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CLINICAL TRIAL REPORT

Efficacy and Safety of General Anesthesia Induction with Ciprofol in Hip Fracture Surgery of Elderly Patients: A Randomized Controlled Trial

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Background: Ciprofol is a new intravenous sedative / anesthetic drug. In recent years, many clinical studies have also confirmed the sedative effect of ciprofol. However, more clinical research is still needed on its clinical application characteristics in special populations.

Objective: The aim of this study was to compare the clinical effects of ciprofol and propofol in general anesthesia induction of elderly patients.

Methods: 60 elderly (aged ≥ 75 years) patients underwent hip fracture surgery were randomly into two groups of a 1:1 ratio. Group C (ciprofol group): 0.3mg/kg ciprofol was infused. Group P (propofol group): 1.5mg/kg propofol was infused. The observation period was from the infusion of test drug to 5 min after endotracheal intubation. The primary outcomes included the incidence of severe hypotension and hypotension during the observation period. The secondary outcomes were as follows: the success rate of general anesthesia induction, the number of additional sedation, the time of loss of consciousness (LOC), Δ MAP, Δ HR, adverse events and the frequency of vasoactive drugs used.

Results: Finally, 60 subjects completed the study. Compared with Group P, the incidence of severe hypotension in Group C was lower (26.7% vs 53.3%, $P = 0.035$), the incidence of hypotension was also lower (36.7% vs 63.3%, $P = 0.037$), Δ MAP in Group C was significantly lower (31.4 ± 11.4 vs 39.6 ± 15.7, $P = 0.025$), the frequency of ephedrine used and the incidence of injection pain in Group C were also significantly lower.

Conclusion: Ciprofol showed similar efficacy to propofol when used for general anesthesia induction in elderly patients underwent hip fracture surgery and could maintain more stable blood pressure.

Keywords: Ciprofol, elderly, Hip fracture surgery, general anesthesia, hypotension

Introduction

The most common adverse event during the induction of general anesthesia is hypotension, and age is one of the main risk factors.[1] Intraoperative hypotension is associated with serious postoperative complications, and severe hypotension (MAP ≤ 55 mmHg) is associated with an increased risk of acute kidney injury (AKI) and myocardial injury in a short duration.[2] Elderly patients with hip fracture are often in a debilitating state, with a variety of comorbidities, and are more prone to hypotension induced by general anesthesia induction.[3] Endotracheal intubation is usually required after successful general anesthesia induction, which is also prone to cause huge fluctuations in hemodynamics. Therefore, it is very important to select general anesthesia induction drugs suitable for elderly patients. Propofol is a classic anesthetic drug used for general anesthesia induction. The advantages include rapid onset of sedation and rapid awakening, but it is prone to cause hypotension.[4] Ciprofol is a novel sedative and anaesthetic, which shows stable pharmacokinetic

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characteristics, pharmacodynamic response and safety at the study dose, and is a promising anesthetic candidate.[5] Studies demonstrated that the efficacy of anesthetic induction with ciprofol is similar to propofol, while ciprofol was associated with lower risks of hypotension and pain on injection.[6] However, at present, there is no study on the efficacy and safety of ciprofol for the general anesthesia induction in elderly patients (aged ≥ 75 years). Therefore, this study was designed to a randomized, double-blind study, with propofol as the control drug, in order to explore that ciprofol can maintain more stable hemodynamics during the general anesthesia induction in elderly patients.

Methods

Ethics and Trial Registration

The study was approved by the local institutional Ethics Committee, Lishui People's Hospital (Wenzhou Medical University Lishui Hospital)(approval number: 2022–130) and registered at Chinese Clinical Trial Registry (Registration number: ChiCTR2400080294). All subjects or authorized family provided written informed consent forms.

Inclusion and Exclusion Criteria

This study was a randomized, double-blind study, involved 60 elderly patients who were admitted to Lishui People's Hospital (Wenzhou Medical University Lishui Hospital) for hip fracture surgery from February 2024 to April 2024.

