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CLINICAL TRIAL REPORT

Intravenous Anesthesia with Ciprofol and Remimazolam Besylate for Painless Gastroscopy: A Prospective, Single-Center, Randomized Controlled Trial

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Purpose: To evaluate whether combining ciprofol and remimazolam offers superior safety and efficacy compared to propofol or ciprofol monotherapy for sedation during painless gastroscopy. We hypothesize improved hemodynamic and respiratory stability with the combination.

Methods: A total of 641 patients undergoing gastroscopy were randomly assigned to one of three groups. Group P (Propofol) received an intravenous bolus of propofol at a dose of 1.5 mg/kg. Group CR (Ciprofol + Remimazolam) received an initial intravenous dose of remimazolam (0.08 mg/kg), followed by ciprofol (0.25 mg/kg). Group C (Ciprofol) received an intravenous bolus of ciprofol at a dose of 0.4 mg/kg. Sedation depth was maintained within the target range (Bispectral Index 40–60) through the administration of supplemental doses: propofol (10–20 mg boluses) in Group P, and ciprofol (2.5–5 mg boluses) in Groups CR and C.

Results: Compared with group P, groups CR and C demonstrated significantly lower incidences of hypotension (CR: 7.8% vs P: 21.6%; C: 12.3% vs P: 21.6%; all P values < 0.001), mild hypoxia (CR: 8.8% vs P: 18.1%, $P = 0.005$; C: 7.7% vs P: 18.1%, P=0.001), and severe hypoxia (CR: 4.6% vs P: 9.8%, $P = 0.038$; C: 4.1% vs P: 9.8%, $P = 0.020$). Group C exhibited significantly longer induction time (1.62 ± 0.66 min, $P < 0.001$), recovery time (13.73 ± 3.82 min, $P < 0.001$), and operating room time (23.05 ± 6.38 min, $P < 0.001$) compared to both other groups. Additionally, gastroenterologist and anesthesiologist satisfaction was significantly higher in group CR than in groups P and C (all P values < 0.001).

Conclusion: The combination of ciprofol and remimazolam exerts a lesser impact on the respiration and circulation of patients undergoing gastroscopy, and demonstrates superior safety and efficacy compared to the use of propofol or ciprofol alone.

Keywords: sedation, ciprofol, remimazolam, propofol, painless gastroscopy

Introduction

Diagnostic gastroscopy is considered one of the "gold standards" for diagnosing upper gastrointestinal diseases and is also the most widely used method in clinical practice.[1] Painless gastroscopy refers to a procedure in which short-acting sedative and analgesic drugs are intravenously administered to eliminate patient discomfort during the examination, allowing individuals to undergo the procedure smoothly while in a state of reduced consciousness.[2] In developed countries, the utilization rate of painless gastroscopy exceeds 80%; in contrast, in other regions, its adoption ranges from 10% to 50%, with a steadily increasing trend observed year by year.[3,4]

Due to its rapid onset of action and quick recovery characteristics, propofol has become one of the most widely used sedative agents in painless gastroscopy. However, it is associated with several dose-dependent adverse effects. The incidence of respiratory depression ranges from 10% to 50%, hypotension occurs in 22% to 35% of cases, and injection

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pain can occur in 30% to 90% of cases.[5] These side effects have significantly impacted the safety and patient comfort during painless gastroscopy.[6]

Ciprofol is a novel intravenous sedative agent independently developed in China. It belongs to the class of 2,6-disubstituted phenol derivatives and exhibits a mechanism of action similar to that of propofol.[7] The drug was approved for marketing in China in December 2020. In 2024, it successfully completed a multicenter Phase III clinical trial (NCT05486416) in the United States.[8] Furthermore, ciprofol has been granted patent protections in multiple jurisdictions, including China, the United States, Europe, and Japan.[9] The introduction of a ciprofol group into the molecular structure of propofol enhances its binding affinity to the γ-aminobutyric acid A (GABAA) receptor. Ciprofol exhibits approximately 4–5 times greater potency than propofol. It is characterized by rapid onset, quick metabolism, and complete recovery. Furthermore, its suppressive effects on the cardiovascular and respiratory systems are milder compared to those of propofol.[10,11] However, some studies have reported that ciprofol has a longer onset and recovery time compared with propofol, as well as a higher incidence of body movements. Additionally, increasing the dose of ciprofol may result in dose-dependent hypotension.[11,12]

