

# Efficacy and safety of different doses of ciprofol for general anesthesia induction in elderly patients undergoing hip replacement surgery: a randomized, double-blind, controlled clinical trial

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**Abstract:** Background: Ciprofol can be used for general anesthesia induction in elderly patients undergoing major noncardiac surgery. This trial aimed to compare the efficacy and safety of three more precise doses of ciprofol and explore the optimal dose for induction in elderly patients undergoing hip replacement surgery.

**Methods:** This trial was a prospective, randomized, controlled trial. One hundred and twenty elderly patients scheduled for hip replacement surgery were randomly divided into four groups for general anesthesia induction: PROP group (propofol 1.5 mg/kg), CIP1 (ciprofol 0.25 mg/kg), CIP2 (ciprofol 0.30 mg/kg), and CIP3 group (ciprofol 0.35 mg/kg). The primary outcome was the induction success rate of general anesthesia. The secondary outcomes included the induction success time, eyelash reflex disappearance time, the number of additional anesthetics required and the total dose of successful induction. The safety indicators included the incidence of adverse events such as hypotension, hypertension, tachycardia, bradycardia, hypoxemia, injection pain and body movements.

**Results:** The success rate of general anesthesia induction in the four groups were 100%. There was no statistically significant difference in the induction success time and eyelash reflex disappearance time between the CIP3 group and the PROP group. However, both of these times increased significantly in the CIP1 group and the CIP2 group, and the results showed statistically significant differences. The number of patients who required top-up doses and doses of top-up dose in the CIP1 and CIP2 groups were significantly greater than in the PROP and CIP3 groups. The total dose of successful induction in the PROP group was 4-5 times higher than that of the ciprofol groups. The incidence of hypotension in ciprofol groups was significantly lower than in the propofol group. There was no statistically significant difference in the incidence of hypertension, tachycardia and bradycardia among the four groups. The incidence of injection pain in the PROP group was 50%, whereas no injection pain was reported in three CIP groups. All subjects did not experience body movements and respiratory depres-

sion.

**Conclusions:** Ciprofol (0.25-0.35mg/kg) could be safely and effectively used for general anesthesia induction in elderly patients undergoing hip replacement surgery. The anesthetic efficacy of 0.35mg/kg ciprofol was not inferior to that of 1.5mg/kg propofol and had higher safety and comfort.

**Keywords:** Ciprofol, Elderly patients, General anesthesia induction, Hip replacement surgery

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## Introduction

The global elderly population (>65 years) is estimated to reach 1.6 billion by 2050, suggesting that an increasing number of elderly patients with multiple comorbidities will require surgery and anesthesia<sup>[1]</sup>. Elderly patients are less tolerant of anesthesia and have a higher probability of various adverse events during anesthesia, especially during induction of general anesthesia. Therefore, anesthesiologists need to adjust anesthesia drugs and techniques according to the physiological characteristics of elderly patients<sup>[2]</sup>.

Propofol is the most commonly used drug for general anesthesia induction and maintenance. Its modified form, ciprofol (HSK3486), was launched in December 2020. Based on the chemical structure of propofol, ciprofol is a 2,6-disubstituted phenol derivative. It is introduced to form a chiral structure, which increases the steric effect, enhances the affinity with its receptor gamma-aminobutyric acid-A (GABAA), and increases the potency<sup>[3,4]</sup>. Compared with propofol, ciprofol has good efficacy and safety profiles, reduces injection pain, and decreases respiratory and hemodynamic depression<sup>[5,6]</sup>. Therefore, ciprofol can be regarded as a good alternative to propofol for general anesthesia induction in elderly patients.

The research by Yun-ying Ding et al. indicated that ciprofol 0.2-0.4 mg/kg can be safely and effectively used for general anesthesia induction in non-cardiac surgeries in the elderly<sup>[7]</sup>. Another result of a clinical trial showed that the effect of 0.3mg/kg ciprofol for general anesthesia induction in the elderly patients was similar to that of 0.4mg/kg in young and middle-aged patients<sup>[8]</sup>. However, the precise dose for general anesthesia induction in elderly patients needs to be further explored. This trial aimed to compare the efficacy and safety of three more precise doses of ciprofol and propofol to explore the optimal dose for induction in elderly patients undergoing hip replacement surgery.

