed using the analysis of variance for comparisons between groups, and the least significant difference test was used for pairwise comparisons. If the assumption of homogeneity of variance was not satisfied, the Welch analysis of variance and the Games–Howell test were used for pairwise comparisons between groups. The data within group were compared using the repeated-measures analysis of variance.Each time point is defined as follows: T0: Admission (basal); T1: Before endotracheal intubation; T2: 10 s after endotracheal intubation; T3: 3 min after endotracheal intubation; T4: 5 min after endotracheal intubation.

Abbreviation: BIS, bispectral index.

[a]$p < .05$ compared with T0.

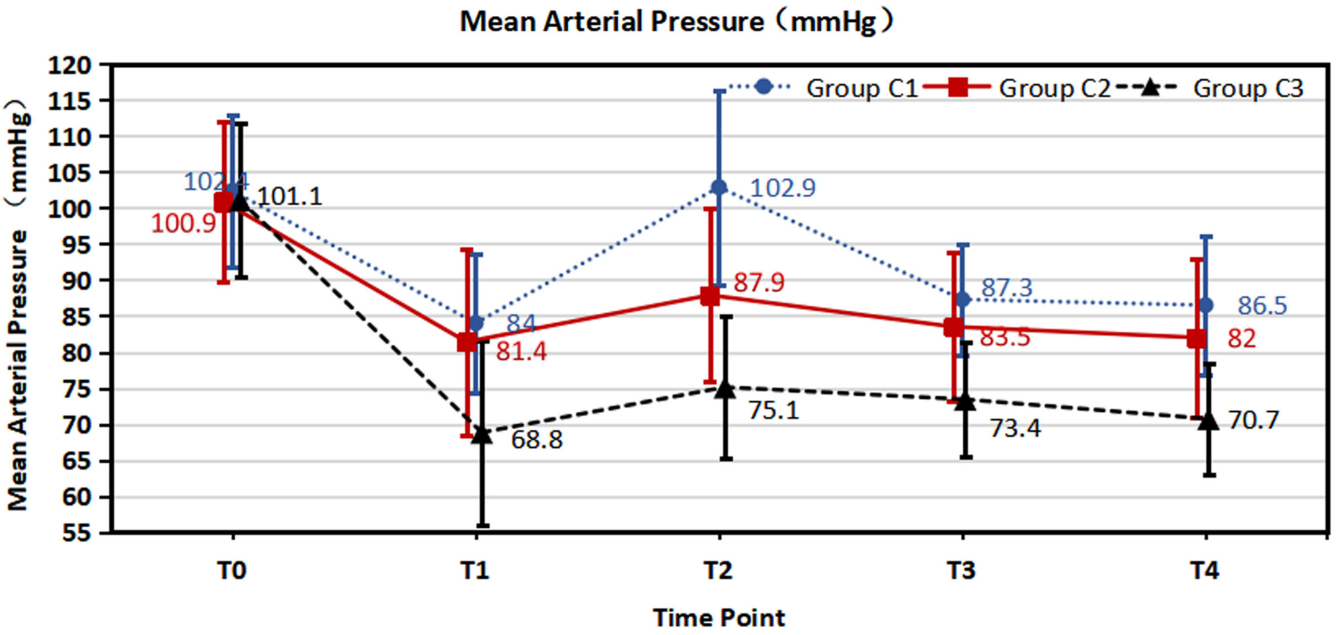


**FIGURE 2** Comparisons of mean arterial pressure (MAP) among the three groups.

It can also cause arrhythmia and serious cardiovascular diseases, such as myocardial infarction, cerebral hemorrhage, and cerebral infarction.[13] Therefore, to ensure the quality and safety of anesthesia in elderly patients, an individualized anesthesia plan should be developed, with emphasis on ensuring hemodynamic stability and selecting an appropriate general anesthesia induction protocol for elderly patients.

Ideally, an appropriate depth of anesthesia should be maintained while minimizing interference of physiological function. The BIS is the most widely used clinical index of anesthetic depth, and its accuracy is widely recognized.[14,15] The BIS can determine the effectiveness of general anesthetic drugs during general anesthesia by dynamically monitoring the cortical functional status in real time using numerical indicators. It can also be used to compare the drug onset time in induction of general anesthesia and provides an effective reference for the timing of tracheal intubation.[16]

Ciprofol is an isomer or small molecule substance with an (R) configuration. It is a short-acting gamma-aminobutyric acid (GABA) receptor agonist, and its mechanism is to increase the internal flow of chloride ions mediated by GABA receptor to produce sedative and anesthetic effects. Ciprofol has the characteristics of rapid onset and recovery, high potency, and minimal injection pain. At present, it can be safely used to induce general anesthesia.[17] However, no studies have examined the efficacy and safety of ciprofol for the induction of general anesthesia in elderly patients. This study aimed to investigate the appropriate dose of ciprofol for sedation during the induction of general anesthesia in elderly patients, which effectively suppresses noxious stimuli without causing great hemodynamic fluctuations.