The novel ultra-short-acting benzodiazepine, remimazolam besylate integrates the pharmacodynamic characteristics of midazolam with the pharmacokinetic advantages of remifentanil.[13] It offers benefits such as rapid and controllable awakening, minimal hemodynamic impact, and metabolism that is independent of liver or kidney function. This agent demonstrates notable efficacy and safety in anesthesia for elderly and obese patients.[13,14] However, evidence suggests that the incidence of coughing and body movement during monotherapy sedation is relatively high. Therefore, combination with opioid agents is often required to enhance sedative effects and reduce the occurrence of adverse events.[15–17]

Clinically, the combined administration of sedatives and opioids, or the combination of two sedatives, is frequently utilized to achieve improved clinical outcomes. Given the potential synergistic effects between ciprofol and remimazolam, we investigated the use of these two agents in combination during painless gastroscopy, aiming to achieve rapid onset of action, controllable recovery, minimal respiratory and circulatory depression, and a low incidence of adverse events such as body movement, coughing, and injection pain. Therefore, this study aims to evaluate the safety and efficacy of combining ciprofol with remimazolam in painless gastroscopy procedures.

Materials and Methods

Patients and Grouping

This prospective, single-center, double-blind, randomized controlled trial was conducted in accordance with the principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of the General Hospital of Central Theater Command of PLA (approval number: [2023]046–1). Written informed consent was obtained from all participants. The clinical trial is registered with the number ChiCTR2400079998.

This study included patients who underwent diagnostic painless gastroscopy at our hospital from February 1, 2024, to June 30, 2024. These patients were aged 18 to 79 years, had a body mass index (BMI) ranging from 18 to 28 kg/m², and were classified as American Society of Anesthesiologists (ASA) physical status grades I to III. Patients were randomly assigned to three groups using computer-generated random number tables created in Excel: the control group (propofol group, P group), the ciprofol combined with remimazolam group (CR group), and the ciprofol-only group (C group), with 220 cases in each group.

Exclusion Criteria

The exclusion criteria are as follows: patients who refuse to participate in the study; those with pre-existing cognitive impairments or psychiatric disorders; those with a history of allergy to the medications used in this study; those with severe organ dysfunction (eg, cardiac, pulmonary, hepatic, or renal); individuals diagnosed with obstructive sleep apnea-hypopnea syndrome(OSAHS); those with a history of alcohol or substance abuse within three months prior to the peri-examination period; and those undergoing painless gastroscopy specifically for therapeutic purposes.

Randomization and Masking

A random number table was generated by an independent researcher using Excel software. The numbers in this table were randomly encoded and assigned in a 1:1:1 ratio to represent three distinct experimental groups. These assignments were sealed in opaque envelopes to ensure allocation concealment. The anesthesiologist responsible for performing the painless gastroscopy sequentially opened the envelopes and implemented the corresponding interventions based on the group allocation. Patients were unaware of their assigned group. Data observation and recording were conducted by a dedicated researcher who was not involved in any other stages of the study. Additionally, the anesthetic nurse responsible for post-procedure recovery did not enter the examination area. As a result, both the study participants and the observers remained blinded throughout the study, ensuring the objectivity of the research process.