Inclusion criteria were as (1) age of 75 to 90 years, body mass index: 18.5–27.9 kg/m^2; (2) American Society of anesthesiologists (ASA) grade II ~ III, (3) hip fracture surgery was planned under general anesthesia.

Exclusion criteria were as (1) patients with neurological or psychiatric diseases or communication disorders before operation; (2) allergic to the drugs in this study; (3) long-term use of antipsychotics or antidepressants; (4) preoperative ECG showed that patients with severe arrhythmia: Bradycardia (HR < 50 bpm) or second-degree or third-degree heart block; (5) preoperative respiratory failure: PaO_2 < 60mmHg; (6) preoperative cardiac failure: New York Heart Association (NYHA) class III or IV.

Randomization and Masking

Subjects were randomly assigned into 2 groups according to the computer generated random numbers: Group C (30 subjects) and Group P (30 subjects). Study drugs will be prepared by independent research nurses who are not involved in patient care. During the study, all surgeons, anesthesiologists, and researchers of data collection were blinded to the group assignments.

Perioperative Management and Interventions

None of the patients received any premedication. When the patient arrived in operating room, the hand vein was established for infusion, and a catheter was inserted in the patient's radial artery to monitor the continuous invasive mean arterial pressure (MAP). The Carestation 620 A2 monitor (GE Healthcare, Chicago, IL, USA) continuously monitored and recorded electrocardiogram (ECG), noninvasive blood pressure, heart rate (HR), respiratory rate (RR), pulse oxygen saturation (SpO_2).

The bispectral index (BIS) sensor (Canwell Medical Co., Ltd., Jinhua, Zhejiang, China) was also used to adjust the appropriate depth of anesthesia. No regional nerve blocks were performed in all patients. The mean of the MAP and HR by 3 measurements under the resting supine position was defined as the base value. After patients received pure oxygen for 3 minutes by mask (flow rate of 5 L/min), both groups were given experimental drugs intravenously (injection time was 30s), (1) Group C: 0.3mg/kg ciprofol (Liaoning HISCO Pharmaceutical Co., Ltd).; (2) Group P: 1.5mg/kg propofol (Beijing Fresenius Kabi Pharmaceutical Co., Ltd., Beijing, China).Intravenous 0.3–0.4 μg/kg sufentanil (Hubei, Yichang Humanwell Pharmaceutical Co., Ltd.) and 0.15mg/kg cis-atracurium (Jiangsu Hengrui Pharmaceutical Co., Ltd.) after clinical LOC (Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S) ≤ 1). After BIS value is stable below 60 and muscle relaxation, endotracheal intubation is performed, tracheal intubation is required to be successful at one time. Volume-controlled mechanical ventilation was used to maintain an end-tidal carbon dioxide ($EtCO_2$) of 30–45 mmHg. General anesthesia was maintained by continuous intravenous infusion of propofol and sevoflurane inhalation (Jiangsu Hengrui Pharmaceutical Co., Ltd., Jiangsu, China).Successful induction

of general anesthesia should meet two conditions as follows: MOAA/S ≤ 1 and BIS value ≤ 60. If these two conditions were not met at the same time after 1 min of the first anesthetic induction dose, additional sedation is required. The Group C was given 0.1mg/kg ciprofol each time, and the Group P was given 0.5mg/kg propofol each time for additional sedation. The administration time was 10 seconds, and the interval between each addition was over 1 min, which was added twice at most. When induction remained unsuccessful after the administration of two additions, it was defined as failure induction of anaesthesia, then propofol could be selected as rescue sedative.During the observation, if hypotension, severe hypotension, bradycardia, hypertension or tachycardia occurred and lasts for more than 1 min, we treated them with vasoactive drugs as follows: ephedrine, atropine, urapidil and esmolol.

The time points of detection were defined: T0: baseline; T1: after successful induction; T2: before tracheal intubation; T3: 1 min after tracheal intubation; T4: 3min after tracheal intubation; T5: 5min after tracheal intubation.

