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Ciprofol versus propofol for anesthesia induction in cardiac surgery: a randomized double-blind controlled clinical trial

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Abstract

Background Ciprofol, a novel intravenous general anesthetic with a chemical structure similar to propofol, exhibits significantly enhanced potency. It offers a rapid onset, reduced incidence of injection pain, and has comparable effects on heart rate and blood pressure to propofol. However, clinical data on its use for anesthesia induction in cardiac surgery remain limited.

Methods Seventy-eight patients undergoing coronary artery bypass grafting or valve replacement surgery were randomly assigned to receive either ciprofol ($N=40$) or propofol ($N=38$) for anesthesia induction. Variables recorded included changes in mean arterial pressure and heart rate during anesthesia, alterations in the oxygenation index and lactic acid concentration before and 10 min after anesthesia induction, and the incidence of adverse events such as bradycardia, hypotension, and injection pain.

Results The incidence of anesthesia-induced injection pain was significantly lower in the ciprofol group compared to the propofol group (3% vs. 18%, $P<0.05$). The incidence of other adverse events was similar between the groups. No significant differences in hemodynamics or oxygenation index were observed during anesthesia induction between ciprofol and propofol.

Conclusions Ciprofol demonstrated a significantly lower incidence of injection pain compared to propofol, potentially improving patient comfort during anesthesia induction. Additionally, ciprofol showed comparable circulatory stability to propofol during anesthesia induction in cardiac surgery, suggesting it may be a suitable alternative to propofol for this application.

Trial registration The trial was registered at the ClinicalTrials.gov on 03/10/2024 (NCT06312345).

Keywords Ciprofol, Propofol, Coronary artery bypass graft, Heart valve replacement, Anesthesia induction

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Introduction

The prevalence of heart diseases, such as coronary heart disease and heart valve disease, continues to rise due to demographic shifts and an aging population [1–3]. Patients unresponsive to medical treatment often necessitate cardiac surgery, which presents unique challenges due to significant hemodynamic fluctuations during anesthesia induction and an elevated incidence of adverse events [4]. Propofol is a common choice for anesthesia induction in various surgical procedures, including cardiac surgery [5, 6]. However, it exhibits significant cardiovascular and respiratory depression effects, and propofol infusion syndrome, a rare yet life-threatening adverse effect [7–9].

Ciprofol (HSK3486) is a recently developed short-acting sedative with greater potency than propofol and a chiral structure that enhances its affinity for $GABA_A$ receptors [10–12]. A phase 3 clinical study of ciprofol demonstrated a BIS change pattern similar to propofol, stability during anesthesia maintenance, comparable safety, and a lower incidence of injection pain [13]. Ciprofol's rapid onset, swift recovery, reduced injection pain, and stable cardiopulmonary function position it as a promising alternative to propofol [14]. However, no existing literature explores the use of ciprofol for anesthesia induction in cardiac surgery. As such, we conducted a randomized, double-blind study to investigate the safety and hemodynamic effects of ciprofol in inducing anesthesia for cardiac surgery.

Methods

Study design and participants

Prior to participation, written informed consent was obtained from all patients. A member of the research team explained the study procedures, potential risks, and benefits to the participants. Patients were assured that their participation was voluntary and that they could withdraw from the study at any time without consequences. The study protocol was approved by the Ethics Committee of East Hospital (2022/No.171), Tongji University, Shanghai, China, and was registered on ClinicalTrials.gov (NCT06312345). The trial enrolled patients who underwent cardiac surgery at Shanghai East Hospital between March 2024 and May 2024. The study focused on elective surgery patients aged 55 to 75 with New York Heart Association class II or III cardiac function who were scheduled for coronary artery bypass grafting or heart valve replacement via median sternotomy. Exclusion criteria included a history of benzodiazepine allergy, significant liver or kidney insufficiency, coagulation disorders, neurological or psychiatric conditions, or major surgery within the preceding three months.Patients were randomly allocated to one of two groups, receiving either propofol or ciprofol for anesthesia induction. A nurse anesthetist conducted the randomization process utilizing computerized software prior to the patients entering the operating room. The nurse prepared the anesthetic medications according to the group assignments but did not partake in the anesthesia induction. The anesthesiologist administered anesthesia using the prepared medications and documented the relevant data. Subsequently, the nurse anesthetist transferred the experimental data to an independent statistician for analysis. Consequently, patients, anesthesiologists, and nurses remained blinded to the group allocations by having identical preparation and labeling of the treatment (ciprofol and propofol), so the treatments are indistinguishable.