Sedation Protocols and Monitoring

The gastroscopy examinations for all patients were conducted by the same team of experienced gastroenterologists. This team consists of three members, each with over 10 years of clinical experience, who are specifically responsible for performing diagnostic gastroscopy operations on a daily basis. They currently perform approximately 30 gastroscopy procedures per day. Sedation was administered by two senior anesthesiologists, both with more than 10 years of professional experience. All patients underwent the procedure using the Olympus H290 gastroscope, which has a diameter of 9 mm, a working length of 1030 mm, a total length of 1350 mm, and a field of view of 140°. All patients had intravenous access established upon entering the operating room, and were administered 250 mL of 0.9% sodium chloride solution via intravenous infusion. Nasal cannula oxygen was delivered at a rate of 3 L/min. Routine monitoring included non-invasive blood pressure (with a 3-minute cycle), electrocardiogram (3-leads), and blood oxygen saturation(SpO_2). Before performing painless gastroscopy, non-invasive blood pressure was continuously monitored three times at 5-minute intervals. The lowest blood pressure reading was recorded as the baseline blood pressure, and the lowest heart rate within a 10-minute period was recorded as the baseline heart rate. All patients initially received an intravenous injection of sufentanil (Yichang Renfu Pharmaceutical Industry Co., Ltd, Yichang, China; H20054172) at a dose of 0.1 μg/kg. In group P, patients were administered a 1% propofol (Fresenius Kabi Austria GmbH, Beijing, China; HJ20150660) solution intravenously at a dose of 1.5 mg/kg. In group CR, patients sequentially received intravenous injections of 0.1% remimazolam besylate (Yichang Renfu Pharmaceutical Industry Co., Ltd, Yichang, China; H20200006) at 0.08 mg/kg followed by 0.25% ciprofol (Shenyang Haisco Pharmaceutical Co., Ltd, Shenyang, China; H20200013) at 0.25 mg/kg. In group C, received 0.25% ciprofol intravenously at a dose of 0.4 mg/kg. Additionally, all three groups received an intravenous injection of ondansetron (Qilu Pharmaceutical Co., Ltd., Jinan, China; H10970065) at a fixed dose of 2 mg. The injection rate is set at 3–5 seconds/mL. Bispectral Index (BIS) monitoring is utilized to assess the depth of sedation. Gastroscopy is initiated once the BIS value decreases to below 60, and during the procedure, the BIS value is maintained within the range of 40 to 60. Sedative drugs are administered as needed based on factors such as operation duration, patient movement, or coughing. In Group P, propofol is administered in doses of 10~20 mg per administration. In Groups CR and C, ciprofol is given in doses of 2.5~5 mg per administration, with an interval of more than 2 minutes between administrations.

We utilized the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale to assess the sedation depth of patients. An MOAA/S $\leq$ 1, indicating no response to verbal commands or physical stimulation (eg, shouting and slapping), was considered indicative of an adequate sedation depth. The induction time was defined as the interval from the intravenous administration of sedative drugs until the attainment of the target sedation depth (MOAA/S $\leq$ 1). The operation time was defined as the duration from the insertion of the gastroscope until its removal. The recovery time spans from the administration of sedative drugs until the patient is fully awake and able to follow instructions, as indicated by a MOAA/S score of 4–5. Operating room time is defined as the period from the administration of sedative drugs to the patient's exit from the gastroscopy room. Patients are eligible for discharge when their Steward recovery score exceeds 4, which corresponds to being fully awake, able to move according to medical instructions, and able to stand firmly.

After the administration of sedative drugs, if blood pressure was measured consecutively twice and found to be lower than 20% below the baseline blood pressure recorded upon entering the room or if systolic blood pressure dropped below 90 mmHg, this was defined as hypotension, and 0.5 mg of metaraminol (Jin Yao Heping (Tianjin) Pharmaceutical, Tianjin, China; H12020620) was administered intravenously. During the procedure, if the heart rate decreased to less than 50 beats per minute, this was classified as bradycardia, and 0.5 mg of atropine (Bei Te Pharmaceutical, Chengdu, China; H32021535) was administered intravenously. If the patient's blood oxygen saturation is between 90% and 95% during the procedure, this condition is classified as mild hypoxia. In such cases, the anesthesiologist should manually lift the patient's lower jaw to open the airway. If the patient's blood oxygen saturation drops below 90% during the procedure, it indicates severe hypoxia. Should the measures of lifting the jaw and opening the airway fail to promptly improve oxygenation, the gastroscope must be withdrawn, the procedure paused, and the patient ventilated with assistance using the anesthesia machine mask at an oxygen flow rate exceeding 5 L/min.

Data Collection and Recording

Data observation recording was entirely conducted by a single researcher (anesthesiologist), who was not involved in any other steps of the study. Basic patient information, including baseline blood pressure, heart rate, blood oxygen saturation, and adverse events, was meticulously documented. Additionally, the dosage of sedative drugs administered, induction time, operation duration, recovery time, and total operating room time were recorded. And satisfaction scores (excellent, average, bad) were assigned by the patients, gastroenterologists, and anesthesiologists.

Outcomes

The primary outcome indicators included the incidence of hypotension during painless gastroscopy, recovery time, and awakening quality (including: severe dizziness, postoperative nausea and vomiting).

