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Effects of ciprofol for the induction of general anesthesia in patients scheduled for elective surgery compared to propofol: a phase 3, multicenter, randomized, double-blind, comparative study

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Abstract. – OBJECTIVE: Ciprofol is a newly developed intravenous sedative-hypnotic drug. The objective of the study was to prove whether ciprofol was non-inferior to propofol for the successful induction of general anesthesia. The ideal post-induction sedation level was assessed by comparing patients' clinical symptoms and their hemodynamic effects in responding to noxious stimuli, mostly tracheal intubation and bispectral index (BIS) alterations following ciprofol/propofol administration.

PATIENTS AND METHODS: In this multi-center, randomized, double-blind phase 3 trial, selective surgery patients were randomly assigned in a 1:1 ratio to either ciprofol 0.4 mg/kg (n = 88) or propofol 2.0 mg/kg (n = 88) groups. The primary endpoint was the percentage of patients with successful anesthesia inductions.

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Secondary endpoints included the times to successful induction of general anesthesia and loss of the eyelash reflex, changes in BIS, as well as safety indicators.

RESULTS: The anesthesia induction success rates for both ciprofol 0.4 mg/kg and propofol 2 mg/kg groups were 100.0%, with a 95% CI lower success limit of -4.18% difference between the two groups, indicating that ciprofol was non-inferior to propofol. For secondary outcomes, the average time to successful anesthesia and loss of the eyelash reflex were 0.91 min and 0.80 min for ciprofol and 0.80 min and 0.71 min for propofol, respectively. The pattern of BIS changes with ciprofol was similar to propofol and stable during the anesthesia maintenance period. Safety was comparable with 88.6% TEAEs in the ciprofol group compared to 95.5% in the propofol group. The incidence of injection pain was significantly lower in the ciprofol group compared to the propofol group (6.8% *vs.* 20.5%, $p < 0.05$). In addition, the patients treated with ciprofol had a lesser increase in blood pressure and heart rate, and fewer cases with BIS > 60 within 15 min of intravenous administration, which indicated that ciprofol may provide a better ideal sedation level during the post-induction period under an equivalent dosing regimen to propofol.

CONCLUSIONS: Ciprofol for patients undergoing selective surgery is a new option for the induction of general anesthesia.

Key Words:
Ciprofol, Propofol, General anesthesia, Injection pain, Elective surgery.

Abbreviations

BIS, bispectral index; GABAA, gamma-aminobutyric acid-A; BMI, body mass index; ECG, electrocardiogram; MOAA/S, Modified Observer's Assessment of Alertness/Sedation; SBP, systolic blood pressure; MAP, mean arterial pressure; DBP, diastolic blood pressure; HR, heart rate; SpO_2, pulse oxygen saturation; PACU, post anesthesia care unit; MedDRA, Medical Dictionary for Regulatory Activities; AEs, adverse events; SOC, system organ class; PT, preferred term; TEAEs, treatment emergent adverse events; AESI, AEs of special interest; CTCAE, Common Terminology Criteria for Adverse Events; CI, confidence interval; FAS, full analysis set; PPS, per-protocol set; SS, safety set.

Introduction

Ciprofol (HSK3486), is a new anesthetic that is a 2,6-disubstituted phenolic derivative which binds to the gamma-aminobutyric acid-A ($GABA_A$) receptor[1]. Compared to propofol, ciprofol exhibits stronger binding to the $GABA_A$ receptor and elicits a greater enhancement of $GABA_A$ receptor-mediated neuronal currents *in vitro*[1]. Our phase 1 trial in China showed that a single intravenous injection of ciprofol emulsion into healthy volunteers at a dose range of 0.15-0.90 mg/kg was well-tolerated[2,3] and exhibited a non-linear pharmacokinetic profile over a dose range of 0.40-0.90 mg/kg[3]. A phase 2 general anesthesia induction study was conducted in adults to investigate the efficacy and safety of ciprofol (NCT03698617). These completed trial results revealed that ciprofol in the dose range 0.3-0.5 mg/kg was non-inferior to propofol administered at 2.0-2.5 mg/kg. Furthermore, ciprofol could induce effective sedation with a rapid onset and recovery profile, had minimal residual actions and did not elicit significant pain at the injection site.

However, unbalanced anesthesia will lead to hemodynamic instability, early awareness or delayed recovery, sympathetic responses blood pressure (BP) and heart rate (HR) increases to strong noxious stimuli, such as tracheal intubation[4], and an alteration in BIS. Values of BIS between 40 and 60 reflect adequate hypnotic effect of general anesthesia, with reasonably rapid recovery of consciousness[5].

Here, we report the phase 3 trial results of a randomized, propofol-controlled study, which compared the sedative actions of both propofol and ciprofol in a large cohort of patients, with optimal injected doses of 0.4 mg/kg of ciprofol and 2.0 mg/kg of propofol, based on previous phase 1 and 2 study results.