## Methods

### Study design and ethics

The trial was a prospective, single-center, randomized, double-blind, controlled clinical trial. This clinical trial was conducted at the General Hospital of Northern Theater Command, Shenyang, China. The study protocol was approved

by the Ethics Committee of the General Hospital of Northern Theater Command (Approval NO.2022-065). The Trial was registered at the Chinese Clinical Trials Registry (Identifier: ChiCTR2200063623) and conducted by the World Medical Congress Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was signed by all the participants included in the study.

## Participants

The patients enrolled were age  $\geq 65$  years old, regardless of gender, with American Society of Anesthesiologists (ASA) grade II–III, BMI 18–30 kg/m<sup>2</sup>, and scheduled for elective endotracheal intubation for general anesthesia undergoing hip replacement surgery. Exclusion criteria: ① Allergic to the active ingredient (s) or excipient (s) of ciprofol or propofol injection; ② Difficulty airways, modified Mallampati classification IV; ③ Pregnant, lactating or planned pregnancy within one month after operation; ④ Severe cardiovascular system, respiratory system, nervous system, liver, and kidney diseases; ⑤ Severe disturbance of consciousness or mental system diseases and cognitive dysfunction; ⑥ Long-term smokers, alcohol and drug abusers.

## Procedures

In this trial, one hundred and twenty elderly subjects were randomly divided into four groups in a ratio of 1:1:1:1, PROP group (propofol 1.5 mg/kg), CIP1 (ciprofol 0.25 mg/kg), CIP2 (ciprofol 0.30 mg/kg) and CIP3 group (ciprofol 0.35 mg/kg). The randomization coding table was prepared by SAS 9.4 software (SPSS Inc, Chicago, IL, USA) by an independent investigator who will have no contact with any participant.

Pre-operative anesthetic visits were conducted the day before the elective surgery to screen and decide on the enrolled subjects and to explain the precautions, signing the informed consent for anesthesia and the trial. On the day of surgery, ciprofol and propofol were extracted by a research nurse before the operation, and neither the investigators nor the subjects knew about the type of the drug. After the subjects were admitted to the room, standard 3-lead electrocardiography (ECG), heart rate (HR), pulse oxygen saturation (SpO<sub>2</sub>), systolic blood pressure (SBP), mean arterial pressure (MAP), diastolic blood pressure (DBP) and bispectral index (BIS) were continuously monitored and recorded every 1 min. After preoxygenation for 3 min (mask oxygen 5 L/min), intravenous 0.3 µg/min sufentanil, ciprofol or propofol (administration time 30 s) were injected in sequence.

The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores<sup>[9]</sup>, the disappearance of eyelash reflex, and the occurrence of injection pain were assessed every 30 s until the induction of anesthesia was successful. Successful induction of anesthesia was defined as MOAA/S score  $\leq 1$ . If a patient failed to be induced successfully within 1 minute of receiving the initial dose, a top-up dose (50% of the initial dose) was immediately injected (administered over 10 s less than twice). If the MOAA/S score was  $>1$  at 2 minutes

after administration of the top-up dose, induction of general anesthesia was unsuccessful, and the rescue drug(propofol) was given. After successful induction of anesthesia, rocuronium (0.6 mg/kg) was given, and endotracheal intubation was performed. Until the BIS value returned to 60, inhalation or injection of anesthetic maintenance drugs was started, time was recorded, and the experiment was completed. In the event of hypotension, phenylephrine (20–60 µg) was given through an IV. If the heart rate decreased to under 50 beats per minute, ephedrine (5–10 mg) was used instead. Further doses of phenylephrine or ephedrine could be administered after a minute if required. If the protocol did not result in the target blood pressure, norepinephrine was continuously infused at a rate specified by the attending anesthesiologists.