Outcomes

Primary Outcome

The primary outcomes were the incidence of severe hypotension (MAP of ≤ 55 mmHg) and hypotension (MAP of ≤ 70% of baseline and/or < 65 mmHg) during the observation period.

Secondary Outcomes

1. The success rate of general anesthesia induction was defined as the percentage of successful induction cases in each group, the number of additional sedation, the time to LOC.
2. During the observation period, Δ MAP (maximum difference in MAP), Δ HR (maximum difference in HR), the changes in MAP and HR.
3. Adverse events included hypertension (MAP > 120% of baseline), bradycardia (HR < 45 bpm), and tachycardia (HR ≥ 120% of baseline).[7]
4. Injection pain was assessed during the injection by asking the subjects questions "Do you feel pain in the arm where the drug was injected?". If the answer was "yes", Subjects were asked to describe the intensity of the pain (0 to 10 points indicated "no pain" to "unbearable pain").Injection pain was defined when the numeric rating scale value ≥ 3.[8]
5. The frequency of vasoactive drugs used included ephedrine, atropine, urapidil and esmolol.

Sample Size and Statistical Analysis

30 subjects completed this the pre-experiment. The results of pre-experiment showed that the incidence of severe hypotension was 20% in Group C and 60% in Group P. The sample size was estimated using PASS 15.0 software (PASS, Kaysville, UT), with α=0.05, 2-tailed, and a power of 90%, 54 subjects were needed in our study. Considering the 10% shedding rate, a total of 60 subjects were required (30 subjects in each group).

SPSS 20.0 statistical software (IBM Corp., Armonk, NY, USA) was used for data processing and analysis, with statistical significance set at $p<0.05$.Continuous data were expressed as mean ± standard deviation, and categorical data were expressed as number (percentage). Independent sample *t*-tests were used to compare continuous variables with a normal distribution between groups, and the Mann–Whitney *U*-test was used to compare continuous variables with a non-normal distribution between groups. The chi-square test or Fisher's exact test was used to compare categorical variables between groups. The normality of distribution was analyzed with the Shapiro–Wilk test.

Results

Finally, 70 subjects were initially screened for eligibility, 6 subjects were excluded according to the exclusion criteria and 4 subjects refused to participate in this study.Finally, 60 subjects (30 in Group C and 30 in Group P) were analyzed (Figure 1).

The patient baseline characteristics are summarized in Table 1, there were no significant difference in any characteristics between the two groups, ($P > 0.05$) (Table 1).

There were no significant difference in any efficacy outcomes between the two groups as follows: the success rate of general anesthesia induction, the number of additional sedation, and the time to LOC ($P > 0.05$) (Table 2).

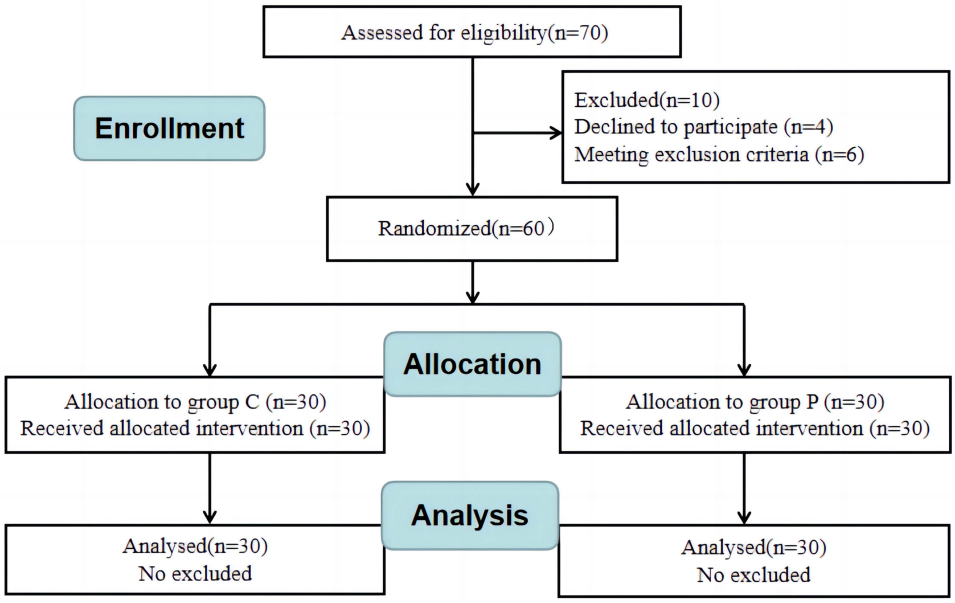

Figure 1 Flow chart of this study.