Patients and Methods

This trial was conducted in 18 hospitals across China after approval from the Ethics Committee of the West China Hospital affiliated to the Sichuan University and all other participating hospitals. All of the patients who participated in the study provided prior written informed consent.

Study Design

A multi-center, randomized, propofol-controlled, double-blind trial was designed to compare the efficacy and safety of ciprofol 0.4 mg/kg and propofol 2 mg/kg for the induction of general anesthesia in patients scheduled for elective surgery requiring tracheal intubation. Considering safety factors, emergency, cardiothoracic and

brain surgery patients were excluded. A complete list of elective surgeries is provided in **Supplementary File 1**.

Based on the results of a phase 2 study (NCT03698617), ciprofol 0.4 mg/kg and propofol 2 mg/kg were used as the initial doses, because propofol at 2.5 mg/kg had previously been shown to produce a greater incidence of drug related adverse events. Figure 1a shows a schematic diagram of the study design and procedures performed at each time point and Figure 1b is the flow chart of the patients' random groupings. All patients were enrolled between March 2019 and August 2019. The trial was registered at ClinicalTrials.gov (NCT03808844).

Patients

The eligibility of patients for the study was determined by strict inclusion and exclusion criteria.

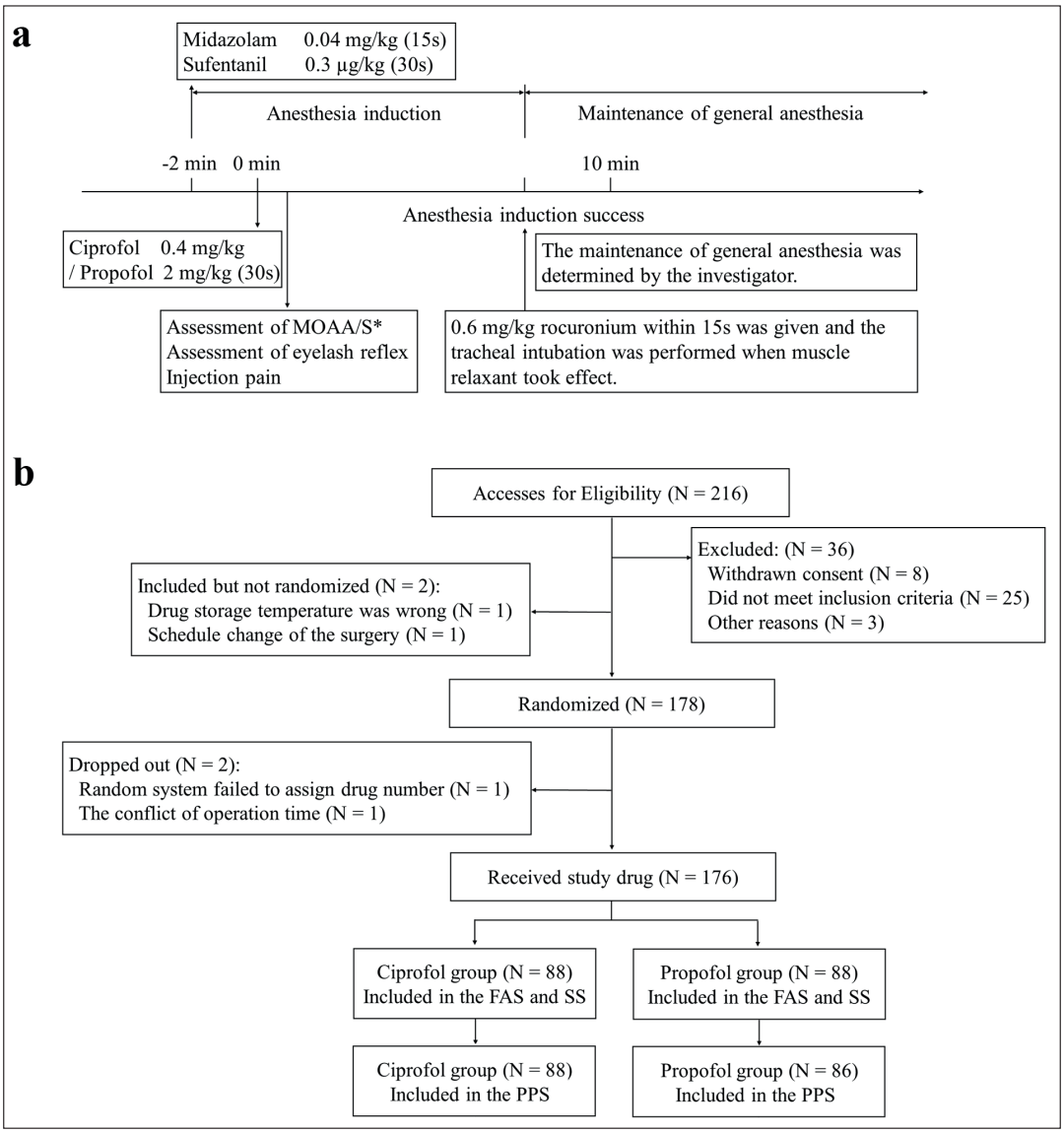

Figure 1. a, Schematic of the study procedures. MOAA/S. *If the patient failed to obtain a MOAA/S ≤ 1 (no response to mild prodding or shaking) within 1 min of the initial doses of the investigational drugs, a top-up (half of the initial dose, 10 s) was injected immediately. If MOAA/S ≤ 1 was not reached within 2 min, the second top-up dose was injected. If it still failed to have the desired effect, the induction of general anesthesia was considered to have failed and the alternative sedative propofol was administered, with the dose being determined by the investigator. **b,** Diagram of patients' flow. In total, 176 patients were included in the FAS and the SS (88 in the ciprofol group and 88 in the propofol group). In the propofol group, 2 patients were excluded because they received an incorrect dose of propofol during the study period. Therefore, data from 86 patients who received propofol and 88 patients who received ciprofol were analyzed in the PPS.

Inclusion Criteria

Patients aged 18-64 years with a body mass index (BMI) between 18 and 30 kg/m^2, American Society of Anesthesiologists physical status of I or II and scheduled to undergo elective surgery under general anesthesia were eligible.

Exclusion Criteria

Patients were excluded according to the following criteria: a history of allergy or hypersensitivity to the study drugs or its excipients which would have been used in the study; those who had clinically significant cardiovascular, respiratory or renal disease; pregnant or had a pregnancy plan within 1 month postoperatively; a family history of malignant hyperthermia; those who had surgery under general anesthesia within 4 weeks perioperatively; those who had previously received sedative/narcotic agents within 3 days of screening and had alcohol or drug abuse within 3 months perioperatively; QTc interval (correction QT interval by Fridericia's formula, [QTc = QT / $3\sqrt{RR}$]; RR = interval between two QRS complexes) $\geq$ 450 ms at screening; those who had previously received drugs that could have affected the QT interval or induced/inhibited P450 or CYP2B6 within 2 weeks perioperatively; those who had abnormal results of laboratory measurements during the screening period.