Secondary outcome indicators included the induction time, total operating room time, the incidence of mild and severe hypoxia during gastroscopy, the frequency of mandibular elevation or mask-assisted ventilation required, the incidence of adverse events related to injection pain, coughing, body movement, and hiccups, as well as the satisfaction levels of patients, gastroenterologists, and anesthesiologists.

Calculation of Sample Size

In order to minimize errors, we conducted a preliminary experiment to determine the minimum required sample size. In the preliminary study, the incidence of hypotension was 16% among 50 patients in group P, 9% among 50 patients in group CR, and 12% among 50 patients in group C. Using PASS 15 software for power analysis, with α set at 0.05 and β at 90%, the calculated minimum sample size was 198. Accounting for a potential 10% dropout rate and loss to follow-up, we planned to recruit 220 patients per group.

Statistics Method

All patient data were analyzed using SPSS 25.0 statistical software. For measurement data that followed a normal distribution and exhibited homogeneity of variance, one-way analysis of variance (ANOVA) was employed, with results expressed as the mean ± standard deviation ($\bar{x} \pm s$). For data that deviated from normality but still demonstrated homogeneity of variance, Welch's test was utilized. The comparison of enumeration data was performed using the chi-square test and Fisher's exact probability method, with results presented as the number of cases and percentage (%). A p-value less than 0.05 was considered to indicate statistical significance.

Results

A total of 660 patients were initially enrolled in this trial. Sixteen patients were subsequently excluded: five due to intraoperative conversion to endoscopic ultrasonography, ten due to conversion to endoscopic polypectomy, and one due to conversion to a detailed endoscopic examination. Consequently, a total of 644 patients were ultimately included in the final analysis (Figure 1). No significant differences existed among the groups in baseline characteristics, including age, gender, BMI, ASA classification, Mallampati classification, smoking history, hypertension history, or pre-procedure vital signs ($P > 0.05$) (Table 1).

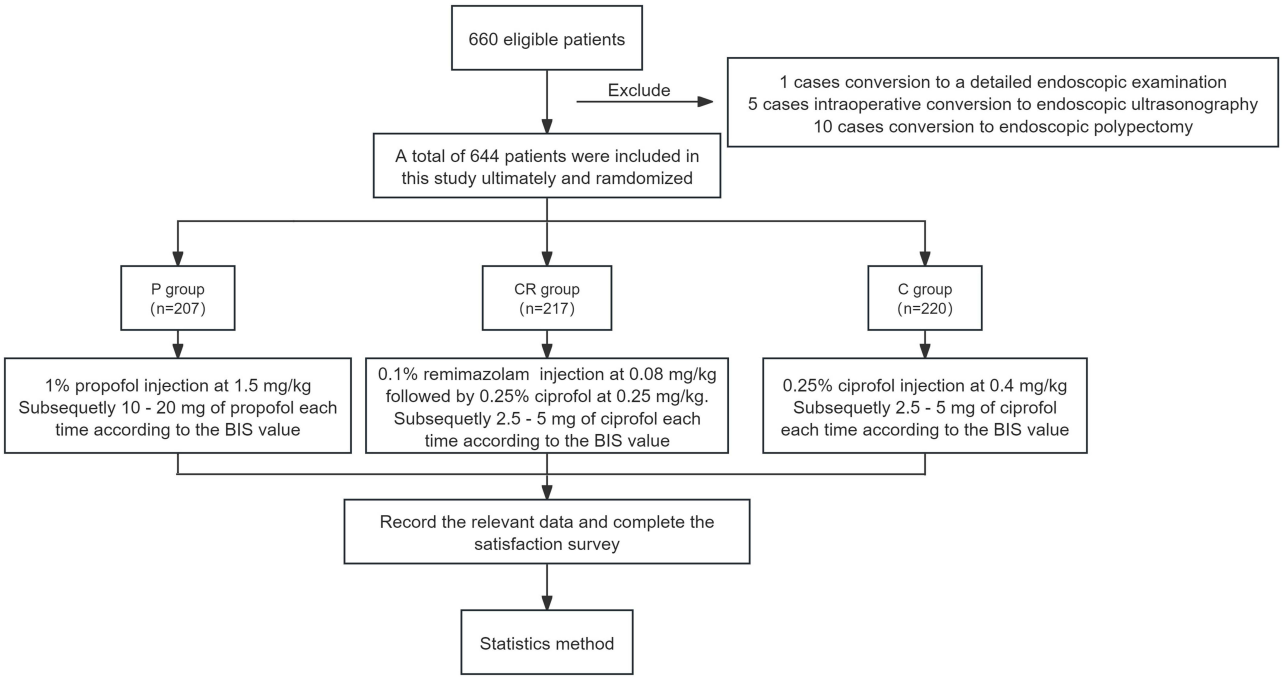

Figure 1 Patient recruitment and analysis.