As shown in Table 3, compared with Group P, the incidence of severe hypotension was lower in Group C (26.7% vs 53.3%, $P = 0.035$), the incidence of hypotension was also lower in Group C (36.7% vs 63.3%, $P = 0.037$) and more subjects expressed injection pain in Group C (10% vs 50%, $P = 0.001$). Δ MAP in Group C was significantly lower than

Table 1 Patient Baseline Characteristics

	Group C (n=30)	Group P (n=30)	*P*
Age (years)	78.7±3.2	79.3±3.9	0.540
Height (cm)	157.0±5.3	158.3±5.2	0.336
Weight (kg)	59.4±8.5	58.3±7.5	0.615
Sex (Male / Female)	10/20	14/16	0.292
ASA (II / III)	22/8	23/7	0.766
Level of education, n (%)			0.803
<Elementary school	12	14	
Elementary school	10	10	
≥Secondary school	8	6	
Type of surgery[n (%)]			0.598
Total hip arthroplasty	17	19	
Proximal femoral nail antirotation	13	11	

Notes: Data were showed as mean ± standard deviation. No statistically significant differences between groups were noted.
Abbreviation: ASA, American Society of Anesthesiologists.

Table 2 Efficacy Outcomes

	Group C (n=30)	Group P (n=30)	*P*
Successful general anesthesia induction, n (%)	30 (100)	30 (100)	–
Additional dose, n (%)	3 (10)	1 (3.3)	0.612
Rescue sedation with propofol, n (%)	0 (0)	0 (0)	–
Time to LOC (s)	51.1±8.8	48.0±7.4	0.149

Note: Data were showed as mean ± standard deviation or number (percentage). Abbreviations: LOC, loss of consciousness.

Table 3 Safety Outcomes

	Group C (n=30)	Group P (n=30)	*P*
Severe hypotension, n (%)	8 (26.7) *	16 (53.3)	0.035
Hypotension, n (%)	11 (36.7) *	19 (63.3)	0.037
Injection pain, n (%)	3 (10.0) *	15 (50.0)	0.001
Hypertension, n (%)	1 (3.3)	3 (10.0)	0.612
Bradycardia, n (%)	0 (0)	2 (6.7)	0.492
Tachycardia, n (%)	2 (6.7)	2 (6.7)	> 0.999
Δ MAP (mmHg)	31.4±11.4*	39.6±15.7	0.025
Δ HR (bpm)	24.7±10.4	24.1±5.8	0.267

Note: Data were showed as mean ± standard deviation or number (percentage). *$p < 0.05$, compared with group P.
Abbreviations: MAP, mean arterial pressure; HR, heart rate.

Table 4 Frequency of Vasoactive Drugs Used

	Group C (n=30)	Group P (n=30)	*P*
Ephedrine, n (%)	5 (16.7) *	12 (40.0)	0.045
Atropine, n (%)	0 (0)	1 (3.3)	> 0.999
Urapidil, n (%)	0 (0)	0 (0)	> 0.999
Esmolol, n (%)	0 (0)	0 (0)	> 0.999

Note: Data were showed as number (percentage). *$p < 0.05$, compared with group P.

that in Group P (31.4 ± 11.4 vs 39.6 ± 15.7, $P = 0.025$). In addition, the incidence of other adverse events was similar between the two groups ($P > 0.05$).

As shown in Table 4, compared with Group P, the frequency of ephedrine used was significantly less in Group C (16.7% vs 40%, $P = 0.045$), and there was no significant difference in the frequency used of other vasoactive drugs between the two groups, ($P > 0.05$).

