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ORIGINAL RESEARCH

# Efficacy and safety of ciprofol compared to propofol during hysteroscopy: a single-centre, randomized, positive-controlled study

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## Abstract

**Background**: Sedation is frequently performed to alleviate the discomfort associated with hysteroscopy. Ciprofol, an isomer of propofol, exhibits rapid onset and recovery characteristics and may serve as an alternative sedative agent. This single-centre, randomized, positive-controlled study aimed to compare the efficacy and safety of ciprofol and propofol during hysteroscopy. **Methods**: A total of 94 women undergoing hysteroscopy were randomly allocated to receive either ciprofol or propofol. The primary endpoint was the sedation success rate, and the secondary endpoints included the time to effective sedation onset, time to full alertness, time to exit the operating room, cumulative sedative dose, incidence of injection pain, satisfaction levels, and occurrence of respiratory and circulatory adverse events (RAEs and CAEs). **Results**: Both groups achieved a 100% anesthesia success rate with no differences observed in time to effective sedation onset (40.0 $\pm$ 12.3 s *vs.* 44.9 $\pm$ 12.1 s, $p = 0.056$), time to full alertness (3.8 $\pm$ 1.8 min *vs.* 4.6 $\pm$ 2.9 min, $p = 0.096$), or time to exit the operating room (8.5 $\pm$ 2.6 min *vs.* 9.5 $\pm$ 4.6 min, $p = 0.2$) in the ciprofol versus propofol groups. The cumulative dose of ciprofol was 6 times lower than that of propofol (62.5 $\pm$ 26.7 mg *vs.* 380.6 $\pm$ 172.8 mg, $p < 0.01$). Compared with ciprofol, propofol resulted in a lower patient satisfaction rate (57.4% *vs.* 100%, $p < 0.001$) and a significantly higher incidence of injection pain (42.6% *vs.* 0.0%, $p < 0.001$). Additionally, RAEs and CAEs occurred more frequently in the propofol group than in the ciprofol group. **Conclusions**: Ciprofol provided sedation efficacy comparable to propofol during hysteroscopy, while demonstrating advantages in terms of lower anesthetic dosage, reduced incidence of injection pain, higher patient satisfaction, and fewer respiratory and circulatory adverse events. **Clinical Trial Registration**: This study was registered at http://www.chictr.org.cn (13 December 2022, ChiCTR2200066674).

## Keywords

Propofol; Ciprofol; Anesthesia; Sedation; Hysteroscopy

## 1. Introduction

With the continuous advancement of minimally invasive techniques, hysteroscopy has become widely utilized for the diagnosis and treatment of endometrial and other intrauterine disorders [1]. Despite its diagnostic and therapeutic value, the procedure often causes substantial discomfort, prompting the integration of sedation strategies to achieve painless management. Among the available agents, propofol is most frequently used due to its favorable pharmacokinetic profile, characterized by a rapid onset of action and quick recovery [2]. However, the use of propofol is associated with several limitations, including a high incidence of adverse effects such as injection pain, respiratory depression, circulatory instability, and the rare but serious complication of propofol infusion syndrome [3, 4]. These limitations present significant challenges in maintaining both patient comfort and procedural safety during hysteroscopy.

Ciprofol is an isomer of propofol that contains a cyclopropyl group, which enhances its affinity for Gama-aminobutyric acid (GABA) receptors and promotes greater chloride ion influx, thereby producing sedative and anesthetic effects. Preclinical studies have shown that ciprofol has the advantages of rapid onset and prompt recovery, and compared to propofol, it also exhibits a wider safety margin, with a therapeutic index that is approximately 2.4 times higher [5]. A clinical trial demonstrated that 0.4–0.5 mg/kg of ciprofol could produce sedative and anesthetic effects comparable to 2.5 mg/kg of propofol, with similar recovery durations [6]. Other studies have reported that ciprofol is 4–5 times more potent than


