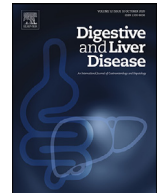




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Digestive Endoscopy

Comparison of ciprofol–alfentanil and propofol–alfentanil sedation during bidirectional endoscopy: A prospective, double-blind, randomised, controlled trial

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ABSTRACT

Background: Although propofol is widely used for gastrointestinal endoscopic sedation, cardiopulmonary adverse events remain common. Ciprofol is a new intravenous anaesthetic agent demonstrating respiratory and hemodynamic stability.

Aims: This study aimed to clarify the benefits of ciprofol combined with alfentanil in bidirectional endoscopy (esophagogastroduodenoscopy followed by colonoscopy) to reduce adverse events and improve post-endoscopic recovery.

Methods: A total of 185 patients scheduled to undergo bidirectional endoscopy were randomly divided into two groups: ciprofol combined with alfentanil or propofol combined with alfentanil. All patients received 7 µg/kg alfentanil intravenously before the study drugs were administered. The propofol group received a bolus of 1.2 mg/kg (0.12 ml/kg) propofol intravenously, whereas the ciprofol group received a bolus of 0.3 mg/kg (0.12 ml/kg) ciprofol intravenously. The primary outcome was the proportion of patients with cardiopulmonary adverse events (i.e., any one of the airway obstruction, apnoea, hypotension, hypertension, bradycardia, tachycardia or arrhythmias).

Results: Compared with propofol, ciprofol reduced cardiopulmonary adverse events by 43.51 % (34.4% vs. 60.9 %, $P < 0.001$), mitigated respiratory adverse events by 54.74 % (17.2% vs. 38.0 %, $P = 0.002$) overall and by 59.05 % (12.9% vs. 31.5 %, $P = 0.002$) during the induction period.

Conclusions: Ciprofol can significantly decrease respiratory depression events and provides a better sedative efficacy than propofol with higher recovery quality and satisfaction.

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1. Introduction

Gastrointestinal (GI) endoscopy is a crucial method for diagnosis and cancer surveillance. Sedative-endoscopy can alleviate patient discomfort and allow the endoscopist to perform an accurate examination under stable conditions [1]. However, hypoxaemia, airway obstruction and cardiovascular events induced by anaesthesia remain challenges [2,3]. Thus, it is vital to seek new anaesthetics or combination schemes with fewer cardiopulmonary adverse events.

Due to its excellent sedative properties and short half-life, propofol is the most commonly recommended sedative-hypnotic

drug for GI endoscopy [4,5]. However, propofol-sedation is associated with an increased occurrence of dose-dependent respiratory depression and cardiovascular events; [4,6] injection pain and hypertriglyceridemia also cannot be ignored. Consequently, a novel regimen with rapid induction and recovery time that lacks these drawbacks is urgently needed.

Ciprofol (HSK3486), is a new intravenous anaesthetic compound that adds a cyclopropyl group to the side chain of the core structure of propofol [7–9]. Structural modification makes ciprofol more efficient at binding to gamma-aminobutyric acid-A (GABA_A) receptors and generating stronger neuronal currents in vitro [10–12]. But the pharmacokinetic properties of ciprofol are similar to propofol [9]. Furthermore, ciprofol is reported to be a more potent sedative for decreasing respiratory and hemodynamic depression [12–15]. Hence, ciprofol may be a better alternative to propofol in terms of sedation for GI endoscopy.

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While combining opioids can reduce sedative-hypnotic consumption, potent opioids may result in respiratory depression [4,16]. Consequently, alfentanil is an appealing alternative for GI endoscopy: (1) an onset time of 45 s [17] and time to peak drug effect of 1.4 min; [18] (2) an analgesia duration of approximately 15 min, [17] which is well-suited to bidirectional endoscopy; and (3) its rapid recovery time, which is due to the high rate of metabolic clearance, is suitable for outpatient procedures [19].

We hypothesised that ciprofol combined with alfentanil may result in improved safety and faster recovery after GI endoscopy. Although the safety of ciprofol has been reported in advanced endoscopic procedures, such as colonoscopy [15], evidence on the safety of ciprofol combined with alfentanil for endoscopic procedures and especially bidirectional endoscopy that requires a longer duration is lacking. Therefore, we compared the safety profiles – including the incidence of cardiopulmonary adverse events and quality of recovery – between ciprofol and propofol to achieve moderate sedation in patients undergoing bidirectional endoscopy.

2. Materials and methods

2.1. Study design

This single-centre, prospective, double-blind, randomised, controlled clinical study was performed at the endoscopic centre of Gansu Provincial Hospital, Lanzhou, Gansu, China. The protocol was approved by the Institutional Ethics Committee of Gansu Provincial Hospital (Chairperson Prof Cai) on 23 July 2021 and registered at Chinese Clinical Trial Registry (number ChiCTR2100049609) and conducted according to the Declaration of Helsinki and guidelines for Good Clinical Practice promulgated by the International Conference on Harmonization. In China, ciprofol for induction and maintenance of general anaesthesia (approval no. H20200013) and alfentanil for perioperative analgesia (approval no. H20203054) have been approved by the National Medical Products Administration. Prior to enrolment, all patients were informed about the study and provided written informed consent.

2.2. Study population

Inpatients aged 18–65 years scheduled to undergo diagnostic endoscopy (esophagogastroduodenoscopy followed by colonoscopy), including polypectomy, were enrolled. The exclusion criteria are listed in Supplementary Table 1.

2.3. Randomisation

Using a computer-generated randomisation sequence, patients were randomly assigned to the ciprofol or propofol group in a 1:1 ratio. The allocations were concealed and kept in sealed envelopes; an assistant nurse opened the envelope and prepared the sedation agents. Intravenous sedation was standardised and performed blindly by the same independent anaesthetist who was not involved in data collection or patient care. Only the investigator and nurse who prepared the drugs knew the group allocation. Because both ciprofol and propofol were administered as milk-like aqueous solutions, they could not be visually identified. Therefore, the anaesthetist, endoscopist, patients and data collection observers were blinded to the randomisation.