During the observation period, the changes of MAP in Group C was more stable than Group P. Moreover, at T1 and T4, the MAP of the Group C was significantly higher than that of the Group P (Figure 2). There was no significant difference in HR between the two groups at each time point (Figure 3).

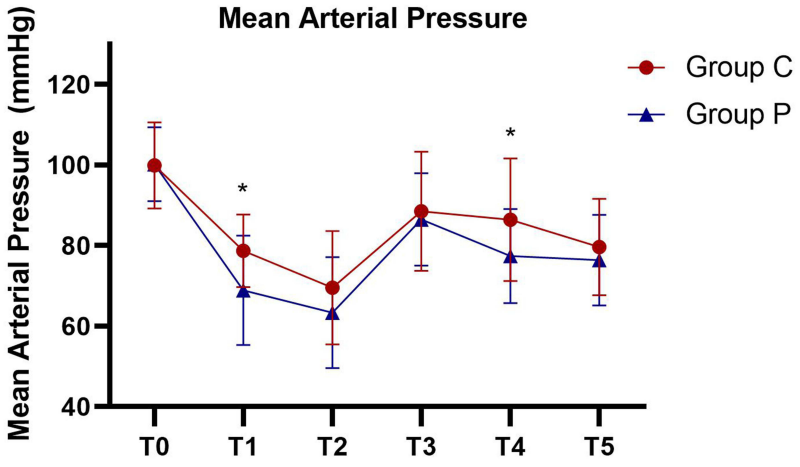

Figure 2 MAP changes during observation period. T0: baseline; T1: after successful induction; T2: before tracheal intubation; T3: 1 min after tracheal intubation; T4: 3 min after tracheal intubation; T5: 5 min after tracheal extubation. Data were presented as mean ± standard deviation. *$P<0.05$ compared with Group P.
Abbreviation: MAP, mean arterial pressure.

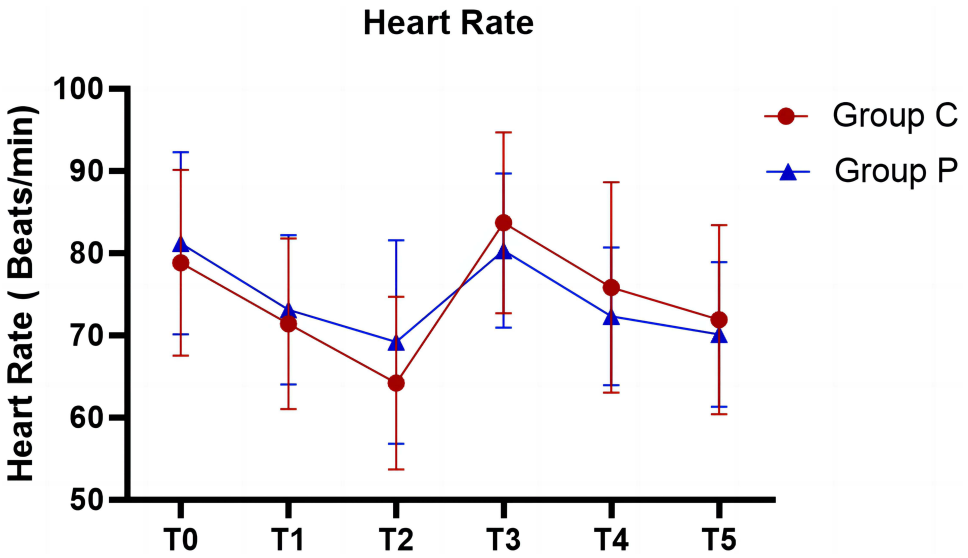

Figure 3 HR changes during observation period. T0: baseline; T1: after successful induction; T2: before tracheal intubation; T3: 1 min after tracheal intubation; T4: 3 min after tracheal intubation; T5: 5 min after tracheal extubation. Data were presented as mean ± standard deviation.
Abbreviation: HR, heart rate.