  

propofol, thereby allowing for a significant reduction in the required anesthetic dosage, less pain at the injection site, and a lower incidence of respiratory-related adverse events [7, 8]. Similar findings have been observed in patients undergoing fiberoptic bronchoscopy and in those admitted to intensive care units (ICUs), where ciprofol provided equivalent anesthetic and sedative effects to propofol, while maintaining approximately fivefold greater potency [9, 10]. In addition, ciprofol has shown better overall safety, reflected by a lower frequency and reduced severity of drug-related adverse events, as well as decreased lipid intake. Clinical trials have also reported a 100% success rate for general anesthesia induction with ciprofol. Compared with propofol, ciprofol was better tolerated, showing smaller hemodynamic fluctuations, fewer drug-related adverse events, and milder injection pain [11].

Given these advantages, the present study was designed as a randomized positive-controlled trial to compare the efficacy and safety of ciprofol and propofol in patients undergoing hysteroscopy, with the aim to provide new clinical evidence regarding the application of ciprofol in procedural sedation and anesthesia.

## 2. Methods

### 2.1 Study design

This single-centre, randomized, positive-controlled, non-inferiority trial was conducted at Heyuan People's Hospital between 01 May 2022, and 31 December 2022. A total of 94 participants were enrolled and randomly assigned using a computer-generated randomization tool in a 1:1 ratio to receive either ciprofol (n = 47) or propofol (n = 47).

### 2.2 Eligibility criteria for participants

Patients were considered eligible if they met the following criteria: (1) aged between 18 and 65 years; (2) body mass index (BMI) ranging from 18 to 30 kg/m$^2$; (3) classified as American Society of Anesthesiologists (ASA) physical status I or II; (4) scheduled for elective hysteroscopy under sedation; and (5) meeting the following baseline vital signs: respiratory rate (RR) of 10–24 breaths/min, peripheral oxygen saturation ($SpO_2$) $\geq$95%, systolic blood pressure (SBP) of 85–140 mmHg, diastolic blood pressure (DBP) of 50–90 mmHg, and heart rate (HR) of 50–100 beats/min.

Participants were excluded if they met any of the following criteria: (1) history of alcohol abuse; (2) known allergy to general anesthetics; (3) long-term use of sedative-hypnotic or anti-anxiety medications; (4) history of poorly controlled or malignant hypertension; (5) presence of severe ischemic heart disease, renal, or hepatic dysfunction; (6) pregnancy or lactation; (7) recent respiratory tract infection; or (8) neurological or psychiatric disorders associated with impaired communication.

### 2.3 Randomization and blinding

Randomization was performed using computer-generated random numbers created in Microsoft Excel 2010 (Microsoft Office, Redmond, WA, USA). The participants were assigned sequentially to either ciprofol or propofol according to the predefined number sequence. An independent researcher conducted the randomization process to ensure allocation concealment and minimize bias. The randomization list was generated and sealed before the start of the trial and was not disclosed until data collection was completed. A single-blind design was implemented, whereby participants and data recorders remained blinded to group assignments throughout the study.

### 2.4 Interventions

The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is presented in Fig. 1. Throughout the surgical procedure, continuous monitoring was performed for mean arterial pressure (MAP), SBP, DBP, HR, $SpO_2$, RR, and electrocardiography (ECG). Baseline data such as age, height, weight, BMI, procedure duration, and ASA physical status classification were recorded before the administration of the study drugs. All patients underwent preoperative fasting for at least 8 hours and were restricted from clear liquids for a minimum of 2 hours before operation. Additionally, an intravenous infusion of compound sodium chloride (300–500 mL) was administered within 60 minutes before drug administration.