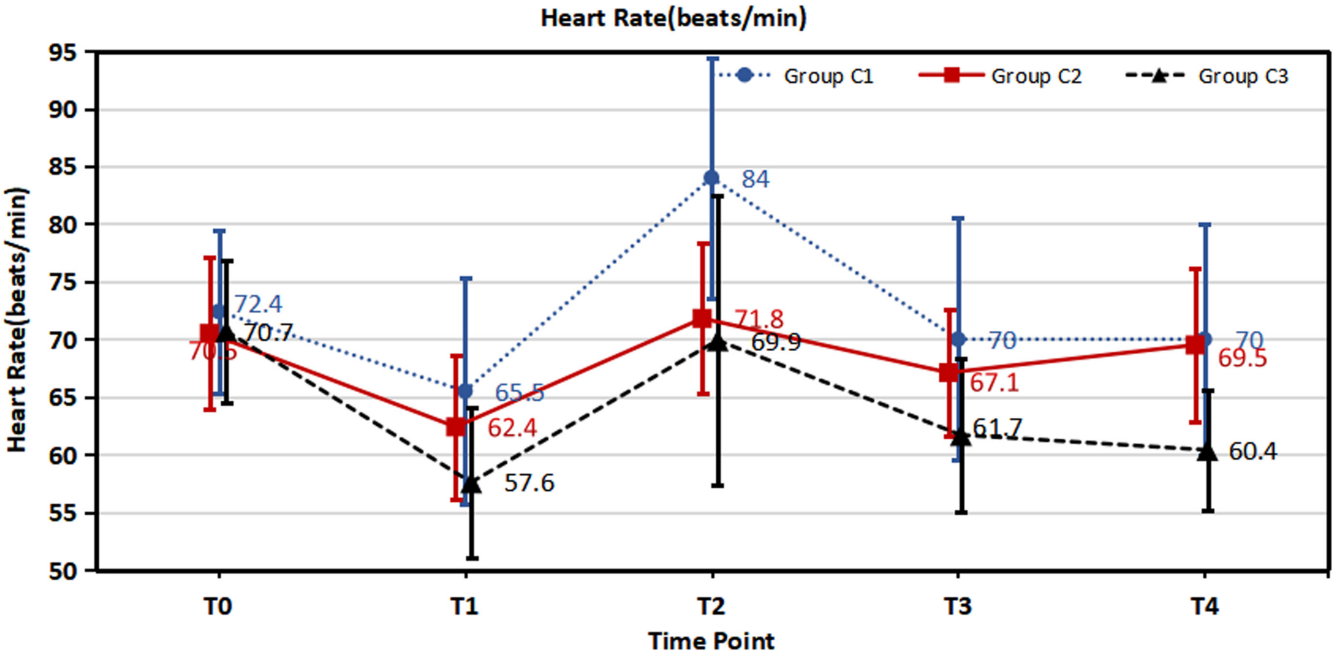


FIGURE 3 Comparisons of heart rate among the three groups.