The mean propofol dosage in Group P was 1.70 mg/kg. Group CR received 0.26 mg/kg ciprofol plus 0.08 mg/kg remimazolam, while Group C received 0.44 mg/kg ciprofol. No significant intergroup differences were observed in operation time. However, both induction and recovery times were significantly prolonged in Groups CR and C compared to Group P. Induction time: Group P vs CR: 1.24 vs 1.37 min ($P = 0.003$); Group P vs C: 1.24 vs 1.62 min ($P < 0.001$). Recovery time: Group P vs CR: 10.97 vs 12.79 min ($P < 0.001$); Group P vs C: 10.97 vs 13.73 min ($P < 0.001$). Group C further exhibited longer induction time (1.62 vs 1.37 min; $P < 0.001$) and recovery time (13.73 vs 12.79 min; $P < 0.001$) than Group CR. Operating room time was significantly longer in Group C (23.05 min; $P < 0.001$), but it did not differ significantly between Groups P and CR (Table 2).

Table 1 The Clinical Characteristics of the Patient

	P Group	CR group	C group	P
Age, mean (SD), (age range)	46.57 (15.83) (18–75)	48.29 (16.16) (18–77)	47.99 (16.21) (19–80)	0.504
Gender, n (%)				0.24
Male	106 (32.9)	99 (30.7)	117 (36.3)	
Female	98 (30.7)	118 (37.0)	103 (32.3)	
BMI, mean (SD), (Kg/m^2)	22.65 (2.78)	22.87 (3.03)	23.19 (2.74)	0.146
Mallampati class, n				0.245
I	131	129	136	
II	56	64	52	
III	17	24	32	
ASA class, n				0.08
I	85	117	107	
II	112	89	104	
III	7	11	9	

(*Continued*)

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Table 1 (Continued).

	P Group	CR group	C group	*P*
Smoking, n				0.092
Smokers	56	63	45	
Nonsmokers	148	154	175	
History of hypertension				0.309
Hypertension	46	52	40	
No hypertension	158	165	180	
Baseline SBP, mean (SD), (mmHg)	129.01 (19.26)	129.04 (18.11)	132.65 (19.76)	0.074
Baseline DBP, mean (SD), (mmHg)	76.71 (11.60)	76.70 (12.48)	79.14 (12.15)	0.054
Baseline HR, mean (SD), (beats/min)	73.99 (12.69)	73.57 (11.40)	72.40 (12.60)	0.378
Baseline SpO_2, mean (SD), (%)	99.50 (0.75)	99.40 (0.94)	99.33 (1.10)	0.157
Baseline RR, mean (SD), (beats/min)	14.33 (1.58)	14.07 (1.76)	14.04 (2.18)	0.228

Notes: Data are presented as Mean(SD), Numbers (Percentage).
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SpO_2, pulse oxygen saturation; RR, Respiration Rate.

Table 2 Comparison of Research Parameters Among Each Group

	P Group	CR Group	C Group	*P*
The cumulative dosage of sedative drugs				
Range of propofol (mg)	67.5–190.0			
Range of ciprofol (mg)		10.0–30.0	15.0–50.0	
Range fo remimazolam (mg)		3.2–8.1		
Average of propofol (mg/kg)	1.695 (0.329)			
Average of ciprofol (mg/kg)		0.262 (0.038)	0.436 (0.066)	
Average of remimazolam (mg/kg)		0.08		
Induction time (min)	1.224 (0.460)	1.371 (0.325)^{a}	1.618 (0.661)^{aa,bb}	<0.001
Operation time (min)	4.358 (1.805)	4.076 (1.448)	4.394 (1.638)	0.063
Recovery time (min)	10.966 (3.837)	12.793 (2.915)^{aa}	13.725 (3.815)^{aa,b}	<0.001
Operating room time (min)	20.657 (5.669)	20.895 (3.995)	23.048 (6.381) ^{aa,bb}	<0.001

Notes: Data are presented as Mean(SD). Compared to group P, ^{a}indicates $P < 0.05$, ^{aa}indicates $P < 0.01$; Compared to group CR, ^{b}indicates $P < 0.05$, ^{bb}indicates $P < 0.01$.