Study Procedures

Randomization and Blinding

The randomization schedule was computer-generated by employing a permuted block algorithm using Medidata Rave software (Medidata ID, Inc., USA). Patients were randomized on the day of surgery after investigators confirmed that the patients met the eligibility criteria. Then, two research nurses obtained the random numbers for preparing the investigational drug. Randomization was assigned sequentially as patients entered the study without site stratification.

All investigators and patients were blinded to the study drugs, except for the nurses who prepared them. It was not possible for a patient or the investigators who assessed consciousness status and adverse events (AEs) to know which drug was administered, thus maintaining the double-blind nature of the study.

Measurements During the Study Procedure (Pre-Operation, Intra-Operation, Post-Operation)

Before starting administration of the study drugs, a baseline 12-lead electrocardiogram (ECG) and laboratory measurements (routine blood tests, blood biochemistry analyses, urinalysis) were conducted for every patient. Two min prior to administration of the study drugs, 0.04 mg/kg midazolam (within 15 s) and 0.3 μg/kg sufentanil (within 30 s) were administered intravenously. Subsequently, in the operating room, patients received a bolus intravenous injection (over 30 s) of 2 mg/kg propofol or 0.4 mg/kg ciprofol. The injection pain was assessed, and the Modified Observer's Assessment of Alertness/Sedation (MOAA/S)[6] and the eyelash reflex were measured every 30 s after administration. Once a MOAA/S $\leq$ 1 (no response to mild prodding or shaking) was achieved, 0.6 mg/kg rocuronium was administered over a 15 s time period and tracheal intubation was performed after skeletal muscle relaxation occurred. If a patient failed to achieve MOAA/S $\leq$ 1 within 1 min of receiving the initial dose, a top-up dose (half of the initial dose administered over 10 s) was immediately injected. If patient did not reach MOAA/S $\leq$ 1 within 2 min, a second top-up dose was given as rescue medication. If this procedure was not effective, then the induction of general anesthesia with the investigational drug was defined as having failed, and rescue propofol was administered according to the investigator's clinical judgement. Patients were also monitored with a BIS sensor (Covidien IIc, Mansfield, MA, USA) positioned on the forehead and received oxygen through a face mask (1-4 L/min). Systolic blood pressure (SBP), mean arterial pressure (MAP) and diastolic blood pressure (DBP) were monitored during the induction of anesthesia and for the duration of the surgical procedure. Parameters including HR, pulse oxygen saturation (SpO_2), standard 3-lead ECG and the BIS score were recorded continuously during surgery.

At post-operation, all patients were extubated in the operating theatre, then transferred to the post anesthesia care unit (PACU) for observations until they were fully alert. A 12-lead ECG and clinical laboratory assessments (routine blood tests, blood biochemistry tests, urinalysis) were conducted on patients before discharge and at the follow-ups.

Endpoints

Primary Endpoint

The primary endpoint was the percentage of patients with successful general anesthesia inductions, which was defined according to the following criteria: (1) MOAA/S ≤ 1 after administration of a study drug (up to 2 top-up doses given); (2) did not require an alternative sedative.