Patients randomized to the ciprofol group received an intravenous bolus of ciprofol at 0.4 mg/kg, delivered over 30 seconds. This dosing regimen was based on a randomized phase III trial, which demonstrated the non-inferiority of 0.4 mg/kg ciprofol compared to 2.0 mg/kg propofol for anesthesia induction [12]. Hysteroscopy was initiated once the Modified Observer's Alertness/Sedation (MOAA/S) score was confirmed to be $\leq$2 [13]. If the MOAA/S score $\leq$2 was not achieved within 2 minutes following the initial dose, an additional 0.2 mg/kg of ciprofol was administered intravenously over 10 seconds. Subsequent supplemental doses of ciprofol (0.2 mg/kg) were permitted as indicated by MOAA/S evaluations, with a maximum of five supplemental doses allowed within 15 minutes. If the target sedation level could not be achieved within these limits, a propofol-based rescue protocol was initiated.

Patients randomized to the propofol group received a standardized induction protocol with 2.0 mg/kg of propofol. Hysteroscopy was initiated after confirming a MOAA/S score $\leq$2. If this sedation level was not reached within 2 minutes of the induction dose, an additional 1.0 mg/kg of propofol was administered. Supplemental doses of propofol (1.0 mg/kg) were administered as needed based on MOAA/S assessments to maintain adequate sedation. All patients received preprocedural oxygen supplementation via face mask at a rate of 6 L/min for at least 3 minutes prior to induction, and oxygenation was continued throughout the procedure until full recovery.

### 2.5 Endpoints

#### 2.5.1 Primary endpoint

The primary efficacy endpoint was the hysteroscopy anesthesia success rate, which was defined by the simultaneous fulfillment of two conditions: (1) successful completion of the hysteroscopy procedure, and (2) administration of the study

