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CLINICAL TRIAL REPORT

Efficacy and Safety of Ciprofol for Anesthesia in Painless Colonoscopy with Varying Body Mass Indices Patients: A Prospective, Single-Center, Observational Study

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Background: Ciprofol, a novel intravenous anesthetic derived from propofol, exhibits high lipophilicity. Its pharmacokinetics and pharmacodynamics may vary across different body mass indices (BMI) categories, but data on its optimal dosing as well as its safety and efficacy during colonoscopy anesthesia in varying BMI groups are lacking.

Objective: To evaluate the efficacy and safety of ciprofol during anesthesia for painless colonoscopy in patients with varying BMI, and to explore the correlation between BMI and induction dose.

Methods: The BMI classification standard used in this study followed the criteria used in China. This prospective, single-center, observational study enrolled two hundred patients and they were divided into three groups with BMI: Group A (18.5–23.9 kg/m²), Group B (24–27.9 kg/m²), and Group C (28–39.9 kg/m²). Ciprofol was administered slowly (3 seconds per milliliter) until MOAA/S ≤1. Induction dose, additional ciprofol use, procedure duration, recovery time, vital signs, and adverse events were recorded.

Results: The total induction dose was higher in Groups B and C than in Group A, with Group C receiving the highest dose ($P<0.001$). Dose per kilogram of TBW was lower in Groups B and C ($P<0.001$), while corrected body weight (CBW)-based dosing showed no significant difference between groups ($P=0.287$). There were no significant differences in procedure duration, recovery time, or adverse events among groups.

Conclusion: Ciprofol is safe and effective for colonoscopy anesthesia across BMI groups, offering stable hemodynamics without prolonging recovery or increasing adverse events. CBW is a reliable dosing metric for overweight and obese patients.

Keywords: ciprofol, body mass index, colonoscopy, anesthesia

Introduction

The global prevalence of obesity has risen dramatically in recent decades, presenting significant public health challenges.[1] According to the World Health Organization, 16% of the adult population is now classified as obese,[2] and this percentage continues to grow. In parallel, the demand for painless colonoscopy is also increasing, driven by the rising prevalence of colorectal cancer and the emphasis on early detection through patient-friendly screening methods. In China, the number of obese patients undergoing painless colonoscopy is also steadily increasing, presenting unique challenges for anesthesiologists.[3] Obesity is associated with altered pharmacokinetics and pharmacodynamics of anesthetic agents,[4] complicating the determination of optimal dosing and increasing the risk of complications such as respiratory depression, hemodynamic instability, and prolonged recovery times.[5,6] Given these challenges, selecting an effective and safe anesthetic and establishing optimal dosing guidelines for patients with varying body mass indices (BMI), particularly those who are overweight or obese, is therefore critical.

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Ciprofol is a novel 2.6-disubstituted phenol derivative and new intravenous anesthetic with a chemical structure similar to that of propofol. It introduces a cyclopropyl group into the propofol structure, which increases the spatial effect and enhances the gamma-aminobutyric acid type A (GABAA) receptor-mediated chloride ion channel, leading to increased current conduction that causes neuronal hyperpolarization. This results in dose-dependent central nervous system depression, producing sedative/anesthetic effects similar to those of propofol.[7,8] Numerous preclinical and clinical studies[9–11] have highlighted the advantages of ciprofol over propofol, including its rapid onset, reduced injection pain, and higher potency, which have garnered significant attention. Recent multicenter Phase II and III studies conducted in China have confirmed that, like propofol, ciprofol is safe and effective for the induction and maintenance of general anesthesia in elective surgeries, gastroscopy, colonoscopy, and bronchoscopy in the general population.[7,12–14] However, the safety, efficacy, and optimal anesthetic administration standards of ciprofol for patients with varying BMI remains uncertain. This is particularly important for overweight and obese patients, who may require tailored dosing to prevent drug accumulation and mitigate associated complications.[15,16]

Therefore, we aimed to compare the safety and efficacy of ciprofol in anesthesia for painless colonoscopy among patients with different BMI categories. Our objective was to identify the most appropriate weight-based dosing metric for painless colonoscopy to improve the safety and effectiveness of anesthesia in overweight or obese patients. This research could have significant implications in clinical practice by providing evidence-based guidance on the optimal dosing strategy for ciprofol in diverse patient populations.