2.4. Sedation protocols

A dedicated endoscopy room equipped with advanced cardiopulmonary life support was used for all procedures. Pre-procedure, 0.1 g of lidocaine syrup was applied to the throat of all patients. A nasal catheter was used to supply oxygen at 4 L/min

for at least 2 min before drug administration until patients were fully awake. Automatic non-invasive measurement of blood pressure, bispectral index (BIS) monitoring, pulse oximetry (SpO₂) and electrocardiography were continuously performed. Respiratory activity was assessed using thoracic leads and visual examination of chest-abdominal excursion. All patients received 7 µg/kg alfentanil (alfentanil hydrochloride injection, 1 mg/2 ml/A, Humanwell Pharmaceutical Group Co., Ltd., Yichang, China) intravenously (10 s) before administration of the study drugs. For the propofol group, induction started with a bolus of 1.2 mg/kg (0.12 ml/kg) propofol (propofol injection long chain triglyceride, 200 mg/20 ml/A, Fresenius Kabi Deutschland, Beijing, China) administered intravenously. The ciprofol group received an initial bolus of 0.3 mg/kg [20] (0.12 ml/kg) ciprofol (25 mg/20 ml/A, Haisco Pharmaceutical Group Co., Ltd., Chengdu, China) administered intravenously. The anaesthetist carefully controlled the intravenous injection speed and the initial dose induction was completed in 40 s.

After drug administration, the sedation level was assessed every 3 s. Upper GI endoscopy was performed as soon as the patient reached a score of 3 on the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Scale. [21] After at least 30 s of observation, an additional bolus (2 ml) of sedative was administered if the target sedation depth was not achieved. Post-esophagogastroduodenoscopy, patients received 5 mg (2 ml) of ciprofol or 20 mg (2 ml) of propofol. Colonoscopy was then performed. Following colonoscopy, patients were taken to the post-anaesthesia care unit (PACU) room and their vital signs were continuously monitored. The Aldrete score [22] was assessed every minute; and after three successive Aldrete scores ≥ 9 , patients were moved from the recovery room to the observation room.

2.5. Study endpoint

The primary endpoint was the rate of cardiopulmonary adverse events. Secondary endpoints were the induction/awake/discharge time, anaesthesiologist/endoscopist/patient satisfaction, total dose requirements of propofol or ciprofol, injection pain and post-procedural evaluations.

2.6. Outcome measures and definitions

Three independent, blinded observers collected data pre-operatively (LJ-L), intraoperatively (RR-B. and postoperatively (MJ-X). Evaluation of injection pain was performed 5 s after study drug injection by observing any behavioural signs, e.g., facial grimacing or arm withdrawal. If no response was observed after 10 s, a standard question (Supplementary Table 2) adapted from Niazi et al. [23] and McCrerrick et al. [24] was asked.

The definitions of respiratory- and circulation-related adverse events and time are shown in Supplementary Table 3. After the procedure, the anaesthesiologist and endoscopist rated their satisfaction with sedation and patient cooperation using a visual analogue scale (VAS).

After fully awakening, patients were asked to complete a survey about recovery quality [25–27]. We also briefly inquired about patients' dreams and assessed their emotional state using the Positive and Negative Affect Schedule (PANAS) Scales [28]. The observation room discharge criterion was a score of 10 on the Modified Post-Anaesthetic Discharge Scoring System (MPADSS) scale, which includes five components, i.e., vital signs, ambulation, nausea/vomiting, pain and surgical bleeding [29,30].

2.7. Statistical analysis

According to Kim et al. [25], 51.56 % of patients who underwent upper endoscopic procedures experienced cardiopulmonary

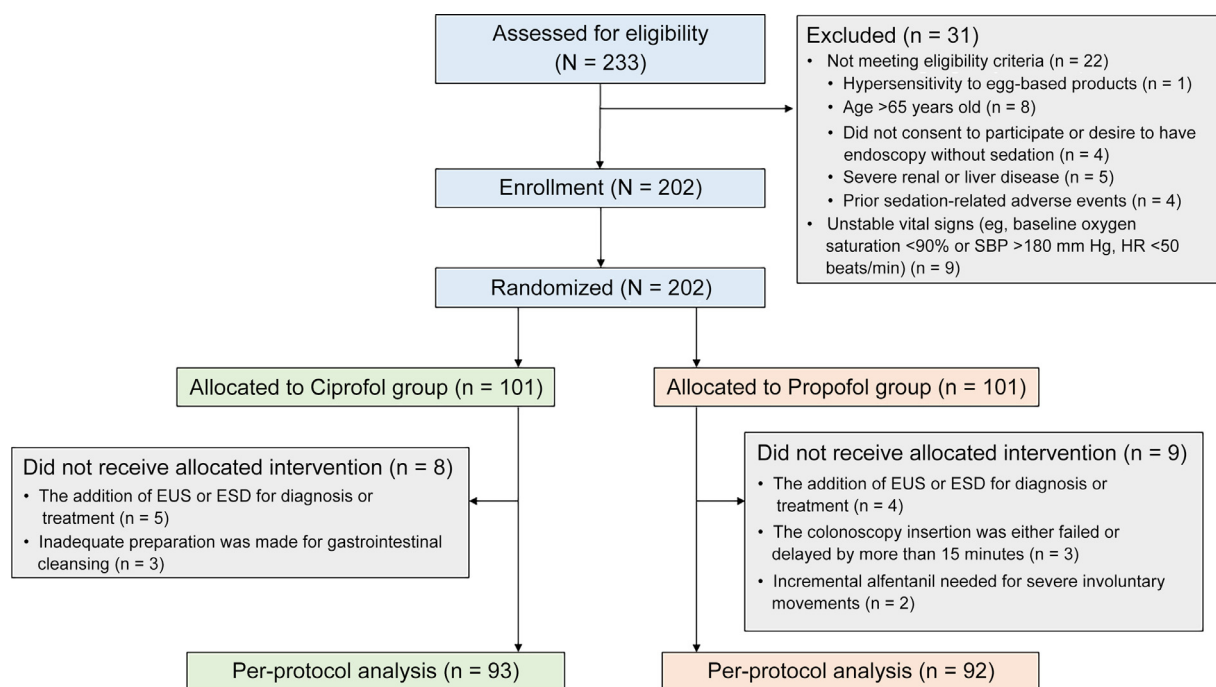


Fig. 1. Flow chart comparing the ciprofol and propofol groups in this randomised trial. SBP, systolic blood pressure.

adverse events after intermittent manually controlled administration of propofol. In our pre-experiment, the incidence of cardiopulmonary adverse events in the ciprofol group was 25.80 %. Thus, to detect differences between the ciprofol and propofol groups at an alpha level of 0.05, 86 samples per group were needed to achieve a power of at least 0.95 to detect a moderate effect size. With an assumed 10 % dropout rate, we recruited a final sample size of 94 patients per group. The sample size calculation was performed using PASS software (version 21.0.3, NCSS, LCC, Kaysville, UT, United States).