Anesthesia procedures

Before surgery, patients were visited, informed consent was obtained, and they were instructed to fast for 8 h and abstain from water. In the operating room, patients' ECG, pulse oximetry, and electroencephalographic bispectral index (BIS) were monitored. Under local anesthesia using lidocaine, a radial artery catheter was inserted to enable continuous monitoring of arterial blood pressure. Arterial blood samples were obtained for blood gas analysis, while venous blood was collected to assess activated clotting time (ACT). Upon establishing peripheral venous access, anesthesia was induced, followed by the placement of a triple-lumen catheter through puncture of the right internal jugular vein.

Induction of anesthesia

Prior to anesthesia induction, patients underwent preoxygenation for 3 min. Midazolam and sufentanil were administered intravenously at doses of 0.03 mg/kg and 0.5 μg/kg, respectively. Patients were subsequently administered either 0.3 mg/kg of ciprofol or 1.5 mg/kg of propofol over a period of 30 s while asking the patient if they felt pain at the injection site VAS > 5. Upon loss of corneal reflex, rocuronium bromide 1.0 mg/kg was administered. Tracheal intubation was performed 1 min later. Hypotension, defined as a mean arterial pressure below 60 mmHg, was treated by administering a single intravenous injection of 40 μg phenylephrine. Severe bradycardia, defined as a heart rate below 45 beats per minute, was treated with a single 0.25 mg dose of atropine. Hypoxia was identified when oxygen saturation fell below 90%, and tachycardia was recognized when heart rate exceeded 120 beats per minute. The administration frequency of phenylephrine and atropine was recorded.

Anesthesia maintenance

Both groups received propofol (3–8 mg/kg/h), sufentanil (0.8 μg/kg/h), dexmedetomidine (0.5 μg/kg/h), and

rocuronium bromide (0.6 mg/kg/h) for the maintenance of anesthesia. During the maintenance of anesthesia, the mechanical ventilation settings were standardized for all patients. The respiratory rate was adjusted to maintain an end-tidal carbon dioxide tension (EtCO2) between 35 and 40 mmHg, as measured by capnography. The fraction of inspired oxygen (FiO2) was set at 0.6 to maintain arterial oxygen saturation (SpO2) between 95 and 99%, as monitored by pulse oximetry. Tidal volume was set at 7 ml/kg, and the positive end-expiratory pressure (PEEP) was maintained at 5 cmH2O to prevent atelectasis. These settings were adjusted as necessary to ensure optimal oxygenation and ventilation for each patient. The BIS value was sustained within a range of 40–60.

Outcome measures

The primary outcome measure was to evaluate hemodynamic fluctuations during anesthesia induction, specifically the changes in mean arterial pressure (MAP) and heart rate (HR). MAP was recorded at four critical time points: before induction of anesthesia (T1), before tracheal intubation (T2), 1 min after tracheal intubation (T3), and five minutes after tracheal intubation (T4). The incidence of hypotension and bradycardia during induction and the number of doses of phenylephrine and atropine were also recorded. The secondary outcomes were the incidence of injection pain, latency to loss of corneal reflex (LOC), oxygen saturation, and oxygenation index before and ten minutes after induction of anesthesia.