### **Study outcome assessments**

The primary outcome was the induction success rate of general anesthesia. The secondary outcomes include the effectiveness indicators: 1) time to successful induction of general anesthesia; 2) eyelash reflex disappearance time; 3) number of patients who required top-up doses and number of doses of top-up dose; 4) the total dose of successful induction. The safety indicators: 1) hypotension (SBP<90 mmHg, or more than 20% decrease from baseline); 2) hypertension (SBP>180 mmHg, or more than 20% increase from baseline); 3) tachycardia (HR>100 beats/min) ; 4) bradycardia (HR<60 beats/min for more than 15s); 5) Reduced oxygen saturation(SPO<sub>2</sub> <90% for more than the 30s) or respiratory depression (respiratory rate <10 breaths/min and assisted ventilation were taken); 6) injection pain; 7) body movements.

### **Statistical analysis**

All statistical analyses were done using SPSS software (version 25.0, IBM, New York, USA). Count data were described as rates, and the chi-square test was used to compare the overall differences between the four groups, and the Bonferroni corrected chi-square test was used for two-by-two comparisons between groups. Measurement information was described as mean ± standard deviation ( $\bar{x} \pm s$ ), and one-way ANOVA was used to compare the overall differences between the four groups, with two-way comparisons using the Turkey test. Differences were considered statistically significant with a P value of less than 0.05.

## **Results**

### **Patients' disposition and baseline characteristics**

A total of 171 patients were screened, of whom 120 were randomized and received CIP1(n=30), CIP2(n=30), CPI3(n=30) and PROP (n=30). Figure 1 displays the flow diagram of the study. There was no significant statistical difference in the baseline characteristics of the subjects in the four groups ( $P > 0.05$ ), as shown in **Table 1**.