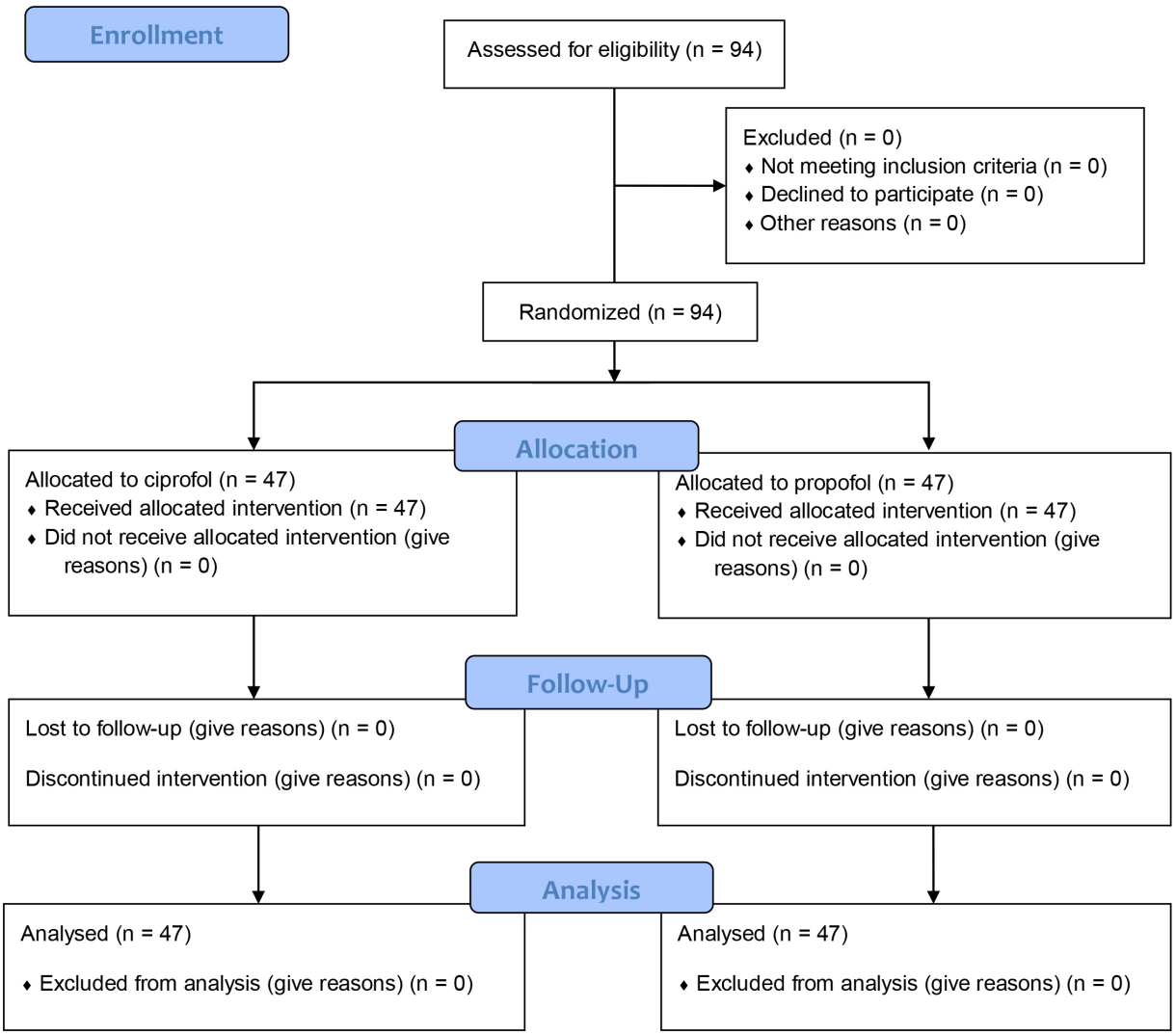


**FIGURE 1. CONSORT Flow Diagram for participant selection.**

drug fewer than five times within 15 minutes without the need for rescue sedatives or anesthetics throughout the procedure.

### 2.5.2 Secondary endpoints

The secondary endpoints included: (1) time to effective sedation onset, defined as the interval between the initial administration of the study drug and achievement of a MOAA/S score $\leq$2; (2) time to being fully alert, defined as the duration from the end of the procedure to the first occurrence of three consecutive MOAA/S scores of 5; (3) time to exit from the operating room, defined as the interval from the end of the procedure to attainment of a Steward score $\geq$4 on three consecutive assessments; (4) the average dosage of study drugs administered per subject; (5) satisfaction with sedation and anesthesia as reported by the surgeons, and subjective comfort reported by the patients; (6) incidence of injection pain; and (7) occurrence of involuntary body movement during the procedure.

### 2.5.3 Safety

Safety in this study was evaluated based on the occurrence rate of RAEs including hypoxia ($SpO_2$ <95% and duration >30 s), respiratory depression (respiratory rate <8 breaths/min and duration >30 s) and CAEs comprising bradycardia (HR <55 beats per min and duration >30 s), hypotension (SBP <90 mmHg or DBP <60 mmHg or MAP $\leq$30% of baseline value and duration >2 min) and arrhythmia. Changes in MAP, HR, $SpO_2$ and RR were recorded at five predefined time points: before anesthesia (T0), 2 minutes after induction (T1), at cervical dilatation (T2), at the end of the operation (T3), and during awakening (T4). Postoperative complications, including dizziness, nausea, and vomiting, were also monitored and recorded.

The severity of Adverse Events (AEs) was defined as Grade 1 (mild): asymptomatic or mild, without medication treatment; Grade 2 (moderate): clinical symptoms that require medication treatment; or Grade 3 (severe): Severe clinical symptoms leading to prolonged hospitalization, restricted daily activities, disability or death.

## 2.6 Sample size calculation

This trial adopted a non-inferiority design to test whether sedation with ciprofol is not inferior to propofol during hysteroscopy. Assuming a success rate of 98% for both groups based on evidence from clinical practice, a total of at least 94

participants, including an estimated 10% dropout rate, were required to demonstrate non-inferiority with a margin ($\Delta$) of 10%, 90% statistical power, and a one-sided significance level ($\alpha$) of 0.025.