Secondary Endpoints

Secondary endpoints were the times to anesthesia induction success and to loss of the eyelash reflex, which was evaluated during the induction period, and were defined as the time from the first administration of the study drug until a patient obtained a MOAA/S of ≤ 1, and to the time until complete loss of the eyelash reflex, respectively.

Changes in BIS values were continuously monitored from the beginning of administration of a study drug until the end of surgery and recorded at scheduled time points to measure any changes in trends of BIS during anesthesia.

Data obtained on the usage of the study drugs and alternative agents were used to evaluate ciprofol and propofol dosing, from the first administration of the study drug to successful induction of anesthesia (including top-up times, numbers of patients given top-up dose, each additional drug dose and the total dose). Evaluations of the use of the alternative (rescue) drug propofol from the beginning of administration of the study drug to successful induction with the alternative drug (propofol) were made, including top-up times, numbers of patients given top-up dose, each additional drug dose and total dosage, and the proportion of patients using the rescue drug for all patients in the different dosage groups.

Satisfaction evaluation of anesthesia induction, which included the anesthetist's satisfaction rating for the induction process, the depth of anesthesia, the anesthesia induction process and evaluation of additional drug use was estimated according to the score for a standard question, and total scores based on stored records.

Safety Indicators

Safety was assessed by physical examination, vital signs (supine HR; SBP; DBP and MBP, and the respiration rate and temperature), ECG. AEs of special interest (AESI) and SAE records were analyzed using Medical Dictionary for Regulatory Activities (MedDRA), ver. 22.0. AEs were classified according to the system organ class (SOC) and preferred term (PT), with frequency, severity and correlations between the drug or treatment and AEs. Treatment emergent AEs (TEAEs) were defined as those that occurred from the first administration of a study drug to the end of the investigation. AESI included: (1) hypoxemia (oxygen saturation < 90% for > 30 s); (2) bradycardia (HR < 45 beats/min for > 30 s); and (3) hypotension (systolic BP < 90 mmHg or it decreased by 30% from the baseline value for > 2 min). The corresponding severity of AEs was graded using Common Terminology Criteria for Adverse Events (CTCAE, ver. 5.0) namely: mild: grade 1; moderate: grade 2; and severe ≥ grade 3.

Sample Size and Power

Sample size calculations for this non-inferiority trial were based on the previous literature and a phase 2 study of ciprofol, in which the sedation success rate for propofol 2 mg/kg was 99% and the non-inferiority margin was 8%[7-12]. At a one-sided significant level of 0.025 and a power of 80%, 176 patients were required for the 2 groups, allowing for a possible dropout rate of 15%. Finally, each group was comprised of a cohort of 88 patients.

Statistical Analysis

Statistical analyses were carried out using SAS software version 7.1 (SAS Institute Inc., North Carolina, NC, USA). The primary efficacy was analyzed using the Newcombe-Wilson scoring method[13]. Differences in the success rate of induction of general anesthesia and the bilateral-sided 95% confidence interval (CI) were evaluated. Ciprofol 0.4 mg/kg was considered not inferior to propofol 2 mg/kg if the lower limit of the 95% CI for the success rate was > -8%. The other efficacy endpoints were analyzed using a log-rank test or Student's *t*-test. Vital signs were evaluated by repeated measurement data analysis of variance and AEs were compared using a chi-squared or Fisher's exact test. A p-value < 0.05 was considered to be statistically significant.

The efficacy data were analyzed for the full analysis set (FAS) and per-protocol set (PPS). The safety analyses were performed on the safety set (SS), which included all the randomized patients who had received at least one of the study drugs and who completed the safety assessment.

Results

A total of 216 potentially eligible patients were screened in 18 hospitals from March 2019 to August 2019. Finally, 176 patients (88 in the propofol group, 88 patients in the ciprofol group) were included in FAS and SS. In the propofol group, 2 patients were excluded as they received the wrong dose of propofol during the study period (Figure 1b). Therefore, PPS analysis included 86 patients who received propofol and 88 patients who received ciprofol. Demographics and baseline hemodynamics were carefully balanced between the 2 groups (Table I).

Table I. Demographics baseline and clinical hemodynamics*.

	Ciprofol (N = 88)	Propofol (N = 88)
Sex (M/F)	32/56	31/57
Age (years)	38.5 (12.1)	41.1 (11.1)
Weight (kg)	62.2 (11.1)	61.4 (10.6)
Height (cm)	163.0 (8.5)	162.1 (8.1)
BMI (kg/m^2)	23.3 (2.9)	23.3 (3.1)
ASA status (I/II)	51/37	48/40
SBP (mmHg)	121.8 (17.5)	122.2 (16.2)
DBP (mmHg)	75.3 (10.7)	75.6 (10.2)
MAP (mmHg)	88.4 (12.5)	89.3 (12.3)
HR (bpm)	72.1 (10.2)	70.8 (10.1)