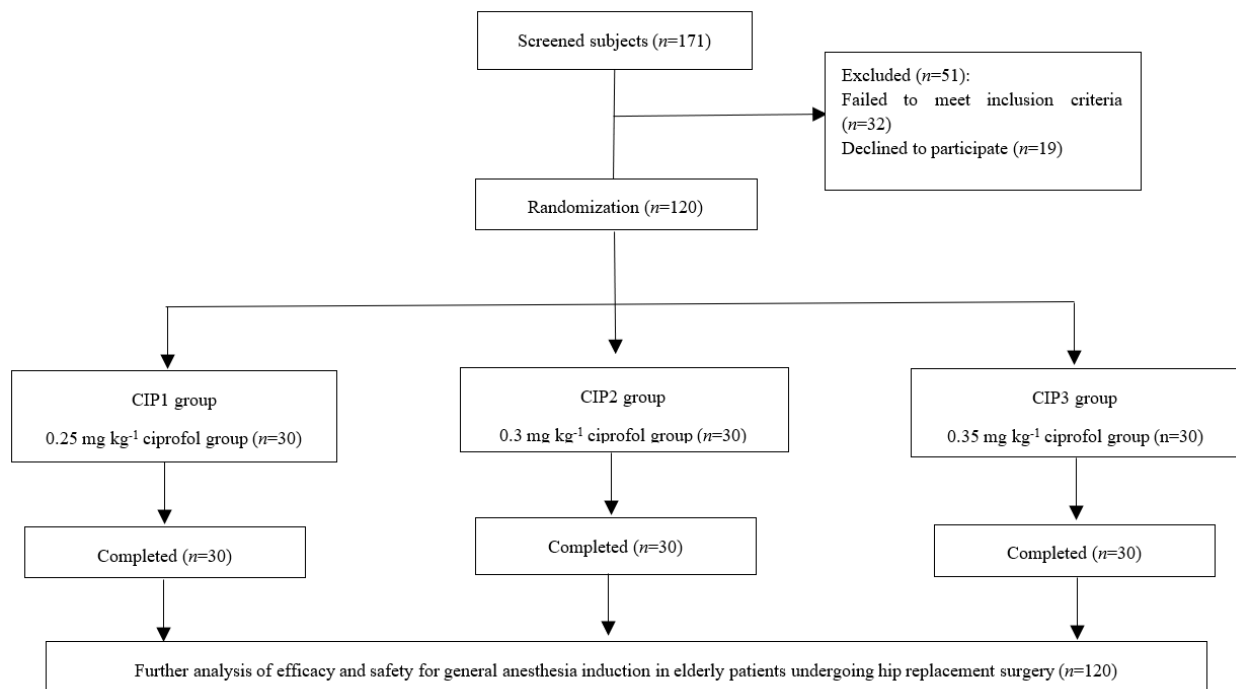


**Fig 1.** Flow diagram of the study.

**Table 1.** Patients' disposition and baseline characteristics.

| Variables                          | CIP1 group (n=30) | CIP2 group (n=30) | CIP3 group (n=30) | PROP group (n=30) |
|------------------------------------|-------------------|-------------------|-------------------|-------------------|
| Age (years)                        | 66.5±3.2          | 67.4±1.9          | 67.6±3.9          | 66.2±4.2          |
| Sex, Female                        | 12(40%)           | 14 (47%)          | 13(43%)           | 13(43%)           |
| Weight (kg)                        | 66.4 ± 9.4        | 67.1 ± 7.4        | 67.7 ± 8.3        | 66.1 ± 8.3        |
| Height (cm)                        | 164.3 ± 8.7       | 164.6 ± 7.0       | 165.2 ± 7.0       | 165.7 ± 7.5       |
| BMI (kg m <sup>-2</sup> )          | 24.2 ± 2.6        | 24.4 ± 1.8        | 24.8 ± 1.8        | 24.5 ± 2.3        |
| ASA status(II)                     | 15(50%)           | 16(53%)           | 16 (53%)          | 15 (50%)          |
| Hypertension                       | 22 (73%)          | 23 (77%)          | 25(83%)           | 23 (77%)          |
| Diabetes                           | 12 (40%)          | 11 (37%)          | 14 (47%)          | 13 (43%)          |
| Hyperlipidemia                     | 15 (50%)          | 17 (57%)          | 16 (53%)          | 16 (53%)          |
| Creatinine (umol L <sup>-1</sup> ) | 71.6 ± 12.1       | 69.4 ± 14.5       | 65.0 ± 10.0       | 68.0 ± 12.7       |

Data are presented as mean ± SD or number of patients (%). Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index.

## Primary outcome

Successful induction of anesthesia was defined as MOAA/S score ≤1. The success rate of general anesthesia induction in CIP1, CIP2, CIP3, and PROP groups was 100%.

## Secondary outcomes

### Induction success time and eyelash reflex disappearance time

Compared with the PROP group, the differences in induction success time and eyelash reflex disappearance time in the CIP3 group were not statistically significant. The induction success time and eyelash reflex disappearance

time in the CIP1 and CIP2 groups were significantly increased compared with that in PROP and CIP3 group. There was no statistically significant difference between the C1 and C2 groups in induction success and eyelash reflex disappearance time (**Table 2**).

**Table 2.** Comparison of induction success time and eyelash reflex disappearance time in four groups of subjects (s)

| Variables                         | CIP1                    | CIP2                    | CIP3      | PROP     |
|-----------------------------------|-------------------------|-------------------------|-----------|----------|
| induction success time            | 87.5±30.6 <sup>ab</sup> | 76.2±19.7 <sup>ab</sup> | 67.8±18.5 | 66.7±7.2 |
| eyelash reflex disappearance time | 97.6±33.0 <sup>ab</sup> | 88.5±20.7 <sup>ab</sup> | 78.0±17.6 | 77.8±8.2 |

Data are presented as mean ± SD. Compared with PROP group, <sup>a</sup>P<0.05. Compared with CIP3 group, <sup>b</sup>P was <0.05.

### Number of patients who required top-up doses and number of top-up

Two patients needed top-up doses in the PROP and CIP3 groups, respectively ( $P > 0.05$ ). In the CIP1 and CIP2 groups, 12 and 9 patients required top-up doses, of which 5 and 2 needed top-up doses twice. The number of patients who required top-up doses and doses of top-up dose in the CIP1 and CIP2 groups were significantly greater than in the PROP and CIP3 groups ( $P < 0.05$ ), as shown in **Table 3**.