### 2.7 Statistical analysis

All statistical analyses were conducted using SPSS Statistics software version 25.0 (Statistical Product and Service Solutions, Chicago, IL, USA). Quantitative variables following a normal distribution, verified by the Shapiro-Wilk test, were expressed as mean ± standard deviation and compared between groups using the independent samples *t*-test. Non-normally distributed continuous variables were analyzed using the Wilcoxon signed-rank test. For variables measured at multiple time points, repeated-measures analysis of variance (ANOVA) was applied. Mauchly's test was used to assess the sphericity assumption; when this assumption was violated, the Greenhouse-Geisser correction was applied. *Post-hoc* analysis of time effects was performed using Bonferroni correction. Categorical variables were expressed as counts and percentages, and group differences were analyzed using Pearson's chi-square test. A $p$-value $< 0.05$ was considered statistically significant.

## 3. Results

### 3.1 Baseline characteristics of enrolled patients

From May 2022 to December 2022, all 94 randomized female participants successfully completed the study without any protocol deviations. No statistically significant differences were observed between the two groups in terms of age, height, weight, procedure duration, or ASA physical status. All participants underwent the same type of surgery, and no intraoperative complications occurred. After matching, no significant differences in potential confounding factors were found between the groups (Table 1).

### 3.2 Primary endpoint

The primary endpoint, defined as successful hysteroscopy anesthesia, was achieved in 100% of patients in both the ciprofol and propofol groups.

### 3.3 Secondary endpoints

#### 3.3.1 Time to effective sedation onset

The mean time to effective sedation onset was 40.0 ± 12.3 seconds in the ciprofol group and 44.9 ± 12.1 seconds in the propofol group, but this difference was not statistically significant ($p = 0.056$; Table 2).

#### 3.3.2 Time to being fully alert and time out of the operating room

The mean time to full alertness was 3.8 ± 1.8 minutes in the ciprofol group and 4.6 ± 2.9 minutes in the propofol group ($p = 0.096$). Similarly, the mean time out of the operating room was 8.5 ± 2.6 minutes versus 9.5 ± 4.6 minutes, respectively, with no significant difference between the two groups ($p = 0.199$; Table 2).

#### 3.3.3 Cumulative doses of study drugs

The median of cumulative doses of study drugs in ASA I patients was 157.5 (56.0, 342.5) mg, and that of ASA II was 78.0 (61.80, 300.0) mg. There was no significant difference between cumulative doses of study drugs of ASA I patients and that of ASA II ($p = 0.433$; **Supplementary Table 1**). The total drug dose was significantly lower in the ciprofol group compared to the propofol group (62.5 ± 26.7 mg *vs.* 380.6 ± 172.8 mg, $p < 0.01$; Table 2).

#### 3.3.4 Satisfaction of patients and surgeons

In the trial, the surgeons' satisfaction was comparable between the two groups (100% *vs.* 89.4%, $p > 0.05$). However, patients' satisfaction was significantly higher in the ciprofol group than in the propofol group (100% *vs.* 57.4%, $p < 0.001$; Table 2).

**TABLE 1. Baseline demographic characteristics of patients by treatment group.**

| Characteristic* | Propofol Group (N = 47) | Ciprofol Group (N = 47) | *p* value |
|---|---|---|---|
| Age (yr) | 41.0 ± 10.2 | 40.0 ± 8.7 | 0.618 |
| Height (cm) | 156.7 ± 4.5 | 156.5 ± 4.3 | 0.796 |
| Weight (kg) | 55.4 ± 6.4 | 53.7 ± 7.5 | 0.236 |
| Procedure duration (SD, min) | 32.9 ± 21.9 | 32.3 ± 15.8 | 0.863 |
| ASA status classification, n (%) | | | |
| I | 41 (87.2%) | 38 (80.9%) | 0.398 |
| II | 6 (12.8%) | 9 (19.1%) | |

*ASA: American Society of Anesthesiologists; SD: Standard Deviation; *: numerical characteristics are presented as mean ± SD while categorical variables as n (%).*

### 3.3.5 Body movement

Involuntary body movements were observed in 2 patients (4.3%) in the ciprofol group and 6 patients (12.8%) in the propofol group. This difference was not statistically significant ($p = 0.267$; Table 2).