Note: *Data are expressed as the mean (SD). Demographics and baseline hemodynamics were compared using a Student's *t*-test, chi-squared test or a Wilcoxon rank-sum test. There were no significant differences between the 2 groups with respect to demographics and baseline hemodynamics. ASA, American Society of Anesthesiologists; BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

Primary Efficacy Outcome for the Study Drug

The success rate of induction of general anesthesia in the 2 groups was 100%. The difference in the anesthesia induction success rate between the two groups was 0%, with a 95% CI of -4.18% to 4.18% in FAS. This result indicated that ciprofol at a dose of 0.4 mg/kg was not inferior to propofol 2 mg/kg for successful induction of anesthesia, based on the intravenous administration of 0.04 mg/kg midazolam (within 15 s) and 0.3 mg/kg sufentanil (within 30 s) for the induction of general anesthesia in patients scheduled for elective surgery (Table II).

Secondary Endpoints

For the secondary endpoints, the time to the successful induction of general anesthesia and time to loss of the eyelash reflex in the ciprofol group were longer than in the propofol group ($p < 0.05$). The time to successful induction of anesthesia exhibited significant differences, being 0.91 ± 0.03 min for the ciprofol group and 0.80 ± 0.03 min for the propofol group ($p < 0.05$, Figure 2a). The time to loss of the eyelash reflex was longer (0.80 ± 0.03 min) in the ciprofol group compared to the propofol group (0.71 ± 0.03 min) (Figure 2b).

Within 30 min of induction of general anesthesia, the objective sedation level assessed by changes in BIS values were evaluated. In general, the pattern of sedation level changes elicited by ciprofol was comparable to the propofol group. In the initial induction phase, BIS value in both the ciprofol and propofol groups decreased rapidly, with an almost identical pattern, except for slightly less reduction in the ciprofol group at 2 min, which reached the nadir point at the same time of 4 min (Figure 2c). At 4 min after initiation of drug administration, the mean BIS value (SD) of the ciprofol group was

Table II. Comparison of anesthesia induction success rates*.

	Group	Success (%)	Difference (%)	95% CI
FAS	Ciprofol	88 (100.0)	0	(-4.18%, 4.18%)
	Propofol	88 (100.0)	0	
PPS	Ciprofol	88 (100.0)	0	(-4.18%, 4.28%)
	Propofol	86 (100.0)	0	

Note: *The anesthesia induction success rate was analyzed using the Newcombe-Wilson score method. Differences in the success rate of anesthesia induction and the bilateral-sided 95% CI were evaluated. The lower limit of the 95% CI for the difference in anesthesia induction success rates was > -8% in FAS and PPS, which proves that ciprofol 0.4 mg/kg was not inferior to propofol 2 mg/kg for the anesthesia induction success rate. Data are expressed as numbers (%). CI, confidence interval; FAS, full analysis set; PPS, per-protocol set.

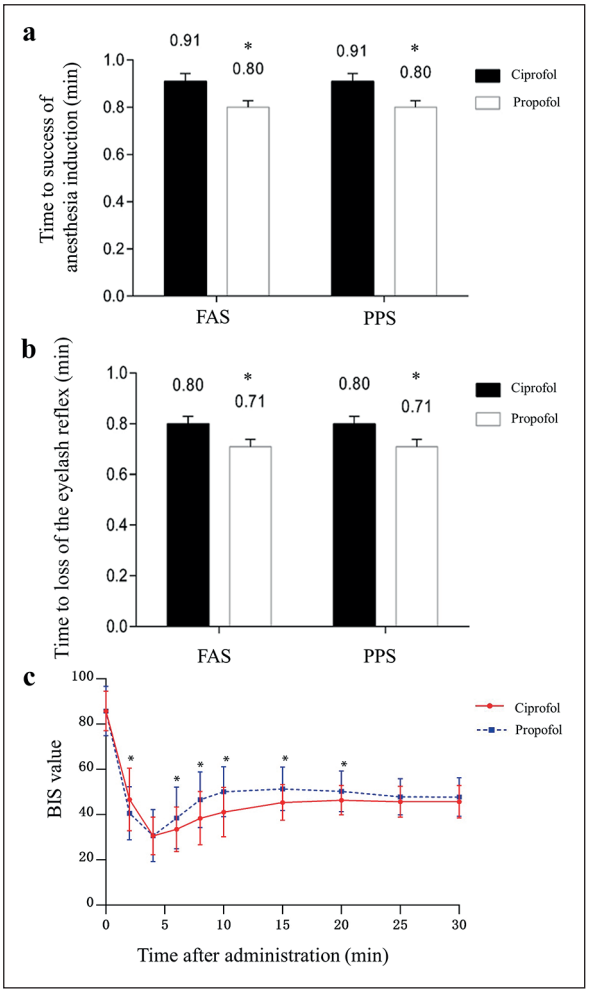

Figure 2. a, b, Comparison of the times to anesthesia induction successes and loss of the eyelash reflex in the ciprofol and propofol groups. The times to successful induction of anesthesia and loss of the eyelash reflex in the ciprofol group were prolonged compared to the propofol group ($^{*}p < 0.05$). FAS, full analysis set; PPS, per-protocol set. **c,** Within 30 min of administration, the average BIS values were higher in the ciprofol group compared to the propofol group at 2 min ($p < 0.05$), similar at 4 min, but lower between 6 and 20 min ($p < 0.05$). The lowest BIS values of the ciprofol group and propofol group were all obtained 4 min after induction of anesthesia. $^{*}p < 0.05$ between the 2 groups.