Materials and Methods

This prospective clinical trial was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Jiangxi Provincial People's Hospital (The First Affiliated Hospital of Nanchang Medical College) [reference No. Kekuai 2023(40); December 29, 2023], and registered at https://www.chictr.org.cn (ChiCTR2400079345). Informed consent was obtained from all patients and their families prior to the procedure.

Patients who underwent painless colonoscopy at Jiangxi Provincial People's Hospital (The First Affiliated Hospital of Nanchang Medical College) between January 2024 and June 2024 were enrolled in this study. The inclusion criteria were as follows: age 18–80 years, BMI 18.5–39.9 kg/m², and American Society of Anesthesiologists (ASA) classification I–II. The exclusion criteria were as follows: patients who refused or were uncooperative with anesthesia and sedation (eg, those with a history of psychiatric disorders); patients with severe arrhythmias or cardiopulmonary diseases; a history of myocardial infarction or unstable angina within the past 6 months; respiratory diseases or a pulse oxygen saturation (SpO_2) <95% without oxygen supplementation; pregnant or breastfeeding women; known allergies to eggs, soy products, opioids, antagonists, or propofol; participation in other drug clinical trials as a subject within the past 3 months; or any other conditions deemed unsuitable for trial participation by the researchers. The required sample size was estimated using NCSS-PASS software version 15.0. Based on the results of the preliminary study, the calculation was performed with a two-sided significance level (α) of 0.05 and a statistical power (1-β) of 0.9, with an assumed dropout rate of 20%. The analysis indicated that a minimum of 42 patients per group was required. Thus, a total of 214 patients were recruited in the study and classified into three groups based on their BMI values: Group A (normal weight), BMI 18.5–23.9 kg/m²; Group B (overweight), BMI 24–27.9 kg/m²; and Group C (obese), BMI 28–39.9 kg/m². The BMI classification standard used in this study followed the criteria used in China, where BMI ≥28 kg/m^2 was defined as obesity. A professional anesthesiologist administered the drugs based on the patient's modified observer's assessment of alertness/sedation (MOAA/S) score and their motor and verbal responses during the procedure. Another anesthesiologist evaluated the study endpoints and collected data. All personnel involved in data analysis and endoscopy operators were blinded to the study details.

All patients underwent standardized bowel preparation. Before entering the examination room, the patients were placed in a waiting area where a peripheral intravenous line was established. Lactated Ringer's solution was infused at a rate of 1 mL/kg/min to maintain an adequate volume. Patients were advised to relax and alleviate any anxiety or nervousness to ensure that they were fully prepared for the procedure. Upon entering the examination room, electrocardiogram monitoring was initiated to track the blood pressure, heart rate (HR), and oxygen saturation. Nasal cannula

oxygen was administered at the standard flow rate of 6 L/min. After the patient was placed in the left lateral decubitus position with the knees flexed, ciprofol (HaiSiKe, Liaoning, China) was slowly injected at a rate of 3s/mL. Drug administration ceased when the patient's MOAA/S score reached≤1, at which point an experienced endoscopist began the colonoscopy. The time points for the procedure were defined as follows: T0-patient enters the examination room, T1-beginning of the colonoscopy, T2-examination of the cecum, and T3-completion of the procedure. At each time point, the mean arterial pressure (MAP), HR, SpO_2, and occurrence of perioperative adverse events (respiratory depression, hypotension, bradycardia, nausea and vomiting, dizziness, and muscle twitching) were recorded. During the procedure, additional ciprofol was administered intermittently based on the patient's physical movements to maintain an MOAA/S score of 1. In cases of a significant blood pressure drop, where MAP decreased by more than 20% from baseline or systolic blood pressure fell below 90 mmHg, the infusion rate of crystalloids was increased. If hypotension persisted, ephedrine 5–10 mg was administered. If the patient developed bradycardia with a HR of <50 bpm, atropine 0.5 mg was administered. If intraoperative hypoxemia occurred (1) (SpO_2 < 90%), the following interventions were sequentially applied: a chin-lift maneuver (performed by the anesthesiologist using the middle, ring, and little fingers to lift the mandibular angle while closing the patient's mouth with the thumb and index fingers); (2) If SpO_2 did not improve within 30s or continued to drop below 80%, positive-pressure ventilation with a face mask was performed; and (3) intubation and mechanical ventilation were employed if necessary. At the end of the endoscopic examination, the patients were transferred to the post-anesthesia care unit (PACU) for observation for at least 30 min. Postoperative adverse events (nausea, vomiting, and dizziness) were assessed. Patients were discharged from the PACU with their family members once their Modified Aldrete score reached ≥ 9.