## 3.4 Safety assessments

### 3.4.1 Incidence of pain on injection

Injection pain occurred in 42.6% of patients in the propofol group, whereas no cases were reported in the ciprofol group ($p < 0.001$; Table 3).

### 3.4.2 Adverse events

The incidence of respiratory and circulatory adverse events was lower in the ciprofol group. Specifically, hypoxia occurred in 5 patients (10.6%) in the propofol group and in 1 patient (2.1%) in the ciprofol group. Respiratory depression was observed in 6 patients (12.8%) in the propofol group, while none was observed in the ciprofol-treated patients. Hypotension was recorded in 24 patients (51.5%) receiving propofol and in 8 patients (17.0%) receiving ciprofol. Dizziness occurred in 3 patients (6.4%) in the propofol group but none in the ciprofol group. No incidents of bradycardia or nausea/vomiting were reported in either group (Table 3).

**TABLE 2. Summary of secondary endpoints between the two treatment groups.**

| Secondary endpoint* | | Propofol group (N = 47) | Ciprofol group (N = 47) | *p* value |
|---|---|---|---|---|
| Time to effective sedation onset (s) | | 44.9 ± 12.1 | 40.0 ± 12.3 | 0.056 |
| Fully alert time (min) | | 4.6 ± 2.9 | 3.8 ± 1.8 | 0.096 |
| Time out of the operating room (min) | | 9.5 ± 4.6 | 8.5 ± 2.6 | 0.199 |
| Cumulative doses of study drugs (mg) | | 380.6 ± 172.8 | 62.5 ± 26.7 | <0.001 |
| Body movement, n (%) | | 6 (12.8%) | 2 (4.3%) | 0.267 |
| Satisfaction ratings, n (%) | | | | |
| Patients | | | | |
| | Satisfaction | 27 (57.4%) | 47 (100.0%) | |
| | General satisfaction | 20 (42.6%) | 0 (0.0%) | <0.001 |
| | Dissatisfaction | 0 (0.0%) | 0 (0.0%) | |
| Surgeons | | | | |
| | Satisfaction | 42 (89.4%) | 47 (100.0%) | |
| | General satisfaction | 5 (10.6%) | 0 (0.0%) | 0.066 |
| | Dissatisfaction | 0 (0.0%) | 0 (0.0%) | |

*SD: Standard Deviation; *: numerical endpoints are presented as mean ± SD while categorical variables as n (%).*

**TABLE 3. Summary of adverse events in the two treatment groups.**

| | | Propofol Group (N = 47), n (%) | Ciprofol Group (N = 47), n (%) | *p* value |
|---|---|---|---|---|
| Hypoxia | | 5 (10.6%) | 1 (2.1%) | 0.206 |
| Respiratory depression | | 6 (12.8%) | 0 (0.0%) | 0.035 |
| Bradycardia | | 0 (0.0%) | 0 (0.0%) | 1.000 |
| Hypotension | | 24 (51.5%) | 8 (17.0%) | <0.001 |
| Pain on injection | | 20 (42.6%) | 0 (0.0%) | <0.001 |
| Dizziness | | 3 (6.4%) | 0 (0.0%) | 0.241 |
| Nausea/vomiting | | 0 (0.0%) | 0 (0.0%) | 1.000 |
| Severity of AEs | | | | |
| | Mild | 29 (62.0%) | 9 (19.0%) | |
| | Moderate | 0 (0.0%) | 0 (0.0%) | <0.001 |
| | Severe | 0 (0.0%) | 0 (0.0%) | |

*AEs: Adverse Events.*

### 3.4.3 Changes in circulation

Compared to T0, reductions in MAP, HR, and $SpO_2$ were observed at time points T1 through T4 in both groups; however, all values remained within clinically acceptable limits. Notably, $SpO_2$ fluctuations were smaller in the ciprofol group, while MAP and HR showed no significant differences between the groups (Fig. 2A–C).