**Table 3.** Comparison of number of patients who required top-up doses in four groups of subjects (n,%)

| Group | Number of patients who required top-up doses | Once to top-up        | Twice to top-up       |
|-------|----------------------------------------------|-----------------------|-----------------------|
| CIP1  | 12(40.0) <sup>ab</sup>                       | 7(23.3) <sup>ab</sup> | 5(16.7) <sup>ab</sup> |
| CIP2  | 9(30.0) <sup>ab</sup>                        | 7(23.3) <sup>ab</sup> | 2(6.7) <sup>ab</sup>  |
| CIP3  | 2(6.7)                                       | 2(6.7)                | 0                     |
| PROP  | 2(6.7)                                       | 2(6.7)                | 0                     |

Data are presented as number of patients (%). Compared with PROP group, <sup>a</sup>P < 0.05. Compared with CIP3 group, <sup>b</sup>P < 0.05.

### The total dose of successful induction

The total dose of successful induction in the CIP1, CIP2, and CIP3 groups were 19.9±5.0mg, 21.5±5.9mg and 22.6±4.1mg, respectively. There was no statistically significant difference among the three groups. The total dose of successful induction in the PROP group was 106.1±24.7mg, 4-5 times higher than that of the ciprofol groups.

### Safety indicators

The total number of adverse events was higher in the PROP group than in the CIP groups. The incidence of hypotension in the CIP1, CIP2, and CIP3

groups was significantly lower than that in the PROP group, and the difference was statistically significant. There was no statistically significant difference in the incidence of hypertension, tachycardia and bradycardia among the four groups. The incidence of injection pain in the PROP group was 50%, whereas no injection pain occurred in all subjects in the CIP groups. All subjects did not experience body movements and respiratory depression, as shown in **Table 4**.

**Table 4.** Comparison of adverse events in four groups of subjects(n,%)

| Group | Hypotension           | Hypertension | Tachycardia | Bradycardia | Hypoxemia | Injection pain | Body movements | The total number of adverse events |
|-------|-----------------------|--------------|-------------|-------------|-----------|----------------|----------------|------------------------------------|
| CIP1  | 5 (16.7) <sup>a</sup> | 2 (6.7)      | 3(10.0)     | 2(6.7)      | 0         | 0 <sup>a</sup> | 0              | 12 <sup>a</sup>                    |
| CIP2  | 7 (23.3) <sup>a</sup> | 0            | 1 (3.3)     | 1(3.3)      | 0         | 0 <sup>a</sup> | 0              | 9 <sup>a</sup>                     |
| CIP3  | 8 (26.7) <sup>a</sup> | 0            | 0           | 3(10.0)     | 0         | 0 <sup>a</sup> | 0              | 11 <sup>a</sup>                    |
| PROP  | 15 (50.0)             | 0            | 0           | 2(6.7)      | 0         | 15(50.0)       | 0              | 32                                 |

Data are presented as number of patients (%). Compared with PROP group, <sup>a</sup>P<0.05.

## Discussion

Patients undergoing hip replacement surgery usually have a certain degree of physical activity limitation before the operation, resulting in a decline in cardiopulmonary function<sup>[10]</sup>. Moreover, the majority of patients are elderly, which brings certain risks and challenges to general anesthesia induction. To maintain the quality and safety of anesthesia of these patients, a personalized anesthesia plan should be created, focusing on hemodynamic stability and appropriate general anesthesia induction drugs and dosages.

Ciprofol is a new type of intravenous anesthetics, it has the advantages of fast onset of action, high potency, low incidence of injection pain and hemodynamic stability<sup>[11-13]</sup>, and may replace propofol as a new choice for induction of general anesthesia<sup>[14]</sup>. The first-phase dose escalation clinical trial of ciprofol in young and middle-aged people (18-49 years old) proved that ciprofol at a dose of 0.4-0.9mg/kg could be well tolerated and had the characteristics of rapid onset and rapid recovery<sup>[15]</sup>. The phase III clinical safety study confirmed that ciprofol at a dose of 0.4mg/kg could be safely used for general anesthesia induction among young and middle-aged people (aged 18-64 years). The success rate of intubation induction was comparable to that of propofol at a dose of 2.0mg/kg<sup>[16]</sup>. A comparison result on the induction of general anesthesia with ciprofol in elderly patients and non-elderly patients indicates that induction with 0.3mg/kg ciprofol in the elderly can achieve a similar effect to that of 0.4mg/kg ciprofol in middle-aged and young people, suggesting that 0.3mg/kg may be an appropriate dose for induction with general anesthesia with ciprofol in elderly patients<sup>[8]</sup>. Based on these proofs, our study set a dose gradient of 0.25mg/kg, 0.30mg/kg and 0.35mg/kg with a median of 0.30mg/kg of ciprofol, and the PROP group was set at 1.5mg/