The primary efficacy outcomes were (1) The induction dose of ciprofol and the total number and times of patients who received additional ciprofol. (2) Changes in vital signs at different time periods (ΔMAP, ΔHR, and ΔSpO_2).

The secondary efficacy outcomes included the following:(1) Colonoscopy procedure time (from insertion to withdrawal of the colonoscope). (2) Recovery time (from the end of the procedure to an MOAA/S score of 5). (3) Occurrence of perioperative adverse events, including respiratory depression (SpO_2 continuously below 90% for more than 10 seconds), hypotension (MAP decreased by more than 20% from baseline or systolic blood pressure below 90 mmHg), bradycardia (HR less than 50 bpm), nausea (defined as a specific subjective sensation of stomach discomfort and fullness, often a precursor to vomiting, accompanied by salivation and repeated swallowing movements), vomiting (defined as a strong reflex contraction of the stomach with the rapid expulsion of stomach contents through the mouth from the stomach and esophagus), dizziness (characterized by a sensation of lightheadedness without spatial disorientation), and muscle spasms (involuntary tonic contractions of the muscles).

Statistical analyses were performed using SPSS 25.0 software. The Shapiro–Wilk test was applied to determine whether continuous variables were normally distributed. For normally distributed data, descriptive statistics are presented as mean ± standard deviation. Repeated measures analysis of variance (ANOVA) was used for comparisons at different time points, whereas one-way ANOVA was used for group comparisons, with post-hoc tests conducted using Bonferroni multiple comparisons. Non-normally distributed data were presented as medians with interquartile ranges, and between-group comparisons were performed using non-parametric tests (Kruskal–Wallis test). If a statistically significant difference was detected, pairwise comparisons were conducted using a post-hoc test (Dunn's test) with Bonferroni correction for multiple comparisons. Categorical data are expressed as frequency (%), and comparisons were made using the chi-square test or Fisher's exact test. A *P*-value of <0.05.

Results

From January 2024 to June 2024, 214 patients who underwent painless colonoscopy were recruited at Jiangxi Provincial People's Hospital (the First Affiliated Hospital of Nanchang Medical College). Among these, 10 patients did not meet the inclusion criteria, and 4 patients had colonoscopies that could not reach the cecum. Consequently, the remaining 200 patients were included in this clinical study. Patients were categorized into three groups based on their BMI: Group A (n=73), Group B (n=76), and Group C (n=51) (Figure 1). All 200 patients successfully underwent painless colonoscopy under sedation. During the procedure, no signs of discomfort were observed in their facial expressions. Post-