The distribution of continuous variables was assessed using the Shapiro–Wilk test. Data with a normal distribution are presented as the mean $\pm$ standard deviation (SD) and analysed using the two-sampled independent *t*-test, while data with a non-normal distribution are reported as the median with range and analysed using the Mann–Whitney U test. Categorical variables and ordinal categorical variable are reported as frequencies and percentages, while proportions are compared using the Pearson's chi-squared or Fisher's exact tests, as appropriate. For repeated-measures data, such as blood pressure and heart rate, repeated-measures analysis of variance was used. Results were considered statistically significant with a two-sided *p*-value < 0.05. Data analysis was performed using Statistical Package for the Social Sciences version 26.0 software (IBM SPSS, Chicago, IL, United States).

3. Results

3.1. Patient characteristics

A total of 233 patients scheduled to undergo bidirectional endoscopy were initially identified since August 2021 and ends in June 2022. After applying the exclusion criteria, there were 92 and 93 patients in the propofol and ciprofol groups, respectively. All primary outcome analyses were performed on the full intention-to-treat population (Fig. 1). Baseline demographic, clinical and procedural characteristics were balanced between the two groups (Supplementary Table 4).

3.2. Anaesthetic use and sedation time

Table 1 shows the anaesthetic doses and associated sedation times for the two groups. The total sedative-agent dose of ciprofol was 1/5 that of propofol (28.27 ± 5.35 vs. 151.68 ± 35.2 mg, $P < 0.001$) and the induction dose was 1/4 that of propofol (19.36 ± 3.9 vs. 83.42 ± 20.2 mg, $P < 0.001$). Moreover, the additional ciprofol dose was 1/7 that of propofol (8.89 ± 4.4 vs. 68.26 ± 28.2 mg, $P < 0.001$). During the procedures, 87.1 % of ciprofol group patients received incremental sedatives no more than two times, whereas 65.2 % of propofol group patients received incremental sedatives three times or more. The rate of successful induction by the initial dose to achieve target sedation levels during the induction period was significantly higher with ciprofol than with propofol (95.7 % vs. 81.5 %, $P = .002$). Induction was also achieved faster in the ciprofol group (60.50 ± 18.5 vs. 66.80 ± 23.8 s, $P = 0.021$).

3.3. Adverse events

Cardiopulmonary adverse events were observed in 32 (34.4 %) and 56 patients (60.9 %) in the ciprofol and propofol groups, respectively, which was a significant difference ($P < 0.001$). Thus, ciprofol reduced cardiopulmonary adverse events by 43.51 % compared with propofol (Table 2). However, there was no significant difference in cardiovascular adverse events (22.6 % vs. 33.7 %, $P = 0.093$). Furthermore, hypotension tended to be less common in the ciprofol group (12.9 % vs. 18.5 %, $P = 0.297$). With the exceptions of two propofol group patients and one ciprofol group patient, cardiovascular adverse events were self-limited and did not require specific medical intervention.

Ciprofol mitigated respiratory adverse events by 54.74 % (17.2 % vs. 38.0 %, $P = 0.002$) overall and by 59.05 % (12.9 % vs. 31.5 %, $P = 0.002$) during the induction period compared with propofol. On multivariable logistic regression, ciprofol used (OR, 0.392; 95 % CI, 0.172–0.895, $P = .026$) associated with respiratory adverse events. Apnoea was monitored in six (6.5 %) and two (2.2 %) patients receiving propofol and ciprofol, respectively ($P = 0.144$), but

Table 1
Consumption of anesthetics and sedation-related time.

Variable	Ciprofol group (n = 93)	Propofol group (n = 92)	P-value
Sedative-agent volume (ml), mean (SD)			
Induction	7.74 (1.6)	8.34 (2.0)	.026
Incremental	3.56 (1.7)	6.83 (2.8)	< 0.001
Total sedative	11.31 (2.1)	15.16 (3.5)	< 0.001
Sedative-agent dose (mg), mean (SD)			
Induction	19.36 (3.9)	83.42 (20.0)	< 0.001
Incremental	8.89 (4.4)	68.26 (28.2)	< 0.001
Total sedative	28.27 (5.35)	151.68 (35.2)	< 0.001
Average (mg/kg/min), mean (SD)	0.03 (0.01)	0.183 (0.05)	< 0.001
Total incremental times (no), mean (SD)	1.71 (0.7)	2.87 (1.2)	< 0.001
Total incremental times, n/total N (%)			< 0.001
Zeroth or once	36/93 (38.7 %)	13/92 (13.1 %)	
Twice	45/93 (48.4 %)	19/92 (20.7 %)	
Three times	12/93 (12.95 %)	32/92 (34.8 %)	
≥4 times	0/93 (0.00 %)	28/92 (30.4 %)	
Only initial dose during the induction period, n/total N (%)	89/93 (95.75)	75/92 (81.5 %)	0.002
Alfentanil dose (mg), mean (SD)	459.20 (84.9)	452.17 (83.6)	0.571
Time, mean (SD)			
Induction (sec.)	60.50 (18.5)	66.80 (23.8)	.021
Total procedure (min.)	13.96 (3.0)	14.06 (2.5)	0.800
caecal intubation time (min.)	3.56 (1.3)	3.78 (1.6)	0.371

Values are mean (SD) or n/total N (%), unless otherwise indicated. SD, standard deviation.

Table 2
Adverse events.