Discussion

The results of this study showed that the incidence of severe hypotension and hypotension in the Group C were lower than Group P (26.7% vs 53.3%; 36.7% vs 63.3%). A study showed that the incidence of hypotension induced by general anesthesia induction with a dose of 0.3mg/kg ciprofol in the elderly patients (average age of 70 years) was 26.7%, which was lower than our results.[9] This may be related to the average age (78.7 years) of this study subjects, which further illustrated that the incidence of intraoperative hypotension is closely related to age.

Ciprofol is a close analog of propofol, a novel 2.6-disubstituted phenol derivatives. The effect of ciprofol in anesthesia induction and maintenance is equivalent to propofol.[10] According to the previous research results, the dose of ciprofol selected in this study was 0.3mg/kg, and the corresponding dose of propofol was 1.5mg/kg.[11,12] Elderly patients usually undergo surgery in a state of weakness, severe comorbidities and reduced physiological reserve, which resulted in sustained hypotension events between the general anesthesia induction and the beginning of surgery.[13] Studies have showed that intraoperative MAP < 65 mmhg is associated with organ injury and perioperative mortality.[14] Intraoperative MAP <55 mmhg in elderly patients can not only induce postoperative adverse cardiac events and acute kidney injury, but also cause postoperative delirium.[15]

At T1 and T4, the MAP of the Group C was significantly higher than Group P, and the Δ MAP of Group C was also significantly lower than that of Group P. These results indicated that compared with propofol, the general anesthesia induction with ciprofol in elderly patients (aged ≥ 75 years) can obtain more stable blood pressure changes. This is similar to the research conclusion of Chen BZ et al[8]. This study also showed that the frequency of ephedrine used in the Group C was significantly lower than Group P, indicated that the degree of hypotension caused by ciprofol was lower and easier to reverse. The efficacy of ciprofol for general anesthesia induction has been demonstrated in several studies.[8,16,17] This study showed that the success rate of general anesthesia induction at the dose of 0.3mg/kg ciprofol was 100%, which was consistent with Group P. Among them, 3 patients in the Group C needed additional sedation, and 1 patient in Group P needed additional sedation. This demonstrated again the efficacy of ciprofol in the general anesthesia induction in elderly patients, and also provides an effective dose reference for future clinical research in elderly patients.

Intravenous propofol is prone to injection pain, with an incidence of 50% - 80%.[18] Injection pain will not only cause anxiety and limb movement, but also may affect the hemodynamic stability during the general anesthesia induction.In this study, compared with Group P, the incidence of injection pain in the Group C was also significantly lower, which may be related to the higher hydrophobicity and lower plasma concentration of ciprofol.[10]

There are several limitations in this study. Firstly, we only used one dose of 0.3 mg/kg ciprofol during the experiment. Further clinical trials are needed to demonstrate the clinical effects of more different doses. Secondly, this study is only a single-center trial, so we also look forward to a multicenter study organized by a more advanced research unit to further verify the reliability.Despite the above-mentioned limitations, we believe that the results of this study still has important value. Because in this study, the specific group and standardized anesthesia protocols were selected, in addition, this study is also a double-blind randomized controlled trial.Therefore, we believe that the results of this study are scientificity and credibility.

Conclusions

The success rate of general anesthesia induction in elderly patients (aged ≥ 75 years) with hip fracture at the dose of 0.3mg/kg ciprofol was 100%. Compared with propofol, the blood pressure was more stable during the general anesthesia induction with ciprofol, and the incidence of severe hypotension and hypotension were lower. In conclusion, ciprofol can be a suitable anesthetic for general anesthesia induction in elderly patients.

Data Sharing Statement

All datasets analyzed for this study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

The study was done in accordance with the Helsinki Declaration and followed the CONSORT guidelines.The study was approved by the local institutional Ethics Committee, Lishui People's Hospital (approval number:2022-130) and registered at Chinese Clinical Trial Registry (Registration number: ChiCTR2400080294). All subjects provided written informed consent forms.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflicts of interest.

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