Statistical analysis

We determined the sample sizes required based on the difference in mean arterial pressure (ΔMAP) at the T1 time point. In a preliminary study, we observed a ΔMAP of -15.1 ± 7.3 mmHg and -19.8 ± 6.7 mmHg in the propofol and ciprofol groups, respectively. With an assumed alpha level of 0.05 and a power of 0.80, we calculated that approximately 40 patients would be necessary in each group. The statistical analysis was performed using SPSS version 26.0. The normally distributed measurement data were presented as mean ± standard deviation, and the t-test was used to compare the groups. The $\chi 2$ test was used to compare the enumeration data. Statistical significance was considered at $P < 0.05$.

Results

The study initially screened 87 patients who met the inclusion criteria. Seven patients declined to participate, and two patients were excluded because they did not meet the inclusion criteria after changing their surgical method. Therefore, a total of 78 patients were enrolled in the study and randomized into two groups: the ciprofol group ($N=40$) and the propofol group ($N=38$). All 78 patients successfully completed the anesthesia procedure (Fig. 1).

In terms of baseline characteristics, there were no significant differences observed between the ciprofol group and the propofol group, indicating that the baseline characteristics of the two groups did not affect the results (Table 1).

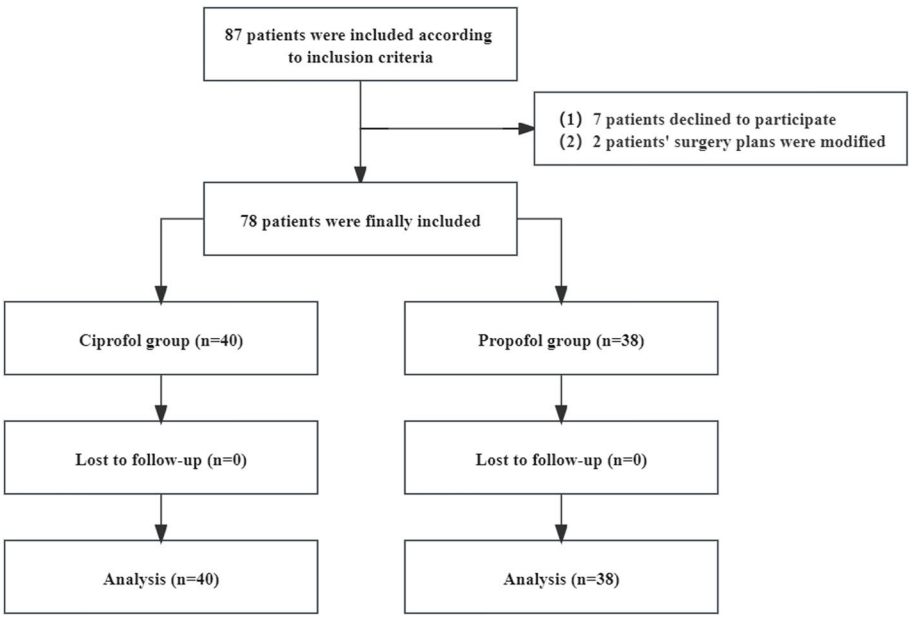

Fig. 1 Participants' flowchart

Table 1 Characteristics of the participants

	Ciprofol group ($n=40$)	Propofol group ($n=38$)	*P*
Biological sex (n)			0.622
Male	22(55%)	23(61%)	
Female	18(45%)	15(39%)	
Age (years)	64.71 ± 6.32	63.18 ± 4.71	0.231
BMI (kg/m$^{2)}$	23.27 ± 2.65	23.89 ± 2.82	0.320
ASA class III	27(67%)	29(76%)	0.387
ASA class IV	13(33%)	9(24%)	
NYHA class II	35(87%)	32(84%)	0.677
NYHA class III	5(13%)	6(16%)	
Merger disease (n)			
Hypertension	31(78%)	27(71%)	0.515
Diabetes	2358%)	19(50%)	0.507
Stroke	3(8%)	3(8%)	0.948
Type of surgery (n)			
CABG	29(73%)	31(82%)	0.342
Heart valve replacement	11(27%)	7(18%)	