Compared with group P, both group CR and group C exhibited lower incidences of hypotension (CR: 7.8% vs P: 21.6%; C: 12.3% vs P: 21.6%; all *P* values < 0.001), mild hypoxia (CR: 8.8% vs P: 18.1%, $P = 0.005$; C: 7.7% vs P: 18.1%, $P = 0.001$), and severe hypoxia (CR: 4.6% vs P: 9.8%, $P = 0.038$; C: 4.1% vs P: 9.8%, $P = 0.020$). The requirement for jaw thrust maneuver was significantly lower in both Group CR (7.4% vs 16.7%, $P = 0.003$) and Group C (5.5% vs 16.7%, $P < 0.001$) compared to Group P. Similarly, the need for mask-assisted ventilation was significantly reduced in Group CR (1.8% vs 7.4%, $P = 0.006$) and Group C (2.7% vs 7.4%, $P = 0.028$) relative to Group P. Among the three groups of patients, the group CR exhibited the lowest incidence of bradycardia (3.7%, $P = 0.008$), the group C demonstrated the lowest incidence of hiccups (0.5%, $P = 0.041$), and the group P had a significantly higher incidence of injection pain compared to both the CR and C groups (42%, $P < 0.001$). No significant differences were observed among the three groups regarding the incidences of coughing, body movement, severe vertigo, and postoperative nausea and vomiting (PONV) (all *P* values > 0.05) (Table 3).

The comparison of satisfaction among the three groups of patients after the painless gastroscopy revealed no statistically significant differences. The satisfaction levels reported by gastroenterologists and anesthesiologists in the CR group were significantly higher than those in the P group and the C group (all *P* values < 0.001). The primary sources of dissatisfaction among patients in group P were injection pain (12 cases), postoperative nausea and vomiting(PONV) (7 cases), and severe vertigo (6 cases). In group CR, the main complaints stemmed from PONV (8 cases), severe vertigo (3 cases), and hiccups (4 cases). For group C, the predominant dissatisfaction was due to PONV (11 cases) and severe

Table 3 Comparison of Adverse Events Among the Three Groups

	P Group	CR Group	C Group	*P*
Hypotension, n (%)	44 (21.6)	17 (7.8)[aa]	27 (12.3)[aa]	<0.001
Bradycardia, n (%)	24 (11.8)	8 (3.7)[aa]	21 (9.5)[b]	0.008
Mild hypoxia, n (%), (SpO_2<95%)	37 (18.1)	19 (8.8)[aa]	17 (7.7)[aa]	0.001
Severe hypoxia, n (%), (SpO_2<90%)	20 (9.8)	10 (4.6)[a]	9 (4.1)[a]	0.026
Chin lift, n (%)	34 (16.7)	16 (7.4)[aa]	12 (5.5)[aa]	<0.001
Assisted ventilation, n (%)	15 (7.4)	4 (1.8)[aa]	6 (2.7)[a]	0.008
Cough, n (%)	32 (15.7)	22 (10.1)	36 (16.4)	0.124
Body movement, n (%)	35 (17.2)	26 (12.0)	40 (18.2)	0.165
Hiccups, n (%)	6 (2.9)	9 (4.1)	1 (0.5)[b]	0.041
Injection pain, n (%)	42 (20.6)	2 (0.9)[aa]	10 (4.5)[aa]	<0.001
Severe vertigo, n (%)	6 (2.9)	3 (1.4)	5 (2.3)	0.547
Nausea after surgical operation, n				0.632
Grade 1	14	10	12	
Grade 2	2	1	2	
Grade 3	0	0	0	
Vomiting after surgical operation, n				0.480
Grade 1	5	2	4	
Grade 2	0	0	0	
Grade 3	0	0	0	

Notes: Data are presented as Numbers (Percentage). Compared to group P, [a]indicates $P < 0.05$, [aa]indicates $P < 0.01$; Compared to group CR, [b]indicates $P < 0.05$.