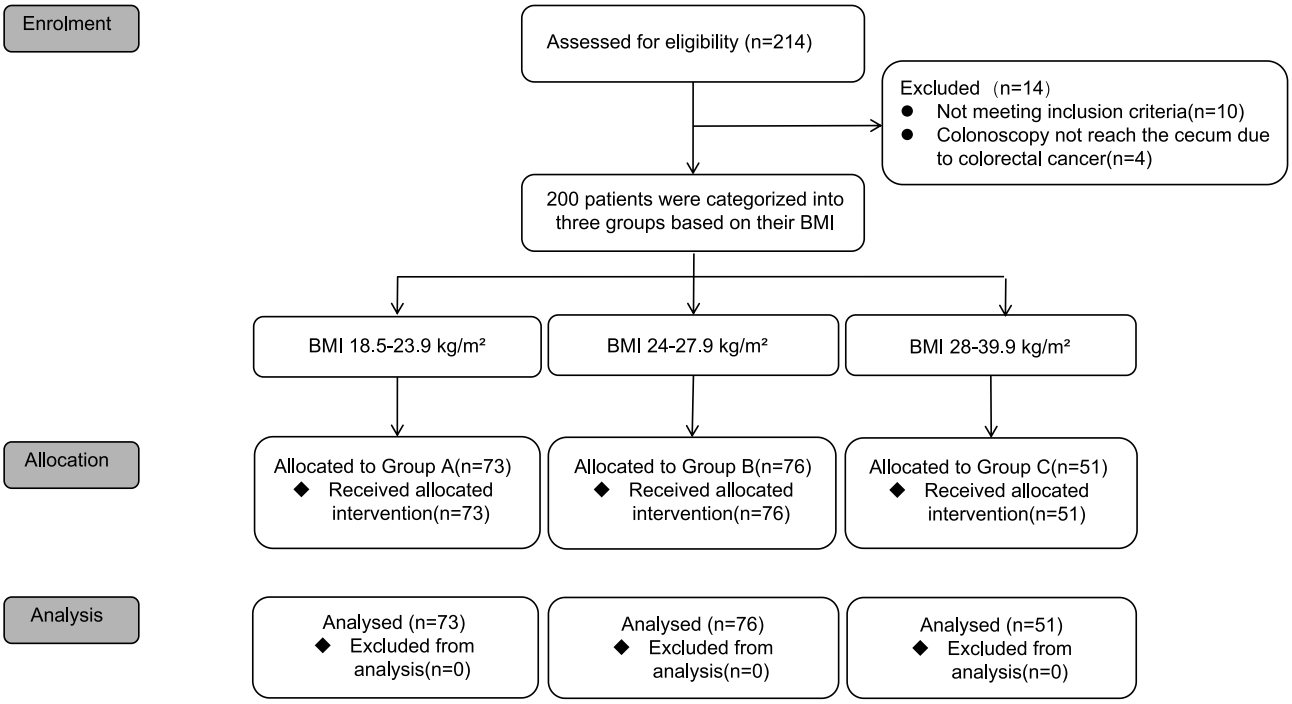

Figure 1 Participant flow diagram.

procedure follow-up confirmed that all patients reported being in a sleep-like state throughout the procedure and did not experience any pain.

Demographic and Clinical Characteristics

There were no significant differences in baseline characteristics (age, gender, ASA) and colonoscopy duration among the three groups (Table 1).

Primary Outcomes: Induction Dose

Based on the induction doses of ciprofol administered during colonoscopy, we calculated the dose per kilogram of the total body weight (mg/TBW), ideal body weight (mg/IBW), lean body weight (mg/LBW), and corrected body weight

Table 1 Patient Demographics and Baseline Values

	Group A (n=73)	Group B (n=76)	Group C (n=51)	$F/\chi^2/H$	P
Age (yr)	51.44±15.93	55.03±12.46	49.33±14.02	2.64	0.073
Gender					
Male	34(46.6%)	49(64.5%)	32(62.7%)	5.65	0.059
Female	39(53.4%)	27(35.5%)	19(37.3%)		
ASA PS					
I	12(16.4%)	10(13.2%)	8(15.7%)	0.34	0.844
II	61(83.6%)	66(86.8%)	43(84.3%)		
Operation time(min)	10(8 to15)	11(9 to14)	9(7 to 12)	4.37	0.112

Notes: Data are presented as mean ± SD, median [IQR] or number (%). *F* for mean ± SD, *H* for median (IQR). χ^2 for number (%).
Abbreviation: ASA PS, American Society of Anesthesiologists Physical Status.