The results showed that there were no significant differences between the ciprofol and propofol groups in terms of mean arterial pressure and heart rate at four time points during induction of anesthesia (Fig. 2A and). The mean arterial pressure decreased in both groups during induction, but there was no significant difference in the magnitude of the decrease between the two groups (T2: − 21.81 ± 10.50 mmHg vs. − 18.08 ± 16.47 mmHg, $P=0.23$) (Fig. 2C). Additionally, both groups experienced a decrease in heart rate during induction, followed by an increase after tracheal intubation, but there was no significant difference in the magnitude of these changes (Fig. 2D). These findings suggest that there were no significant differences in haemodynamic fluctuations between the two groups during induction of anesthesia.

In the ciprofol group, the incidence of anesthesia-induced injection pain was significantly lower compared to the propofol group (3% vs. 18%, $P<0.05$). However, no significant differences were observed in hypotension, bradycardia, hypersensitivity, and the use of phenylephrine and atropine between the two groups (Table 2). While our primary focus was on hemodynamic outcomes, specifically the changes in mean arterial pressure (MAP) and heart rate during anesthesia induction, we

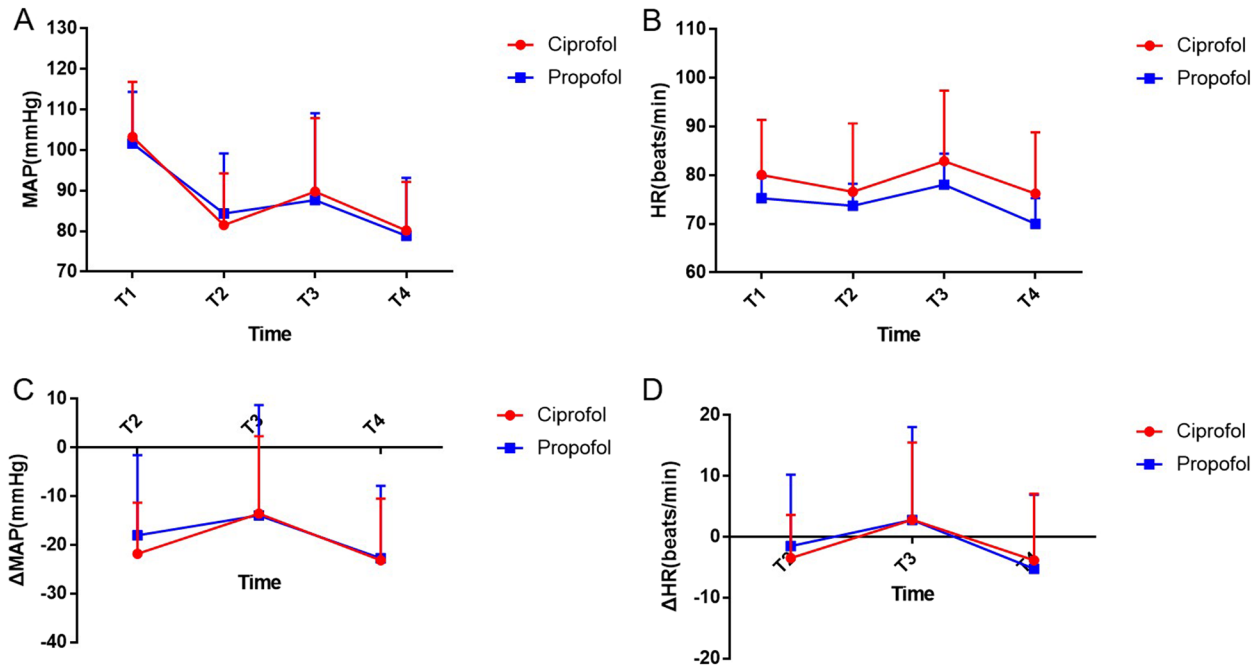

Fig. 2 Variations in heart rate and blood pressure during anesthesia induction. Error bars represent the standard error of the mean (SEM). T1: before induction of anesthesia; T2: before tracheal intubation; T3: 1 min after tracheal intubation; T4: 5 min after tracheal intubation. ΔMAP: the difference in mean arterial pressure (MAP) calculated as the pressure at each time point minus the baseline pressure (T1). A negative ΔMAP indicates a drop in pressure, while a positive ΔMAP indicates an increase. ΔHR: the difference between the heart rate at each time point and the baseline heart rate. **A** Mean arterial pressure (MAP) at different time points during anesthesia induction. **B** Heart rate at different time points during anesthesia induction. **C** ΔMAP at different time points during anesthesia induction. **D** ΔHR at different time points during anesthesia induction

Table 2 Adverse reactions during anesthesia induction