Variable	Ciprofol (n = 93)	Propofol (n = 92)	P-value
Adverse events, n/total N (%)			
Overall cardiopulmonary adverse events	32/93 (34.4 %)	56/92 (60.9 %)	<0.001
Overall cardiovascular disorders	21/93 (22.6 %)	31/92 (33.7 %)	.093
Overall vascular disorders	15/93 (16.1 %)	19/92 (20.7 %)	.427
Induction period (T2) hypotension	3/93 (3.2 %)	9/92 (9.8 %)	.070
Hypotension	12/93 (12.9 %)	17/92 (18.5 %)	.297
Hypertension	3/93 (3.2 %)	2/92 (2.2 %)	1.000
Systolic hypotension	9/93 (9.7 %)	13/92 (14.1 %)	.350
Diastolic hypotension	18/93 (19.4 %)	24/92 (26.1 %)	.274
Overall cardiac disorders	13/93 (14.0 %)	20/92 (21.7 %)	.168
Bradycardia	12/93 (12.9 %)	18/92 (19.6 %)	.219
Tachycardia	1/93 (1.1 %)	2/92 (2.2 %)	.992
Arrhythmia	0/93 (0.0 %)	1/92 (1.1 %)	.497
Vasoactive agents	1/93 (1.1 %)	2/92 (2.2 %)	.992
Overall respiratory disorders	16/93 (17.2 %)	35/92 (38.0 %)	.002
Induction period	12/93 (12.9 %)	29/92 (31.5 %)	.002
Maintenance period	2/93 (2.2 %)	4/92 (4.3 %)	.668
Classification			.053
Mild	3/93 (3.2 %)	8/92 (8.7 %)	
Moderate	6/93 (6.5 %)	13/92 (14.1 %)	
Severe	2/93 (2.2 %)	5/92 (5.4 %)	
Respiratory depression	8/93 (8.6 %)	13/92 (14.1 %)	.236
Respiratory rate≤8 (breaths/minute)	8/93 (8.6 %)	11/92 (12.0 %)	.452
RR≤ 8 duration(seconds), mean (SD)	4.75 ± 2.8	5.82 ± 3.4	.476
apnoea	2/93 (2.2 %)	6/92 (6.5 %)	.144
apnoea duration(seconds), mean (sd)	3.50 ± 0.7	4.50 ± 2.9	.660
Oxygen saturation to <90 %	6/93 (6.5 %)	13/92 (14.1 %)	.085
SpO ₂ Minimum(value), mean (SD)	96.76 ± 4.9	94.82 ± 8.3	.026
Intervention of treatment-emergent	8/93 (8.6 %)	19/92 (20.7 %)	.020
Chin-lift	8/93 (8.6 %)	18/92 (19.6 %)	.032
Increase supplemental oxygen	5/93 (5.4 %)	10/92 (10.9 %)	.171
Bag masque	2/93 (2.2 %)	5/92 (5.4 %)	.432
Tracheal intubation or mechanical ventilation	0/93 (0.0 %)	1/92 (1.1 %)	.497
Burping	9/93 (9.7 %)	5/92 (5.4 %)	.275
Involuntary movements or coughing			.001
Class I	83/93 (89.2 %)	62/92 (66.7 %)	
Class II	6/93 (6.5 %)	16/92 (17.2 %)	
Class III	4/93 (4.3 %)	15/92 (16.1 %)	
Paradoxical reactions require physical restraint	5/93 (5.4 %)	18/92 (19.6 %)	.003

Values are mean (SD) or n/total N (%), unless otherwise indicated. SD, standard deviation.

SpO₂, arterial oxygen saturation; RR, respiratory rate. * *P* < .05.

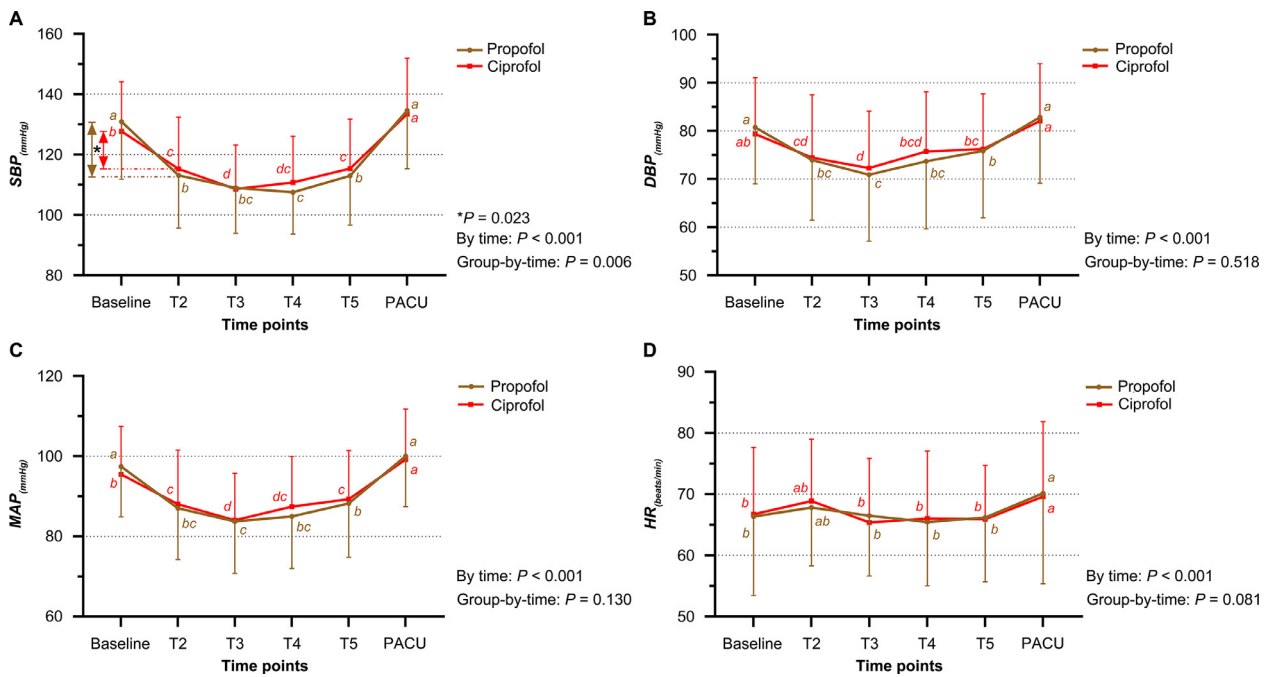


Fig. 2. Vital sign changes. The change in systolic blood pressure (A), diastolic blood pressure (B) and mean arterial pressure (C) and heart rate (D) in the propofol and ciprofol groups. Letter marking method: Time points with the same letter markers for the same group were not significantly different. There were no significant effects of the group-by-time interaction, indicating that sedatives agents did not affect DBP, MAP, and HR patterns during the study period (Fig. 3B, C, and D). At any of the same time points, the blood pressure and heart rate were not significant different. $*P < .005$. SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MAP, Mean arterial pressure; HR, Heart rate. Data are shown as the mean $\pm$ standard deviation.

no group difference in apnoea duration was observed ($P = 0.660$). The rate of oxygen saturation $< 90\%$ did not differ significantly between groups; however, the ciprofol group has a higher proportion of patients with the lowest oxygen saturation ($P = 0.026$). Additionally, ciprofol group patients required fewer respiratory interventions ($P = 0.020$), and a significant difference in the frequency of chin-lift intervention was observed ($P = .032$). Neither group experienced any major adverse events, although one patient in the propofol group required the application of a nasopharyngeal airway. Lastly, significantly more patients in the propofol group required physical restraint due to involuntary movements ($P = 0.003$).