## 4. Discussion

Hysteroscopy plays a vital role in the diagnosis and treatment of infertility, recurrent miscarriage, uterine malformations, and various other intrauterine pathologies. Despite its clinical value, the procedure is often associated with considerable discomfort, particularly during cervical dilation and curettage, making it intolerable for many patients [14, 15]. As a result, anesthesia is commonly required to ensure patient comfort. Currently, intravenous anesthesia, typically involving the administration of intravenous anesthetics in combination with opioids, is the most widely adopted approach for hysteroscopic procedures [16]. This study evaluated the efficacy and safety of ciprofol compared to propofol during hysteroscopy. All the enrolled participants successfully completed the procedure in both groups, yielding a 100% anesthesia success rate. Our findings confirmed that ciprofol was non-inferior to propofol for hysteroscopic sedation, with no participants requiring alternative sedative agents, and all receiving $\leq$5 bolus doses within 15 minutes. Notably, the total amount of drug administered in the propofol group was five to six times higher than that required in the ciprofol group, reflecting the higher potency of ciprofol.

Propofol remains one of the most commonly used intravenous sedatives, favored for its rapid onset, short recovery time, and high metabolic clearance. However, its clinical utility is often limited by adverse effects such as cardiovascular depression, respiratory suppression, and injection site pain. In this present study, ciprofol demonstrated a similarly rapid onset, suggesting comparable induction properties, which aligns with previous phase III trials that reported similar sedation profiles between ciprofol and propofol during procedures such as gastroscopy and colonoscopy [17]. Moreover, no significant differences were observed between the two treatment groups in terms of time to full alertness or time to exit the operating room, consistent with earlier trials evaluating ciprofol's effectiveness in both the induction and maintenance of general anesthesia [18, 19], further supporting its comparable sedative and anesthetic efficacy.

In this study, the higher incidences of hemodynamic instability (notably hypotension), respiratory complications (including hypoxia and respiratory depression), and dizziness observed in the propofol group compared to the ciprofol group may reflect the stronger potentiation of GABA receptors by propofol. No cases of bradycardia or nausea and vomiting were reported in either group. Among the adverse reactions commonly associated with propofol, injection pain, occurring in approximately 70% of administrations, was considered the most frequent and clinically relevant [20, 21]. In our trial, the incidence of injection site pain was significantly higher in the propofol group than in the ciprofol group (42.6% *vs.* 0.0%), a result consistent with findings from previous phase II studies [7]. This is potentially attributed to the unique molecular structure of ciprofol, which incorporates a cyclopropyl group to form a chiral structure based on the propofol backbone. This structural modification enhances the stereoeffect and increases GABA receptor affinity, while also reducing the concentration of free molecules in plasma, which may underlie the observed reduction in injection pain. Most patients expressed satisfaction with their sedation experience. Notably, patient satisfaction was significantly higher in the