Table 2 Comparison of Induction Doses of Ciprofol Among the Groups

	Group A (n=73)	Group B (n=76)	Group C (n=51)	*F*	*P*
Total induction dose (mg)	28.41±4.32	30.56±5.26*	33.73±5.91*#	16.20	0.000
Induction dose per kg TBW (mg/TBW)	0.50±0.09	0.44±0.06*	0.40±0.07*#	27.42	0.000
Induction dose per kg IBW (mg/IBW)	0.50±0.07	0.52±0.07	0.55±0.10*#	7.03	0.001
Induction dose per kg LBW (mg/LBW)	0.69±0.14	0.62±0.09*	0.60±0.13*	9.62	0.000
Induction dose per kg CBW (mg/CBW)	0.50±0.08	0.48±0.07	0.48±0.08	1.26	0.287

Note: Data are presented as mean ± SD, *P<0.05, cf. Group A, #P<0.05, cf. Group B.
Abbreviations: TBW, total body weight; IBW, lean body weight; LBW, ideal body weight; CBW, corrected body weight.

(mg/CBW). (1) The total induction dose was significantly higher in Groups B and C compared to Group A, with Group C receiving more than Group B (28.41±4.32 vs 30.56±5.26 vs 33.73±5.91, P<0.001);

(2) There was no significant difference in the induction dose per kilogram of CBW across the three groups (0.50±0.08 vs 0.48±0.07 vs 0.48±0.08, P=0.287). (3) Groups B and C had lower doses per kilogram of TBW than Group A, and Group C's dose was lower than that of Group B (0.50±0.09 vs 0.44±0.06 vs 0.40±0.07, P<0.001); (4) For the dose per kilogram of IBW, Group C had higher values than both Group A and Group B (0.50±0.07 vs 0.52±0.07 vs 0.55±0.10, P=0.001). The difference between Groups A and B was not statistically significant (0.50±0.07 vs 0.52±0.07, P=0.478). (5) Induction doses per kilogram of LBW were lower in Groups B and C compared to Group A (0.69±0.14 vs 0.62±0.09 vs 0.60±0.13, P<0.001), with no significant difference between Groups B and C (0.62±0.09 vs 0.60±0.13, P=0.572). (Table 2).

Primary Outcomes: Additional Ciprofol

No significant differences were observed among the three groups in the total number (P=0.634) and times (P=0.497) of patients who received additional ciprofol or in the recovery time (P=0.806) (Table 3).

Primary outcomes: Hemodynamics

Similarly, there were no significant differences in the variations in MAP, HR, and SPO_2 among the groups at different time points (P>0.05) (Table 4).

Secondary Outcomes

The incidence of perioperative adverse events (respiratory depression, hypotension, bradycardia, nausea and vomiting, dizziness, muscle spasms) was also comparable across the groups, with no significant differences (P>0.05) (Table 5).

Table 3 Comparison of the Total Number and Times of Patients Who Received Additional Ciprofol and Patient Recovery Times Among the Groups

	Group A (n=73)	Group B (n=76)	Group C (n=51)	χ^2/ *H*	*P*
Received additional ciprofol (numbles)	29(39.7%)	28(36.8%)	16(31.4%)	0.91	0.634
Received additional ciprofol (times)	0(0 to1)	0(0 to1)	0(0 to 1)	1.40	0.497
Recovery time (min)	5(3 to 9)	6(3 to 9)	5(3 to 7)	0.43	0.806

Notes: Data are presented as number (%), median (IQR). χ^2 for number (%), *H* for median (IQR).

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Table 4 Comparison of Changes in Vital Signs Over Different Time Periods