3.4. Vital sign changes

Blood pressure and heart rate were monitored during the earlier stages of the procedure (Fig. 2). Blood pressure and heart rate were significantly affected by time in both groups ($P < 0.001$). There was also a significant group $\times$ time interaction effect for systolic blood pressure (SBP) ($P = 0.006$; Fig. 2A). From baseline to T2, the propofol group showed a significantly greater SBP reduction than the ciprofol group ($P = 0.023$; Fig. 2A), indicating that ciprofol group has a more stable SBP in the induction period. The vital parameters over time are shown in Supplementary Table 5.

3.5. Injection pain and BIS monitoring

Pain at the injection site was significantly lower in the ciprofol group than the propofol group (8.6% vs. 33.7% , $P < 0.001$) (Table 3). There was no group difference in the minimum depth of anaesthesia (ciprofol vs propofol: 52.53 ± 12.6 vs. 50.92 ± 9.4 , $P = 0.328$). The time from induction to achieving BIS-min was faster for ciprofol. However, the propofol group was significantly faster from achieving BIS-min to > 60 ($P = 0.029$). When withdrawing the scope from the colon, the propofol group had higher BIS scores (64.70 ± 9.7 vs. 68.34 ± 10.8 , $P = 0.016$) (Table 3).

3.6. Satisfaction and post-procedural assessments

From the perspective of endoscopists, anaesthesiologists, or patients, ciprofol outperformed propofol in terms of sedation satisfaction based on VAS scores. The ciprofol group was also more cooperative, as evaluated by the anaesthesiologist/endoscopist.

The post-procedural recovery evaluations and durations are shown in Table 4. In the ciprofol group, 60.2% of patients reported no abdominal pain or distention and post-procedure fatigue scores were significantly lower ($P < 0.001$). Furthermore, 63.4% of patients treated with ciprofol reported sedation to be "excellent", whereas 48.9% of patients treated with propofol reported it to be "just right".

The propofol group also had higher recall (awareness level) when leaving the operating room ($P = 0.005$). The ciprofol group had slightly longer eye-opening/awake/recovery times, but the difference was not statistically significant. There was also no difference in the duration of MPADSS score > 9 , although the duration of MPADSS score > 10 was significantly longer in the ciprofol group (8.1 ± 2.6 vs. 6.0 ± 1.8 min, $P = 0.049$).

4. Discussion

Bidirectional endoscopy requires a longer sedation duration than gastroscopy or colonoscopy alone, which increases the risk of cardiopulmonary adverse events. This study explored the combination of ciprofol and alfentanil for bidirectional endoscopic sedation for the first time. The findings are extremely promising and the trial confirms the expected result, with this regimen resulting in successful sedation, reduced respiratory adverse events and improved hemodynamic stability.

Although the time to successful induction in our study was longer in the propofol group, it was much faster than reported by Teng et al. (2.2 min) for 0.3 mg/kg ciprofol [15]. Hu et al. [31] and Wang et al. [32] reported a rapid induction time of approximately

Table 3
Injection pain and BIS monitoring.

Variable	Ciprofol group (n = 93)	Propofol group (n = 92)	P value
Pain score, n/total N (%)			< 0.001
None (0)	85/93 (91.4 %)	61/92 (66.3 %)	
Mild (1)	6/93 (6.5 %)	16/92 (17.4 %)	
Moderate (2)	2/93 (2.2 %)	9/92 (9.8 %)	
Severe (3)	0/93 (0.0 %)	6/92 (6.5 %)	
Summation, mean (SD)	0.12 (0.4)	0.57 (0.9)	< 0.001
BIS, mean (SD)			
Minimum	52.53 (12.6)	50.92 (9.4)	.328
Time from the start of induction to the BIS-min, minutes	2.51 (1.0)	2.68 (1.0)	.208
Time from successful induction (MOAA/S = 3) to the BIS-min, min	1.49 (0.9)	1.65 (0.9)	.203
Time from the BIS-min to 60, minutes	1.58 (1.3)	1.22 (0.9)	.029
BIS $\leq$ 40, n/total N (%)	16/93 (17.2 %)	12/92 (13.0 %)	.430
BIS $\leq$ 40, seconds	24.1 (5.25)	18.7 (7.35)	.217
BIS- scores when removing the colonoscope from the anus	64.70 (9.7)	68.34 (10.4)	.016

Values are mean (SD) or n/total N (%), unless otherwise indicated. SD, standard deviation.

BIS, bispectral index.

1 min for ciprofol and that alfentanil is a short-acting analgesic with high analgesic potency [17]. Hence, we achieved a very rapid induction time using this combination. The time from induction to achieving the BIS-min also suggests more rapid onset of action for ciprofol. Considering that only 81.5 % of propofol group patients achieved successful induction with the initial dose (1.2 mg/kg), subsequent doses may have contributed to the prolonged induction time. The high success rate (95.7 %) in the ciprofol group using the initial induction dose also indicates that 0.3 mg/kg ciprofol was more effective than 1.2 mg/kg propofol. The induction dose suggests that ciprofol is approximately 4–5 times more potent than propofol, which is consistent with findings by Hu et al. [31]. This difference in potency is consistent with preclinical trials reporting that the half-maximal effective inhibitory concentration (EC₅₀) of ciprofol on GABA_A receptor-mediated currents is five times less than that of propofol (5.3 vs. 1.1 μ M, respectively), [13] and that the therapeutic index calculated by LD₅₀ (median lethal dose)/ED₅₀ shows that ciprofol is 2.5 times more potent than propofol [7].

In this study, ciprofol outperformed propofol in terms of minimising adverse respiratory events or interventions, which is in line with previous studies using other medication schemes [10,12,15]. Furthermore, Li and colleagues demonstrated that ciprofol had a remarkably stable respiratory profile in both elderly and non-elderly patients, with a low incidence of respiratory depression [8]. Unlike other opioids, alfentanil does not cause severe respiratory depression at plasma concentrations for treatment of moderate-to-severe pain, as it does not cause a 50 % reduction in CO₂ ventilation response [33]. A International Sedation Task Force studied reported a 20.6 % rate of oxygen desaturation (75–90 %) for < 60 s [2]. In the present study, oxygen saturation < 90 % was observed in 6.5 % of ciprofol patients and 14.1 % of propofol patients, which is generally consistent with Eberl et al.'s results (13.25 % in the propofol combined with alfentanil group) [34]. Rather than administering high oxygen flow via facemasks, we administered 4 L/min oxygen via a nasal catheter to make SpO₂ more sensitive to potential respiratory depression and airway obstruction, and more likely to detect between-group differences. However, this patient management strategy did not result in a high incidence of oxygen desaturation, which is likely due to the slow intravenous injection speed.