	Ciprofol group (*n* = 40)	Propofol group (*n* = 38)	*P*
Time to LOC (min)	0.89 ± 0.35	0.81 ± 0.26	0.26
Injection pain	1(3%)	7(18%)	0.02*
Hypotension	13(33%)	15(39%)	0.82
Bradycardia	5(13%)	3(8%)	0.50
Tachycardia	7(18%)	10(26%)	0.35
Rash	0	1(3%)	0.31
Hypoxia	1(3%)	1(3%)	0.97
Patients given phenylephrine	13(33%)	15(39%)	0.82
Patients given atropine	5(13%)	3(8%)	0.50

Table 3 Effect of induction of anesthesia on oxygenation function

	Ciprofol group (*n* = 40)	Propofol group (*n* = 38)	*P*
SaO_2 (%)			
Before anesthesia	95.9 ± 1.3	96.1 ± 1.2	0.48
10 min after anesthesia	99.2 ± 0.3	99.1 ± 0.3	0.15
PaO_2 (mmHg)			
Before anesthesia	78.9 ± 6.3	81.2 ± 7.1	0.13
10 min after anesthesia	243.8 ± 25.5	221.5 ± 37.5	0.32
PCO_2 (mmHg)			
Before anesthesia	32.3 ± 3.8	34.5 ± 5.2	0.21
10 min after anesthesia	35.2 ± 2.2	34.2 ± 3.1	0.10
Lac (mmol/L)			
Before anesthesia	1.0 ± 0.3	1.1 ± 0.3	0.15
10 min after anesthesia	0.9 ± 0.3	1.0 ± 0.3	0.15

also closely monitored the incidence of hypotension and bradycardia. Although there were no significant differences between the Ciprofol and Propofol groups in these critical hemodynamic parameters, we acknowledge that these findings require a more thorough discussion.

There were no significant differences in oxygen saturation, arterial partial pressure of oxygen, arterial partial pressure of carbon dioxide, or lactate concentration between the ciprofol and propofol groups at baseline and after 10 min of anesthesia induction. (Table 3).

Discussion

Induction of anesthesia for cardiac surgery carries a higher risk than for other types of surgery, with potential complications such as hemodynamic instability, myocardial depression, arrhythmia, and postoperative cognitive dysfunction [15–17]. Among the sedatives used for anesthesia induction in cardiac surgery, propofol, etomidate, and sevoflurane are commonly utilized [18]. Propofol offers several advantages compared to etomidate, such as a faster onset of action, shorter duration of action, and smoother induction process, which facilitates control over the depth of anesthesia. When compared to sevoflurane, propofol is more straightforward to administer. However, propofol also presents some drawbacks, including myocardial inhibition, a predisposition to hypotension, and notable pain upon injection [19, 20].