		Group A (n=73)	Group B (n=76)	Group C (n=51)	*F/H*	*P*
T0-T1	ΔMAP (mmHg)	13.55±9.61	13.28±9.11	12.73±8.60	0.12	0.885
	ΔHR (bpm)	3.25±6.80	3.80±6.72	2.90±4.92	0.33	0.720
	ΔSPO_2 (%)	0(−1 to 0)	0(−1.75 to 0.75)	0(−1 to 1)	0.64	0.731
T0-T2	ΔMAP (mmHg)	13.99±9.52	13.07±9.12	12.63±8.76	0.37	0.694
	ΔHR (bpm)	5.75±4.92	7.76±6.94	6.98±4.81	2.30	0.103
	ΔSPO_2(%)	0(−1 to 0)	0(−2 to 0)	0(−1 to 0)	2.65	0.266
T0-T3	ΔMAP (mmHg)	14.70±11.03	12.97±7.94	10.88±8.95	2.47	0.087
	ΔHR (bpm)	5.58±5.54	6.75±5.10	5.55±4.46	1.27	0.284
	ΔSPO_2(%)	0(−1 to 0)	−1(−2 to 0)	0(−1 to 0)	3.73	0.155

Notes: Data are presented as mean ± SD, median (IQR). *F* for mean ± SD, *H* for median (IQR). Δ refers to the former data minus the latter data.

Abbreviations: MAP, mean arterial pressure; HR, heart rate; SPO_2, pulse oxygen saturation. T0, patient enters the examination room; T1, beginning of the colonoscopy; T2, examination of the cecum; T3, completion of the procedure.

Table 5 Incidence of Adverse Events

	Group A (n=73)	Group B (n=76)	Group C (n=51)	χ^2	*P*
Respiratory depression	0(0.0%)	1(1.3%)	2(3.9%)	2.71	0.261
Hypotension	28(38.4%)	33(43.4%)	15(29.4%)	2.55	0.280
Bradycardia	0(0.0%)	2(2.6%)	0(0.0%)	2.19	0.339
Nausea and vomiting	0(0.0%)	0(0.0%)	0(0.0%)	–	–
Dizziness	4(5.5%)	3(3.9%)	3(5.9%)	0.45	0.847
Muscle spasms	1(1.4%)	1(1.3%)	0(0.0%)	0.86	1.000

Note: Data are presented as number (%).

Discussion

Ciprofol, a structural analog of propofol, exhibits a stronger binding affinity to the γ-aminobutyric acid type A receptor. A Phase I clinical trial[15] evaluating the dose escalation of ciprofol for general anesthesia induction found that doses between 0.4–0.9 mg/kg were well tolerated, with rapid onset and recovery of consciousness, without an increased incidence of adverse events compared to propofol. Despite these findings, most clinical studies on ciprofol dosing have primarily relied on patients' TBW as the basis for dose calculation.[17] Owing to ciprofol's high lipid solubility, overweight or obese patients often require higher doses to achieve adequate plasma concentrations during anesthesia induction. However, using TBW as the dosing metric in these populations increases the risk of drug overdose and associated adverse events.[18] Currently, there is a lack of clinical data on the safety and dosing guidelines for ciprofol in overweight and obese patients, and whether alternative metrics, such as lean body weight (LBW), ideal body weight (IBW), or corrected body weight (CBW), are more appropriate for determining the optimal dose remains unclear.

Therefore, in our study, we recorded the induction dose of ciprofol as well as the total number and times of patients who received additional ciprofol. The results revealed that, as BMI increased, the total induction dose of ciprofol also increased, however, the per-kilogram ciprofol induction dose calculated based on TBW decreased with increasing BMI, indicating that in overweight and obese patients, the dosing during colonoscopy was not necessarily determined according to the fixed per-kilogram regimen recommended in the prescribing information or prior clinical studies. This finding suggests a potential risk of overdose and associated adverse effects in overweight and obese patients when using TBW-based dosing is applied.

Some studies have suggested that LBW is a better dosing metric for propofol in patients.[19,20] However, Subramani et al found that LBW-based propofol dosing may not achieve sufficient depth of anesthesia in morbidly obese patients,

necessitating additional doses.[21] Ciprofol, a propofol analog with high lipid solubility, is theoretically expected to have dosing considerations similar to those of propofol. In our study, we found that CBW-based dosing showed no significant differences in per kilogram induction dose among the three BMI groups or in the number of additional doses required. This suggests that, regardless of a patient's BMI, weight-adjusted dosing based on CBW can achieve comparable sedation effects when adhering to the prescribing information. Therefore, CBW may serve as an ideal dosing metric for colonoscopy anesthesia induction with ciprofol in overweight and obese patients. This finding differs from those of previous studies on propofol, likely due to the unique pharmacological properties of ciprofol, highlighting the need for further large-scale multicenter clinical studies to confirm these results.