In the present study, ciprofol had milder effects on the cardiovascular system than propofol especially during the induction period. Hypotension and bradycardia are the common adverse reactions to anaesthetics, likely because propofol depresses the heart rate and blood pressure via GABA_A receptor-mediated effects on autonomic control in the brainstem [35,36]. Ciprofol has been shown to result in more stable hemodynamic responses during

colonoscopy and general anaesthesia induction [10,11,15,32]. Another study reported that hypotension was caused by dehydration after bowel preparation [37]. The high incidence of hypotension and bradycardia in our study may be due to the absence of saline infusion and different definitions used. Such a regimen is not only beneficial for achieving stable haemodynamic but can also dramatically reduce cardiopulmonary and respiratory adverse events – especially during the induction period.

Up to 64 % of pain associated with propofol injection is widespread [38], which significantly impacts sedation comfort. In line with our findings, several studies have demonstrated ciprofol's excellent ability to almost eliminate injection pain [11,15,32]. Injection pain is reduced when the aqueous phase of the emulsion contains a lower propofol concentration [31,39,40]. Teng et al. and Hu et al. found that the aqueous phase concentration of ciprofol in a 1 % lipid emulsion is significantly lower than that of propofol and that higher hydrophobicity may contribute to reduced injection pain [11,31]. In the present study, the incidence of injection pain was 20.5 % in the propofol group, which is lower than previously reported rates. This difference could be due to preoperative administration of alfentanil.

Another notable advantage of our regimen is the shorter recovery time, which allowed efficient discharge from endoscopy units. The BIS when withdrawing the scope from the anus was significantly higher in the propofol group, which could explain the faster discharge. Although the result was statistically significant, a difference of 2 min is not clinically meaningful. In the study by Teng et al., [15] the alertness time (6.3 min) and recovery time (6.6 min) in the 0.3 mg/kg group were longer than those in our study. This may be because we administered alfentanil and Teng et al. administered fentanyl for the combination [18]. Bian et al. reported that ciprofol has favourable anaesthetic properties with little residual effects and that patients smoothly and quickly recovered within 5–14 min [12]. Additional doses do not need to be given during colonoscopy withdrawal as long as the patient does not manifest discomfort or hemodynamic changes. As a result, some patients reached MOAA/S level 4 or 5 during colonoscopy withdrawal, but did not report any discomfort. It is interesting that an MPADSS score $\geq$ 9 (with one point in the component of ambulation while most patients scored up to two points for each of the other four components) is not an appropriate criterion for patient discharge with assistance in our study, which is inconsistent with Edokpolo et al.'s discharge criteria [29]. Thus, a score T 10 (2 = steady gait/no dizziness) is considered an acceptable discharge criterion.

The anaesthesiologist's satisfaction with sedation is primarily determined by the time to medication onset, incidence of cardiopulmonary adverse events, number of medications added dur-

Table 4

Satisfaction and post-procedural assessments (visual analogue scale, 0–10).

Variable	Ciprofol group (n = 93) no. (%)	Propofol group (n = 92) no. (%)	P value
Satisfaction for sedation			
Anesthesiologist, mean (SD)	8.81 (1.8)	7.88 (1.5)	.003
Anesthesiologist, n/total N (%)			< 0.001
Unsatisfied (0–5)	1/93 (1.1 %)	6/92 (6.5 %)	
Good (6–8)	32/93 (34.4 %)	52/92 (56.5 %)	
Excellent (9–10)	60/93 (64.5 %)	34/92 (37.0 %)	
Endoscopist, mean (SD)	9.29 (1.0)	8.24 (1.2)	< 0.001
Endoscopist, n/total N (%)			< 0.001
Unsatisfied (0–5)	0/93 (0.0 %)	1/92 (1.1 %)	
Good (6–8)	23/93 (24.7 %)	49/92 (53.3 %)	
Excellent (9–10)	70/93 (75.3 %)	42/92 (45.7 %)	
Patients, mean (SD)	8.98 (1.2)	8.59 (1.4)	0.046
Patients, n/total N (%)			.093
Unsatisfied (0–5)	0/93 (0.0 %)	2/92 (2.2 %)	
Good (6–8)	34/93 (36.6 %)	42/92 (45.7 %)	
Excellent (9–10)	59/93 (63.4 %)	48/92 (52.2 %)	
Abdominal pain or distention after awakening, mean (SD)	0.94 (1.3)	1.39 (1.7)	.039
Abdominal pain or distention after awakening, n/total N (%)			.015
None (0)	56/93 (60.2 %)	43/92 (46.7 %)	
Mild (1–2)	23/93 (24.7 %)	27/92 (29.3 %)	
Moderate (3–4)	14/93 (15.1 %)	16/92 (17.4 %)	
Severe (≥5)	0/93 (0.0 %)	6/92 (6.5 %)	
Fatigue after awakening, mean (SD)	0.82 (1.3)	2.09 (1.9)	< 0.001
Fatigue after awakening, n/total N (%)			< 0.001
None (0)	62/93 (66.7 %)	25/92 (27.2 %)	
Mild (1–3)	25/93 (26.9 %)	47/92 (51.1 %)	
Moderate (4–6)	6/93 (6.5 %)	17/92 (18.5 %)	
Severe (7–10)	0/93 (0.0 %)	3/92 (3.3 %)	
Sedation quality by observer, n/total N (%)			<0.001
Poor	9/93 (9.7 %)	22/92 (23.9 %)	
Just right	25/93 (26.9 %)	45/92 (48.9 %)	
Excellent	59/93 (63.4 %)	25/92 (27.2 %)	
Patient cooperation by observer, median [IQR]	10 [9–10]	8 [8–9]	<0.001
Recommend to others, median [IQR]	10 [8–10]	9 [8–10]	.077
Previous colonoscopy experience	58/93 (62.4 %)	64/92 (69.6 %)	.302
Compared with previous colonoscopy, n/total N (%)			.013
More effective	45/93 (77.6 %)	35/92 (54.7 %)	
Similar	13/93 (22.4 %)	28/92 (43.8 %)	
Worse	0/93 (0.0 %)	1/92 (1.6 %)	
Nervous system before discharge, n/total N (%)			
Headache	0/93 (0.0 %)	2/92 (2.2 %)	0.246
Dizziness	3/93 (3.2 %)	7/92 (7.6 %)	0.321
Nausea and vomiting, n/total N (%)	2/93 (2.2 %)	2/92 (2.2 %)	.991
Recall, n/total N (%)			
At endoscope insertion	1/93 (1.1 %)	3/92 (3.3 %)	.606
At any time during the procedure	3/93 (3.2 %)	6/92 (6.5 %)	.484
At endoscope removal	11/93 (11.8 %)	20/92 (21.7 %)	.071
At leaving the operating room	18/93 (19.4 %)	35/92 (38.0 %)	.005
Dream, n/total N (%)	30/93 (32.2 %)	38/92 (41.3 %)	0.202
Pleasant dreams	24/93 (80.0 %)	30/92 (78.9 %)	0.915
PANAS after fully awake			
Positive	36.51 (3.7)	35.32 (2.9)	< 0.001
Negative	22.55 (4.1)	23.00 (5.6)	< 0.001
Time, mean (SD)			
Open eyes time, minutes	1.02 (1.4)	0.97 (1.5)	0.821
Awakening time (minutes)	2.53 (2.2)	2.52 (2.1)	.972
Recovery time (minutes)	3.88 (2.1)	3.78 (2.5)	.761
MPADSS ≥ 9 (minutes)	3.40 (1.3)	3.30 (1.7)	.883
MPADSS ≥ 10 (minutes)	8.1 (2.6)	6.0 (1.8)	.049