Ciprofol, has emerged as an alternative to propofol due to its unique similarity in chemical structure, yet less side effects in terms of pain on injection (Table 4). An intravenous anesthetic, functions as a $GABA_A$ receptor agonist. It influences the chloride channel mediated by $GABA_A$ receptors, enhancing current conduction and causing neuronal hyperpolarization. This hyperpolarization leads to consistent neural signal transmission, decreasing the likelihood of action potential generation and subsequently inhibiting the central nervous system, ultimately

Table 4 Characteristics of ciprofol and propofol

	Ciprofol	Propofol
Chemical Formula	*C14H20O* (R)-2-(1-cyclopropylethyl)-6-isopropylphenol	*C12H18O* 2,6-diisopropylphenol
pKa Value	11.8	11.1
Potency Difference	5 more potent than propofol	-
Solution Type	Lipid-in-water solution	Lipid-based solution
Complications	Hypotension, bradycardia, apnea, respiratory depression, hypoxia	Propofol infusion syndrome
Dosage (Adults)	0.4 mg/kg	Typically 1.5–2.5 mg/kg for induction, followed by maintenance infusion rates
Dosage (Children)	-	Typically 1–3 mg/kg for induction, followed by maintenance infusion rates
Cost Difference	1–2 times higher than propofol	Varies depending on the region and brand

resulting in anesthesia. Ciprofol exhibits favourable safety and tolerability, with pharmacodynamic activity approximately five times that of propofol. Its onset of action is rapid and stable, and it allows for swift and complete recovery upon cessation. Furthermore, the incidence of injection pain associated with ciprofol is exceedingly low. Its respiratory impact is superior to that of propofol, while its effects on heart rate and blood pressure are noninferior. Additionally, ciprofol requires less lipid infusion compared to propofol [14, 21].

This randomized, double-blind, controlled clinical trial aimed to evaluate the safety and hemodynamic effects of ciprofol for anesthesia induction in cardiac surgery. The results demonstrated that the use of ciprofol for anesthesia induction in cardiac surgery patients provided similar hemodynamic stability compared to propofol. Moreover, the incidence of injection pain was significantly lower in the ciprofol group than in the propofol group.

Hemodynamic stability is of paramount importance during anesthesia induction in cardiac surgery, as it helps to minimize the risk of myocardial ischemia and other complications. Our study found no significant differences in mean arterial pressure and heart rate changes between the ciprofol and propofol groups during anesthesia induction, suggesting that ciprofol is as effective as propofol in maintaining hemodynamic stability in cardiac surgery patients. In light of our primary focus on hemodynamic outcomes, it is important to discuss the implications of our findings on hypotension and bradycardia (Fig. 2).

The hemodynamic profiles of ciprofol and propofol were found to be similar, which is crucial for high-risk cardiac surgery patients where maintaining circulatory stability is paramount. Both agents demonstrated comparable effects on mean arterial pressure and heart rate during anesthesia induction, suggesting that ciprofol may be a viable alternative to propofol for maintaining hemodynamic stability in cardiac surgery patients. This similarity is particularly relevant in high-risk patients, where stable hemodynamic parameters are critical to minimizing the risk of complications such as myocardial ischemia. Although no significant differences in the incidence of bradycardia and hypotension were observed between the groups, ciprofol's comparable safety profile makes it a viable alternative to propofol. Further investigation is required to explore whether ciprofol offers additional benefits in specific patient populations. The lower incidence of injection pain observed in the ciprofol group is a notable advantage over propofol. Injection pain can cause discomfort and anxiety in patients during anesthesia induction, potentially affecting the overall patient experience [22]. The significantly lower incidence of injection pain in the ciprofol group could contribute to improved patient comfort during anesthesia induction. While the reduced incidence of injection pain with ciprofol is noteworthy, its clinical impact may be secondary to the need for maintaining hemodynamic control. Thus, ciprofol's ability to provide a smoother patient experience through less injection pain, combined with its similar hemodynamic profile, may enhance patient comfort without compromising safety in this vulnerable patient population. Further research could explore whether ciprofol offers advantages in specific subgroups of high-risk patients, potentially guiding its use in practice. Regarding oxygenation parameters and lactate concentration, no significant differences were found between the ciprofol and propofol groups, indicating comparable respiratory and metabolic effects for both anesthetics. This further supports the potential use of ciprofol as an alternative to propofol for anesthesia induction in cardiac surgery. While the lower incidence of injection pain with ciprofol is a noteworthy finding, we acknowledge the critical importance of hemodynamic stability and respiratory function in cardiac surgery. Bradycardia and hypotension can have significant consequences, including the potential for myocardial ischemia, increased morbidity, and prolonged hospital stays. In our study, although there were no significant differences between the ciprofol and propofol groups in the incidence of bradycardia (13% vs. 8%) or hypotension (33% vs. 39%), these outcomes remain a primary concern. Management of these adverse events typically involves the use of medications such as atropine for bradycardia and phenylephrine for hypotension, as was done in our study. However, the prevention of these events is ideal, and further research is needed to identify strategies to minimize their occurrence. Respiratory depression, another critical concern in anesthesia, can lead to hypoxia and increased risk of postoperative complications. Both ciprofol and propofol have been shown to have minimal effects on respiratory function compared to other anesthetic agents, which is an advantage in cardiac surgery. However, close monitoring and prompt management remain essential. The clinical significance of these adverse events underscores the need for ongoing evaluation and comparison of new anesthetic agents like ciprofol with established agents such as propofol. Future studies should continue to focus on these critical outcomes to ensure the safety and efficacy of new agents in the cardiac surgery population."