Propofol exhibits certain cardiovascular suppressive effects,[22] typically manifested as a decrease in blood pressure and a reduction in heart rate. Obese patients tend to exhibit increased sensitivity to propofol, which may exacerbate these cardiovascular effects.[23] Although ciprofol shares similar pharmacological effects with propofol, our study revealed that after induction, vital signs such as mean arterial pressure, heart rate, and blood oxygen saturation showed varying degrees of fluctuation across all three groups. Importantly, the amplitude of these fluctuations remained within a safe range. Through fluid supplementation and monitoring, the vital signs of all patients normalized without requiring the use of vasoactive drugs. This may be attributed to the relatively milder effects of ciprofol on the respiratory and circulatory systems compared to propofol, and the differences between groups were not statistically significant, which is consistent with the findings of Wang.[24] This suggests that ciprofol provides a relatively stable anesthetic effect across patients with different BMI during colonoscopy anesthesia induction.

The literature indicates that being overweight or obese is an independent risk factor for obstructive sleep apnea (OSA), which can increase the risks.[25] In this study, one patient in Group B and two patients in Group C experienced varying degrees of snoring and tongue falling backward after anesthesia induction, with blood oxygen saturation decreasing to below 90%, resulting in hypoxemia. These conditions were rapidly alleviated and normalized by jaw lifting. This may be due to the increased weight of fat in the thorax and abdomen in overweight or obese patients, which reduces chest wall compliance and increases the mechanical load on the respiratory system, leading to a decrease in functional residual capacity and impaired oxygenation compared to normal-weight patients.[26] All patients successfully completed colonoscopy, with similar recovery times. Although some patients experienced dizziness and muscle twitching, no special treatment was required, and all recovered to normal after observation, with a Modified Aldrete score of $\geq$ 9. These findings are consistent with previous research.[27] In conclusion, despite the occurrence of transient hypoxemia in overweight or obese patients compared to normal-weight patients, the duration was extremely brief and did not lead to severe complications.

Overall, ciprofol is safe and effective for painless colonoscopy anesthesia in overweight or obese patients.

This study has several limitations: (1) It is a small-sample, single-center clinical trial. (2) The study relied solely on the MOAA/S score as the evaluation standard, introducing a degree of subjectivity. (3) Ciprofol plasma concentrations were not measured or compared. Future directions will be to conduct larger multicenter trials incorporating BIS to monitor the depth of anesthesia and compare plasma concentrations of ciprofol in different patient populations so that its clinical application can be more fully evaluated.

Conclusion

This study demonstrates that ciprofol is safe and effective for colonoscopy anesthesia in patients with varying BMI groups, providing stable hemodynamics without prolonging recovery time or increasing the incidence of adverse reactions. Furthermore, CBW appears to be an ideal dosing metric for ciprofol induction in overweight and obese patients undergoing painless colonoscopy.

Abbreviations

BMI, body mass index; GABBA, gamma-aminobutyric acid type A; TBW, total body weight; LBW, lean body weight; IBW, ideal body weight; CBW, corrected body weight; ASA, American Society of Anesthesiologists; SpO_2, pulse oxygen saturation; MOAA/S, modified observer's assessment of alertness/sedation; HR, heart rate; MAP, mean arterial pressure; PACU, post-anesthesia care unit; ANOVA, analysis of variance.

Data Sharing Statement

Data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval and Informed Consent

This prospective clinical trial was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Jiangxi Provincial People's Hospital (The First Affiliated Hospital of Nanchang Medical College) [reference No. Kekuai 2023(40); December 29, 2023], and registered at https://www.chictr.org.cn (ChiCTR2400079345).

Consent for Publication

All authors have approved the manuscript and given their consent for submission and publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether 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.

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Disclosure

The authors report no financial competing interests.

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