Values are mean (SD) or n/total N (%), unless otherwise indicated.

IQR: interquartile range.

ing the procedure and awakening time after the procedure. In contrast, the endoscopist's satisfaction depends mainly on patient cooperation and a more rapid throughput of patients in the gastroenterology suite, which is determined by the speed of awakening. The analgesic effect, injection pain, depth of anaesthesia and quality of recovery after awakening are the main factors that influence patient satisfaction. Notably, ciprofol outperformed propofol in all of these areas. The minimal incidence of postoperative nausea and vomiting in both groups is attributed to the safety of alfentanil, which has been demonstrated elsewhere [41].

There are several limitations of our study. First, capnographic monitoring is routinely performed during GI endoscopic sedation to detect respiratory depression before transient hypoxaemia occurs, but was unavailable for our study. Second, our patients were relatively young. Responses and dose requirements may differ for older patients or those with obstructive sleep apnoea. Third, the sedation level may have decreased or even reached the anaesthesia level following upper GI endoscope insertion during the induction period or after administration of additional intraoperative agents; however, we maintained moderate levels of sedation

for most of the intraoperative period. Due to these limitations, a multi-centre, large-scale trial evaluating the benefits of intravenous ciprofol combined with alfentanil for bidirectional endoscopy sedation in diverse patients is warranted.

In conclusion, this study supports that ciprofol combined with alfentanil is a promising sedation method for bidirectional endoscopy. This regimen can achieve a rapid onset of action of nearly 1 min and awakening time of approximately 2.5 min with good language ability and orientation. Moreover, patients needed < 4 min to meet the PACU exit standard, were discharged within 10 min with a steady gait and showed improvement in post-endoscopic recovery. Considering the findings of this trial, ciprofol could play a central role in endoscopy in the future.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Author contribution

Jiqiang Zhang: Conceptualization, Formal analysis, Validation, Writing – original draft. **Ruijuan Liu:** Writing – original draft. **Ruirui Bi:** Funding acquisition. **Xia Li:** Formal analysis, Validation, Writing – original draft. **Mengjun Xu:** Funding acquisition. **Lijuan Li:** Funding acquisition. **Yuxi su:** Formal analysis, Validation, Writing – original draft. **Wenjun Yan:** Conceptualization, Writing – review & editing.

Authors' contributions

Agreed to be accountable for all aspects of the manuscript and ensure the accuracy and integrity of any part of the manuscript: All authors.