30.6 (8.3) ranging from 14.0 to 54.0 while the mean BIS value (SD) in the propofol group was 30.7 (11.4) ranging from 13.0 to 96.0. At the late induction phase starting from 6 min post initiation of drug administration, the BIS value was significantly lower at 6-20 min in the ciprofol group ($p < 0.05$), and more patients treated with ciprofol maintained BIS scores < 60 during this period of time.

Within 15 min of post induction, the patients with BP increases > 20% were 10 patients in the ciprofol group, less than the patients in the propofol group (n = 24) ($p < 0.05$) (Table III). More patients had mean BIS values > 60 in the propofol group compared with ciprofol group (14 *vs.* 2, $p < 0.05$), which indicates an inadequate sedation status. The average top-up times of drug administrations in the ciprofol and propofol groups were 1.1 and 1.0 times, respectively. The majority of patients did not need to be given the study drugs as top-ups. Only 8 patients (9.1%) in the ciprofol group and 2 (2.3%) in the propofol group received top-ups (Table IV). In addition, the average satisfaction scores for induction of anesthesia provided by anesthetists in the ciprofol and propofol groups were comparable (10.9 and 10.8; the maximum score was 12) **(Supplementary Table I)**.

A total of 78 patients (88.6%) in the ciprofol group exhibited 236 TEAEs and 84 patients (95.5%) in the propofol group experienced 282 TEAEs. The incidence of mild, moderate and severe TEAEs was 67, 49 and 2 in the ciprofol group; 68, 52 and 6, in the propofol group, respectively. Most TEAEs were mild to moderate, and self-limiting that patients recovered after treatment without any obvious residual clinical symptoms. AESIs occurred with a frequency of 103 in 58 (65.9%) patients in the ciprofol group and 106 in 58 (65.9%) patients in the propofol group. There were no significant differences in the AE, TEAE and AESI incidence between the 2 groups (Table V). No patients experienced SAEs in the ciprofol group, while 1 patient went into bronchospasm in the propofol group. The AEs related to ciprofol were hypotension, bradycardia, injection pain, hypoxemia, chill, myoclonus and vomiting (Table V). SBP, DBP, MAP and HR declined from the start of administration of the study drug at 2 min and then SBP, DBP, MAP and HR exhibited a small increase, then the values became stable in the 2 groups (Figure 3). Both groups showed the same change in trends of SBP, DBP, MAP and HR respectively, during the 30 min of anesthesia induction.

Discussion

In the present study, we first confirmed that the anesthesia induction success rate of ciprofol 0.4 mg/kg was non-inferior to propofol 2.0 mg/kg, with both drugs producing 100% anesthesia.

Table III. Comparison of the proportion of patients with BP increased by > 20% or HR increased by > 30% and BIS > 60 within 15 min after induction of general anesthesia by ciprofol and propofol.

Proportion of patients within 15 min post intravenous injection	Ciprofol (N = 88)	Propofol (N = 88)	*p*-value
Any BP increased > 20%	10 (11.4)	24 (27.3)	0.007
Any HR increased > 30%	27 (30.7)	38 (43.2)	0.086
BIS > 60	2 (2.3)	14 (15.9)	0.002
Any BP increased > 20% or BIS > 60	11 (12.5)	37 (42.0)	< 0.001

Note: BIS, bispectral index; BP, blood pressure; HR, heart rate.

Although the time for successful induction of anesthesia and the disappearance of the eyelash reflex were prolonged a little in the ciprofol group, the average time to anesthesia induction success in the 2 groups was still within 1 min, a finding which indicated that the study drugs could induce effective sedative effects with a rapid onset of action. In addition, the average doses of the study drugs used to induce anesthesia were 4-5 times higher in the propofol group compared to the ciprofol group (ciprofol 0.4 mg/kg, propofol 2.0 mg/kg), which suggests that ciprofol likely has stronger $GABA_A$ receptor binding activity[1].

Usually, BIS values measure the anesthetic state and sedation level, with a BIS value < 60 having a high probability of predicting the lack of patient consciousness[14]. BIS value changes showed similar patterns within 30 min of induction of anesthesia after starting administration of a study drug. However, the average changes of BIS values for ciprofol were lower than for propofol from 6 min to 20 min after administration, which might be the reason why ciprofol had a stronger sedative effect at 0.4 mg/kg compared to propofol at 2 mg/kg. It is possible that ciprofol had a different BIS profile late post induction phase compared to propofol. In addition, the

Table IV. Information about usage between the study and alternative drugs – FAS.