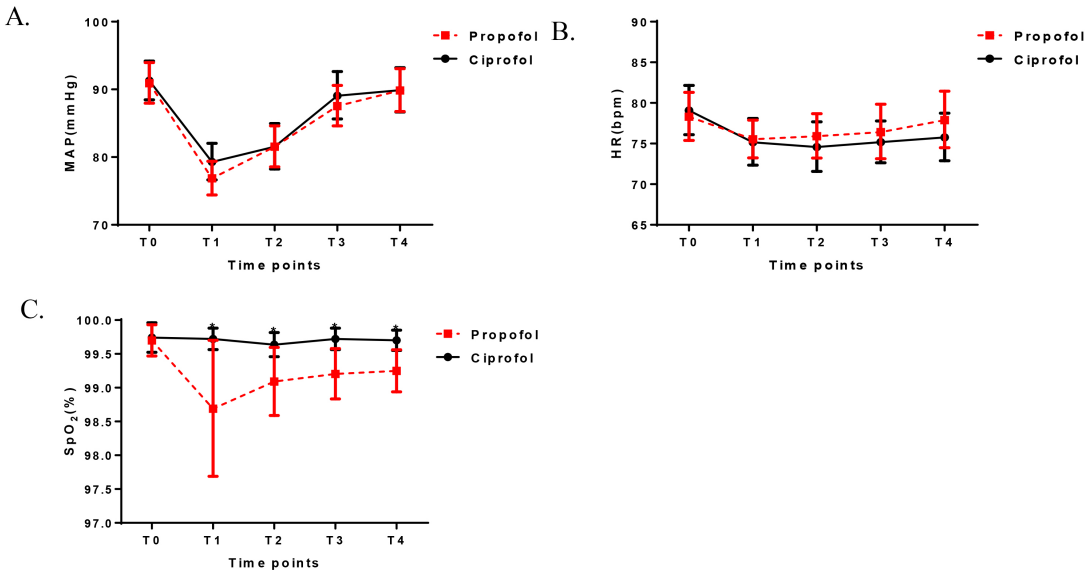


**FIGURE 2. Comparisons of (A) mean arterial pressure (MAP), (B) heart rate (HR), and (C) pulse oxygen saturation ($SpO_2$) between the ciprofol and propofol groups.** Data are mean with the 95% confidence interval. *$p < 0.05$ compared to propofol at the same time points. T0: Pre-anaesthesia; T1: 2 min post induction; T2: The beginning of the operation; T3: The end of the operation; T4: Awakening.

ciprofol group, which may be primarily associated with the absence of injection pain. Notably, our findings indicate that ciprofol induced fewer cardiovascular effects compared to propofol, while maintaining comparable efficacy in stabilizing heart rate and blood pressure. Furthermore, pulse oxygen saturation remained more stable in the ciprofol group, suggesting a superior safety profile in terms of respiratory function. Collectively, these findings support the potential of ciprofol as a safer alternative to propofol for hysteroscopic anesthesia, due to its minimal respiratory suppression and more stable hemodynamic profile during sedation.

## 5. Limitations

This study had several limitations. First, all enrolled participants were classified as ASA physical status I or II, which limits the generalizability of the findings to patients with more complex comorbidities. Further studies are needed to evaluate whether the comparative effects of ciprofol and propofol on circulatory and respiratory systems differ in higher-risk populations. Second, as a single-center trial with a relatively limited sample size, the statistical power to detect subtle intergroup differences was constrained, and thus larger multicenter studies are necessary to validate these results.

## 6. Conclusions

Ciprofol demonstrated sedation efficacy comparable to that of propofol during hysteroscopy, but it did not induce injection pain and was associated with fewer respiratory and circulatory adverse events. Although this single-center trial provides preliminary evidence supporting the clinical utility of ciprofol, future multicenter studies with larger and more diverse patient populations are warranted to establish more definitive clinical recommendations.

### AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

### AUTHOR CONTRIBUTIONS

GLX, WBH and DSP—contributed equally to this work; wrote the manuscript. GLX, WBH, DSP and WYL—designed the research study, analyzed the data. GLX, WBH, DSP, QTC, YHL, QX and SJP—performed the research. All authors read and approved the final manuscript.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Clinical Research Ethics Committee of Heyuan People's Hospital (Approval No. YXLL-2022K05), which was registered at http://www.chictr.org.cn (13 December 2022, ChiCTR2200066674). All patients have signed informed consent for the study.

### ACKNOWLEDGMENT

Not applicable.

### FUNDING

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1972934568091500544/attachment/Supplementary%20material.docx.

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