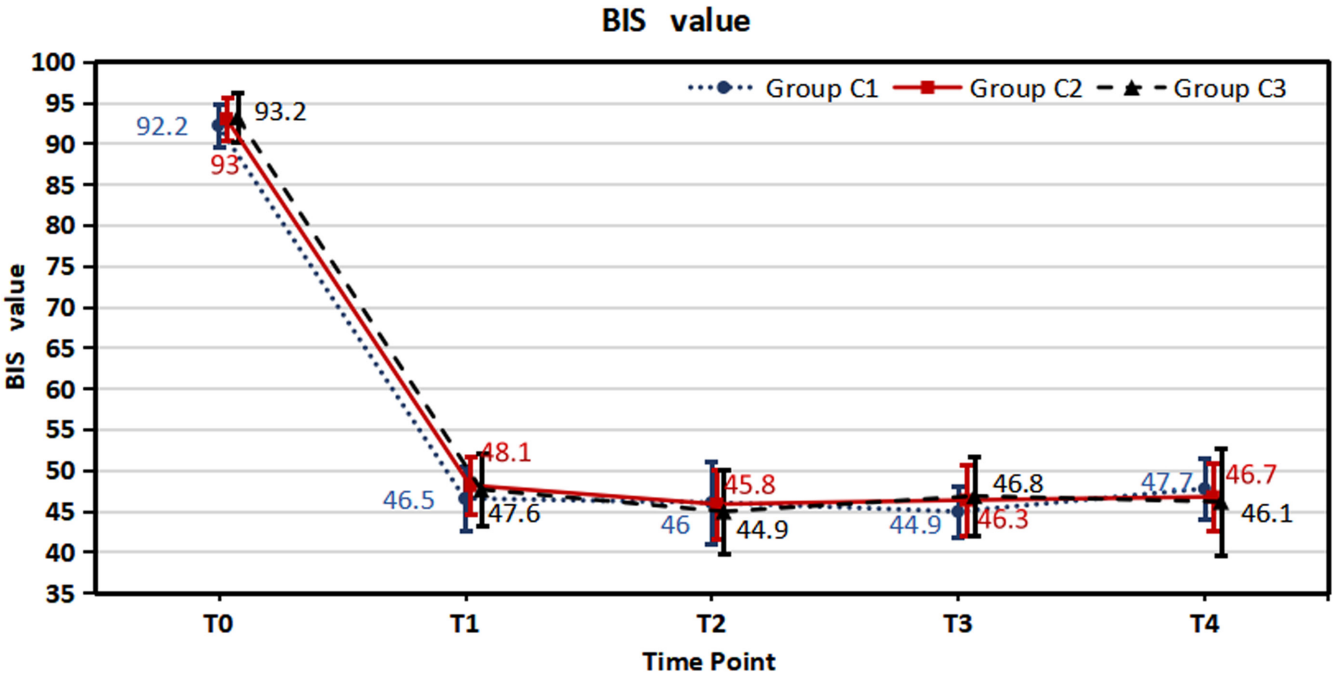


FIGURE 4 Comparisons of BIS values among the three groups.

In this study, on the basis of the results of Teng et al.,[18,19] the selected doses of ciprofol were 0.2, 0.3, and 0.4 mg/kg. After the injection of sufentanil and ciprofol, the time to reach its peak in the blood concentration are 3–5 min and 2–3 min, respectively.[20,21] Thus, sufentanil is administered first, after 2 min, followed by ciprofol and cis-atracurium. After all of the drugs had been injected after approximately 3 min, the time point which is the best time for tracheal intubation.[22] This maximizes the inhibitory reaction of tracheal intubation.

The ideal level of post-induction sedation was also assessed by comparing patients' hemodynamic status and BIS value alterations in response to the induction of general anesthesia and endotracheal intubation. The results show that all patients achieved successful induction of general anesthesia, but the frequency of remedial sedation in group C1 was significantly higher than in group C2 and group C3, indicating that the depth of sedation with 0.2 mg/kg ciprofol was relatively shallow. The BIS value of all patients was stably lower

than 60, and both induction of anesthesia and tracheal intubation were safely completed, indicating that ciprofol provided effective sedation during the induction of general anesthesia.

Compared with group C2, the overall incidence of adverse events was significantly higher in group C1 and group C3. Adverse cardiovascular reactions, such as hypotension and bradycardia, remain a major problem, but we observed no serious adverse events or adverse reactions in the three groups. In addition, the incidence of injection pain and hypoxemia was very low, indicating that ciprofol is comfortable for patients and leads to fewer respiratory insufficiency events. In this study, we showed that group C2 had the least pronounced hemodynamic fluctuations, also had a lower incidence of adverse events, suggesting that ciprofol at a dose of 0.3 mg/kg provides safe sedation during the induction of general anesthesia.

This study had some limitations. First, this is a small-sample, single-center clinical study; thus, the results need to be further confirmed in a larger sample with a more perfect experimental protocol. Second, sufentanil infusion may mask the adverse effect of pain caused by ciprofol injection, and it may also aggravate the occurrence of bradycardia in elderly patients. Finally, we selected surgical patients of ASA grades I–II and thus excluded patients of ASA grades greater than grade III. Moreover, we did not conduct research on patients with severe underlying diseases or frailty. Despite these limitations, this study provides exploratory data for future research.

## 5 | CONCLUSION

Ciprofol at a dose of 0.3 mg/kg has good safety and efficacy in the induction of general anesthesia in elderly patients. The incidence of adverse events is low, and the hemodynamics during induction of general anesthesia are stable. Thus, ciprofol appears to be a viable option for the induction of general anesthesia in elderly patients undergoing elective surgery. Nevertheless, this study was a single-center study, and multicenter studies are recommended to reach more robust conclusions.

### AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the design of this study, data acquisition and interpretation, statistical planning, drafting the manuscript, or revising the manuscript critically. All authors agree to be accountable for all aspects of the work and have approved the final version of the manuscript for submission.

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### CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding authors.

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