	Ciprofol (N = 88)	Propofol (N = 88)
Times of top-up dose		
Patients, n	88	88
Mean (SD) (times)	1.1 (0.3)	1.0 (0.2)
Median (times)	1.0	1.0
Minimum, Maximum (times)	1, 2	1, 2
Numbers of patients given top-up doses		
First administration only (n, %)	80 (90.9)	86 (97.7)
First additional administration only (n, %)	8 (9.1)	2 (2.3)
Second additional administration (n, %)	0	0
Total dose (top-up doses)		
Patients, n	8	2
Mean (SD) (mg)	12.3 (2.7)	56.5 (5.0)
Median (mg)	11.5	56.5
Minimum, Maximum (mg)	9, 18	53, 60
Planned exposure dose for each patient		
Patients, n	88	88
Mean (SD) (mg)	25.5 (5.7)	122.3 (22.1)
Median (mg)	24.5	119.2
Minimum, Maximum (mg)	16.6, 53.5	84.4, 178.5
Actual exposure dose for each patient		
Patients, n	88	88
Mean (SD) (mg)	26.0 (5.8)	121.8 (24.6)
Median (mg)	25.0	120.0
Minimum, Maximum (mg)	17, 54	24, 179
Alternative drugs (rescue drugs)		
Number of patients (n, %)	0	0

Table V. Summary of adverse events and drug-related adverse events.

	Ciprofol (N = 88)	Propofol (N = 88)	*p*-value
Adverse events* [n, N (%)]			
AE	242, 78 (88.6)	287, 84 (95.5)	0.160
TEAE	236, 78 (88.6)	282, 84 (95.5)	0.160
Mild TEAE	154, 67 (76.1)	174, 68 (77.3)	0.860
Moderate TEAE	80, 49 (55.7)	102, 52 (59.1)	0.650
Severe TEAE	2, 2 (2.3)	6, 6 (6.8)	0.280
SAE	0, 0 (0)	1, 1 (1.1)	1.000
AESI	103, 58 (65.9)	106, 58 (65.9)	1.000
Study drug-related adverse events[#] [N (%)]			
Hypotension	48 (54.5)	44 (50.0)	0.651
Bradycardia	11 (12.5)	12 (13.6)	1.000
Injection pain	6 (6.8)	18 (20.5)	0.014
Hypoxemia	2 (2.3)	1 (1.1)	1.000
Chill	1 (1.1)	0	1.000
Myoclonus	1 (1.1)	0	1.000
Vomiting	1 (1.1)	0	1.000
Tachycardia	0	3 (3.4)	0.246
Hypertension	0	1 (1.1)	1.000

Notes: *AE, TEAE, SAE and AESIs are expressed as times or numbers (%). AESI included: (1) hypoxemia (oxygen saturation < 90% for > 30 s); (2) bradycardia (HR < 45 beats/min for > 30 s); and (3) hypotension (systolic BP < 90 mmHg or decreased by 30% from the baseline value for > 2 min). The corresponding severity was graded using Common Terminology Criteria for Adverse Events (CTCAE, ver. 5.0). mild: grade 1, moderate: grade 2, severe: ≥ grade 3. The data were analyzed by Fisher's exact test. There were no significant differences in AE, TEAE, SAE and AESI between the ciprofol and propofol groups. [#]Data are expressed as numbers (%). The AEs related to the study drug were included as related, likely related, and possibly related to the study drug, which were judged by investigators according to a defined table. Hypotension included operative hypotension and a decrease in blood pressure. A hypoxic state included hypoxia and a decrease in oxygen saturation. Bradycardia included sinus bradycardia and a decrease in HR. Tachycardia included sinus tachycardia and an increase in HR. AE, adverse event; AESI, adverse events of special interest; HR, heart rate; SAE, serious adverse event; TEAE, treatment emergent adverse event.