kg in this trial<sup>[17]</sup>.

The results of this study showed that the success rate of induction of general anesthesia with 0.25mg/kg, 0.30mg/kg, and 0.35mg/kg of ciprofol was 100%. Suggesting that ciprofol can be effectively used for the induction of general anesthesia in the elderly patients as propofol. There was no significant difference in the successful induction time and the disappearance time of eyelash reflex between 0.35mg/kg ciprofol and 1.5mg/kg propofol. Both could put the subjects into a sedative state within 90 seconds after administration. It indicates that for the induction of general anesthesia in elderly patients, 0.35mg/kg ciprofol and 1.5mg/kg propofol have similar anesthetic efficacy and take effect rapidly.

This study found that the number of people requiring additional anesthetics and the number of additional doses in the 0.25mg/kg and 0.3mg/kg ciprofol groups were significantly higher than those in the 0.35mg/kg ciprofol group, suggesting that these two doses of ciprofol may be insufficient for general anesthesia induction in elderly patients. Increasing the addition of induction drugs will prolong the induction time and increase the incidence of adverse events during the induction period. Therefore, 0.25mg/kg and 0.3mg/kg ciprofol may be not suitable for for general anesthesia induction in elderly patients undergoing hip replacement surgery.

Hypotension is the most common adverse event during the induction period of general anesthesia<sup>[18]</sup>. Elderly patients are more prone to hypotension during the induction period due to reasons such as reduced cardiac function and decreased vascular elastic tension. Moreover, the elderly patients have poor tolerance to hypotension<sup>[19]</sup>. Long-term hypotension can cause adverse events such as cerebral infarction and acute kidney injury<sup>[20]</sup>. In severe cases, it is prone to induce myocardial ischemia and lead to cardiac arrest<sup>[21]</sup>. The results of this trial showed that the incidence of hypotension were 16.7%, 23.3% and 26.7% in the 0.25mg/kg, 0.3mg/kg and 0.35mg/kg ciprofol groups respectively, all lower than 50% in the propofol group. Moreover, the incidence of hypotension in the 0.35mg/kg ciprofol group was significantly lower than that in the propofol group, indicating that under the same efficacy, the inhibitory effect of ciprofol on the cardiovascular system is milder than that of propofol. Ciprofol can reduce the occurrence of hypotension in the induction period in elderly patients and lower the incidence of related adverse events.

Injection pain can increase the tension and fear of patients during the induction period. In severe cases, it can lead to stress responses and violent fluctuations in circulation, resulting in a poor anesthesia experience for patients<sup>[22]</sup>. In this trial, the incidence of injection pain in the PROP group was 50%, whereas no injection pain occurred in all subjects in the CIP groups. It indicated the good effect of ciprofol as an intravenous anesthetic on injection pain<sup>[23]</sup>. There was no statistically significant difference in the incidence of hypertension, tachycardia and bradycardia among the four groups. In terms of arrhythmia, body movement and respiratory depression, no differences between each group of ciprofol and

propofol were observed in this trial, indicating that there were not significant differences among the groups in these aspects.

## Conclusions

Ciprofol (0.25-0.35mg/kg) could be safely and effectively used for general anesthesia induction in elderly patients undergoing hip replacement surgery. The anesthetic efficacy of 0.35mg/kg ciprofol was not inferior to that of 1.5mg/kg propofol and had higher safety and comfort. It may be the optimal dose for the induction of general anesthesia in elderly patients.

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