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Supplementary materials

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References

- [1] Kim JH, Byun S, Choi YJ, et al. Efficacy and safety of etomidate in comparison with propofol or midazolam as sedative for upper gastrointestinal endoscopy. *Clin Endosc* 2020;53:555–61.
- [2] Mason KP, Roback MG, Chrisp D, et al. Results from the adverse event sedation reporting tool: a global anthology of 7952 records derived from >160,000 procedural sedation encounters. *J Clin Med* 2019;8:2087.
- [3] Nay MA, Fromont L, Eugene A, et al. High-flow nasal oxygenation or standard oxygenation for gastrointestinal endoscopy with sedation in patients at risk of hypoxaemia: a multicentre randomised controlled trial (ODEPHI trial). *Br J Anaesth* 2021;127:133–42.
- [4] Liu J, Liu X, Peng LP, et al. Efficacy and safety of intravenous lidocaine in propofol-based sedation for ERCP procedures: a prospective, randomized, double-blinded, controlled trial. *Gastrointest Endosc* 2020;92:293–300.
- [5] Zhou S, Zhu Z, Dai W, et al. National survey on sedation for gastrointestinal endoscopy in 2758 Chinese hospitals. *Br J Anaesth* 2021;127:56–64.
- [6] Berzin TM, Sanaka S, Barnett SR, et al. A prospective assessment of sedation-related adverse events and patient and endoscopist satisfaction in ERCP with anesthesiologist-administered sedation. *Gastrointest Endosc* 2011;73:710–17.
- [7] Qin L, Ren L, Wan S, et al. Design, synthesis, and evaluation of novel 2,6-disubstituted phenol derivatives as general anesthetics. *J Med Chem* 2017;60:3606–17.
- [8] Li X, Yang D, Li Q, et al. Safety, pharmacokinetics, and pharmacodynamics of a single bolus of the gamma-aminobutyric acid (GABA) receptor potentiator HSK3486 in healthy chinese elderly and non-elderly. *Front Pharmacol* 2021;12:735700.
- [9] Lu M, Liu J, Wu X, et al. Ciprofol: a novel alternative to propofol in clinical intravenous anesthesia? *Biomed Res Int* 2023;2023:7443226.
- [10] Liu Y, Chen C, Liu N, et al. Efficacy and safety of ciprofol sedation in ICU patients with mechanical ventilation: a clinical trial study protocol. *Adv Ther* 2021;38:5412–23.
- [11] Teng Y, Ou MC, Wang X, et al. Pharmacokinetic and pharmacodynamic properties of ciprofol emulsion in Chinese subjects: a single center, open-label, single-arm dose-escalation phase 1 study. *Am J Transl Res* 2021;13:13791–802.
- [12] Bian Y, Zhang H, Ma S, et al. Mass balance, pharmacokinetics and pharmacodynamics of intravenous HSK3486, a novel anaesthetic, administered to healthy subjects. *Br J Clin Pharmacol* 2021;87:93–105.
- [13] Liu Y, Yu X, Zhu D, et al. Safety and efficacy of ciprofol vs. propofol for sedation in intensive care unit patients with mechanical ventilation: a multicenter, open label, randomized, phase 2 trial. *Chin Med J (Engl)* 2022;135:1043–51.
- [14] Wei Y, Qiu G, Lei B, et al. Oral delivery of propofol with methoxymethylphosphonic acid as the delivery vehicle. *J Med Chem* 2017;60:8580–90.
- [15] Teng Y, Ou M, Wang X, et al. Efficacy and safety of ciprofol for the sedation/anesthesia in patients undergoing colonoscopy: phase IIa and IIb multicenter clinical trials. *Eur J Pharm Sci* 2021;164:105904.
- [16] Welzing L, Oberthuer A, Jungheuer S, et al. Remifentanyl/midazolam versus fentanyl/midazolam for analgesia and sedation of mechanically ventilated neonates and young infants: a randomized controlled trial. *Intensive Care Med* 2012;38:1017–24.
- [17] Ziesenis VC, Vaughns JD, Koch G, et al. Correction to: pharmacokinetics of fentanyl and its derivatives in children: a comprehensive review. *Clin Pharmacokinet* 2018;57:393–417.
- [18] Struys M, Absalom AR, Shafer SL. Intravenous drug delivery systems. In: Groppe MA, Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Cohen NH, Leslie K, editors. *Miller's anesthesia*. Elsevier; 2020. p. 747–91.
- [19] Xin Y, Chu T, Wang J, et al. Sedative effect of remimazolam combined with alfentanil in colonoscopic polypectomy: a prospective, randomized, controlled clinical trial. *BMC Anesthesiol* 2022;22:262.
- [20] Duan G, Lan H, Shan W, et al. Clinical effect of different doses of ciprofol for induction of general anesthesia in elderly patients: a randomized, controlled trial. *Pharmacol Res Perspect* 2023;11:e01066.
- [21] Rex DK, Bhandari R, Desta T, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc* 2018;88:427–37 e6.
- [22] Aldrete JA. The post-anesthesia recovery score revisited. *J Clin Anesth* 1995;7:89–91.
- [23] Niazi A, Galvin E, Elsaigh I, et al. A combination of lidocaine and nitrous oxide in oxygen is more effective in preventing pain on propofol injection than either treatment alone. *Eur J Anaesthesiol* 2005;22:299–302.
- [24] McCrirkick A, Hunter S. Pain on injection of propofol: the effect of injectate temperature. *Anaesthesia* 1990;45:443–4.
- [25] Kim MG, Park SW, Kim JH, et al. Etomidate versus propofol sedation for complex upper endoscopic procedures: a prospective double-blinded randomized controlled trial. *Gastrointest Endosc* 2017;86:452–61.
- [26] Sipe BW, Rex DK, Latinovich D, et al. Propofol versus midazolam/meperidine for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Gastrointest Endosc* 2002;55:815–25.
- [27] Cohen LB, Hightower CD, Wood DA, et al. Moderate level sedation during endoscopy: a prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. *Gastrointest Endosc* 2004;59:795–803.
- [28] Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* 1988;54:1063–70.
- [29] Edokpolo LU, Mastriano DJ, Serafin J, et al. Discharge readiness after propofol with or without dexmedetomidine for colonoscopy: a randomized controlled trial. *Anesthesiology* 2019;131:279–86.
- [30] Chung F. Discharge criteria—a new trend. *Can J Anaesth* 1995;42:1056–8.
- [31] Hu C, Ou X, Teng Y, et al. Sedation effects produced by a ciprofol initial infusion or bolus dose followed by continuous maintenance infusion in healthy subjects: a phase 1 trial. *Adv Ther* 2021.
- [32] Wang X, Wang X, Liu J, et al. 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. *Eur Rev Med Pharmacol Sci* 2022;26:1607–17.

- [33] Barash PG CB, Stoelting RK, Cahalan MK, Stock MC. Clinical anesthesia. In: Barbara AC, editor. Opioids. Lippincott Williams & Wilkins; 2009. p. 466–97.
- [34] Eberl S, Koers L, van Hooft J, et al. The effectiveness of a low-dose esketamine versus an alfentanil adjunct to propofol sedation during endoscopic retrograde cholangiopancreatography: a randomised controlled multicentre trial. *Eur J Anaesthesiol* 2020;37:394–401.
- [35] Shirasaka T, Yoshimura Y, Qiu DL, et al. The effects of propofol on hypothalamic paraventricular nucleus neurons in the rat. *Anesth Analg* 2004;98:1017–23.
- [36] McDougall SJ, Bailey TW, Mendelowitz D, et al. Propofol enhances both tonic and phasic inhibitory currents in second-order neurons of the solitary tract nucleus (NTS). *Neuropharmacology* 2008;54:552–63.
- [37] Worthington MT, Antonik LJ, Goldwater DR, et al. A phase Ib, dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy. *Anesth Analg* 2013;117:1093–100.
- [38] Euasobhon P, Dej-Arkom S, Siriussawakul A, et al. Lidocaine for reducing propofol-induced pain on induction of anaesthesia in adults. *Cochrane Database Syst Rev* 2016;2:CD007874.
- [39] McIntosh MP, Rajewski RA. Comparative canine pharmacokinetics-pharmacodynamics of fospropofol disodium injection, propofol emulsion, and cyclodextrin-enabled propofol solution following bolus parenteral administration. *J Pharm Sci* 2012;101:3547–52.
- [40] Li J, Wang X, Liu J, et al. Comparison of ciprofol (HSK3486) versus propofol for the induction of deep sedation during gastroscopy and colonoscopy procedures: a multi-centre, non-inferiority, randomized, controlled phase 3 clinical trial. *Basic Clin Pharmacol Toxicol* 2022;131:138–48.
- [41] Langevin S, Lessard MR, Trepanier CA, et al. Alfentanil causes less postoperative nausea and vomiting than equipotent doses of fentanyl or sufentanil in outpatients. *Anesthesiology* 1999;91:1666–73.