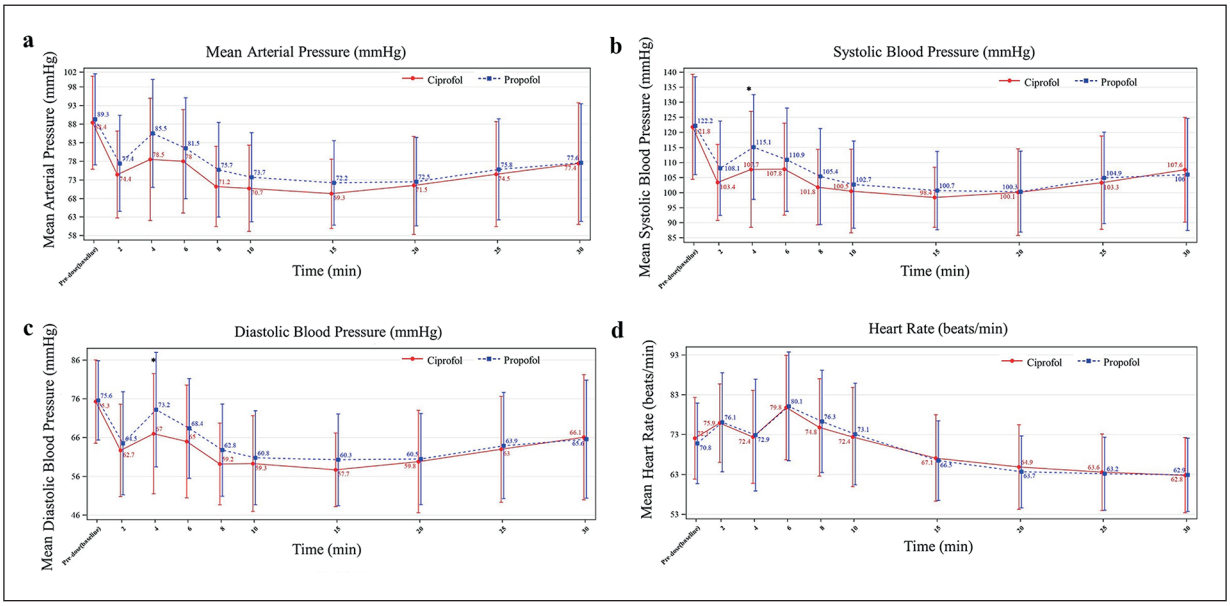

Figure 3. Comparisons of **(a)** mean arterial pressure (MAP), **(b)** systolic blood pressure (SBP), **(c)** diastolic blood pressure (DBP) and **(d)** heart rate (HR) between the 2 groups. The SBP, DBP, MAP and HR decreased from 2 min after administration of the study drug and then increased, possibly due to intubation. Subsequently, SBP, DBP, MAP and HR were decreased and then became stable in both groups of patients. Data are expressed as the mean. * indicates $p < 0.05$ between the 2 groups.

large range of BIS values in the 2 groups during induction of anesthesia revealed individual differences after administration that suggested it was better to carry out personalized treatment using the study drugs.

In addition, within 15 min post-injection of ciprofol and propofol, the proportion of patients with BP increased by > 20%, HR increased by > 30% and BIS > 60 after ciprofol were significantly less than in the propofol group, strongly indicating that ciprofol provided a better ideal sedation level. Note that this ideal level produced by ciprofol is under an equivalent efficacious dosing regimen compared to propofol. Both groups treated with ciprofol and propofol achieved the same successful induction rates and exhibited virtually identical safety profiles in the post induction period.

In this phase 3 clinical study, the AEs distribution for ciprofol was similar to that of propofol, with the AEs being predominantly mild to moderate. No patients experienced SAEs in the ciprofol group while 1 patient went into bronchospasm in the propofol group. The AEs related to the study drug were hypotension, bradycardia, injection pain, hypoxemia, chill, involuntary movement and vomiting. Ciprofol administration produced a similar degree of hypotension and bradycardia compared to propofol.

In the present study, the patients were given assisted ventilation when the investigators found that a patient's MOAA/S was ≤ 1. Therefore, an effect of the drug on the respiratory system was not observed, but the patients' oxygen saturation was within the normal range throughout the procedure in the 2 groups. Previous studies found that ciprofol produced less respiratory related AEs during colonoscopy. Propofol has the common disadvantage of producing pain on injection, which is ranked as the third most commonly avoidable AE associated with the induction of general anesthesia[15]. About 64% (95% CI: 60% to 67.9%) of patients experienced injection pain when propofol alone was used and the injection pain resulted in a very unpleasant experience[16,17]. The concentration of free propofol in the aqueous phase is related to the injection pain[18,19]. In the present study, ciprofol produced a lower incidence of injection pain (6.8% *vs.* 20.5%, $p = 0.014$) compared to propofol because the higher potency of ciprofol provides the potential to produce a lower concentration in the aqueous phase. In addition, the incidence of injection pain was 20.5% in the propofol group, which was lower than reported in the literature, with perhaps pre-operative medication with sufentanil being the main reason[16].

Our study had a number of limitations, for example, a combination of sufentanil and midazolam may confound the sedation effect of the study drug. Propofol combined with sufentanil or midazolam is a combination choice when inducing general anesthesia[20]. Sufentanil and midazolam given before propofol administration can reduce the pain of the propofol injection[16,21] thus improving patient comfort and relieving the fear of the induction pain. It is general clinical practice in China to use an opioid and benzodiazepine together with propofol during the induction of anesthesia.

Conclusions

Ciprofol 0.4 mg/kg and propofol 2 mg/kg were both effective and well-tolerated and ciprofol is a useful alternative general anesthesia option for patients scheduled for elective surgery.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by all authors. The first draft of the manuscript was written by Xia Wang, Xiao Wang and Yunxia Zuo. Xiao Wang, Jin Liu and Yunxia Zuo commented on previous versions of the manuscript. All authors read and approved the final submitted version.

Clinical Trial Registration

Clinicaltrials.gov, under identifier NCT03808844, registered on January 18th, 2019.

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