Limitations

A significant limitation of this study is the sample size, which may be underpowered to detect clinically meaningful differences in adverse outcomes such as bradycardia and hypotension fully capture the safety profile. Secondly, the study only included patients with NYHA

class II or III cardiac function; therefore, the results may not be applicable to patients with more severe cardiac dysfunction. The present study provides valuable insights into the potential use of ciprofol as a suitable alternative to propofol for anesthesia induction in cardiac surgery. While our results suggest that ciprofol offers similar hemodynamic stability and a lower incidence of injection pain compared to propofol, further investigation is warranted to better understand the clinical implications and potential advantages of ciprofol in various settings. While our study focused on the intraoperative hemodynamics and immediate safety profile of ciprofol, we acknowledge the importance of assessing long-term outcomes to fully evaluate the safety and efficacy of new anesthetic agents. The lack of long-term outcome data represents a limitation of this study, particularly given that anesthesia induction is known to have potential longer-term effects, especially in cardiac surgery patients. Future research will aim to address this gap by including extended follow-up to assess key outcomes such as postoperative cognitive dysfunction, respiratory complications, and myocardial injury. These efforts will provide a more comprehensive evaluation of ciprofol's long-term safety and efficacy, building on the current findings.

Conclusions

In summary, this study suggests that ciprofol anesthesia results in a lower incidence of injection pain compared to propofol, potentially enhancing patient comfort during anesthesia induction. Additionally, ciprofol demonstrates circulatory stability comparable to propofol during anesthesia induction in cardiac surgery, indicating that it could be a viable alternative to propofol for this specific application.

Abbreviations

NYHA	New York Heart Association
BIS	Bispectral index
ACT	Activated clotting time
LOC	Loss of corneal reflex
MAP	Mean arterial pressure

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Authors' contributions

Le Yu: Conceptualization, Methodology, Investigation process, Formal analysis, Original draft preparation. Xiang Liu: Methodology, Investigation process, Revising manuscript, Original draft preparation. Xiang Zhao: Interpretation of data, Revising manuscript. Xiu Shan: Investigation process. Evelyne Bischof: Conceptualization, Revising manuscript, Project administration, Revising manuscript. Hui-hong Lu: Conceptualization, Methodology, Resources, Project administration, Revising manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The trial was authorized by the Ethics Committee of East Hospital(2022/No.171), Tongji University, Shanghai, China, and was registered on ClinicalTrials.gov (NCT06312345). The patients/participants provided their written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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