vertigo (5 cases). The dissatisfaction among gastroenterologists was primarily attributed to the following issues: in group P, examination interruptions due to severe hypoxia induced by propofol (12 cases), as well as choking coughs and patient movements during gastroscopy (24 cases); in group CR, intraoperative hiccups (4 cases), severe hypoxia (4 cases), and choking coughs/movements during gastroscopy (10 cases); in group C, prolonged induction time (11 cases), examination interruptions caused by severe hypoxia (5 cases), and choking coughs/movements during gastroscopy (13 cases). The primary causes of dissatisfaction among anesthesiologists in group P were hypotension (20 cases), severe hypoxia (12 cases), injection pain (8 cases), and PONV (10 cases). In group CR, the main reasons for dissatisfaction included severe hypoxia (4 cases), hypotension (5 cases), intraoperative hiccups (4 cases), delayed awakening (awakening time > 20 min, 1 case), as well as choking cough and body movement (6 cases). For group C, dissatisfaction was primarily attributed to prolonged induction time (10 cases), hypotension (10 cases), severe hypoxia (5 cases), delayed awakening (awakening time > 20 min, 11 cases), choking cough and body movement (12 cases), and PONV (3 cases) (Table 4).

Table 4 Comparison of Satisfaction Levels Among Patients, Endoscopists, and Anesthesiologists

	P Group	CR Group	C Group	*P*
Patient satisfaction				0.695
Excellent	179	198	199	
Average	18	15	14	
Bad	7	4	7	
Gastroenterologist satisfaction				<0.001
Excellent	148	193[aa]	166[b]	
Average	44	22	45	
Bad	12	2	9	
Anesthesiologist satisfaction				<0.001
excellent	153	197[aa]	167[bb]	
average	38	17	40	
Bad	13	3	13	

Notes: Data are presented as Numbers (Percentage). Compared to group P, [aa]indicates $P < 0.01$; Compared to group CR, [b]indicates $P < 0.05$, [bb]indicates $P < 0.01$.

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Subgroup Analysis

We analyzed the effects of three sedation regimens across different subgroups. In the subgroup with BMI < 23 kg/m², the incidences of hypotension were lower in both the CR group and the C group compared to the P group ($P = 0.016$). Additionally, the incidence of bradycardia was significantly lower in the CR group than in the P group ($P < 0.001$). In the subgroup with BMI ≥ 25 kg/m², the incidences of hypotension, mild hypoxia, and severe hypoxia in both the CR and C groups were significantly lower than those in the P group (all P values < 0.001). Notably, the CR group exhibited the lowest incidence of hypotension (Table 5).

Among patients younger than 45 years old, the incidences of mild and severe hypoxia were lower in both the CR group and the C group compared to those in the P group ($P = 0.018$ and 0.016, respectively). Among patients aged 45 to 59 years, the incidence of hypotension was significantly lower in the CR group than in the P group ($P < 0.001$). Among patients older than 60 years old, the incidences of hypotension and bradycardia were significantly lower in the CR group compared to those in the P group (both P values < 0.001); additionally, the incidence of hypotension in the C group was lower than that in the P group ($P = 0.030$) (Table 5).

Table 5 Subgroup Analysis Stratified by Patients' BMI, Age, and Gender

	BMI (kg/m^2)			Age (Year)			Gender	
	<23	**23-25**	**≥25**	**<45**	**45-59**	**≥60**	**Male**	**Female**
Hypotension								
P group	23/115	6/42	15/47	8/85	16/68^{e}	20/51^{ee}	21/106	23/98
CR group	10/120^{a}	5/43	2/54^{aa}	2/88	4/66^{aa}	11/63^{aa,ee,f}	8/99^{a}	9/118^{aa}
C group	9/92^{a}	5/49	13/79^{a,b}	3/91	11/66	13/63^{a,ee}	13/117	14/103
P	0.016	0.834	<0.001	0.089	0.019	0.018	0.033	0.004
Bradycardia								
P group	18/115	3/42	3/47	9/85	4/68	11/51^{f}	13/106	11/98
CR group	3/120^{aa}	3/43	2/54	5/88	2/66	1/63^{aa}	2/99^{aa}	6/118
C group	8/92	5/49	8/79	8/91	6/66	7/63	10/117^{b}	11/103
P	0.002	0.856	0.351	0.496	0.347	0.003	0.022	0.201
Mild hypoxia								
P group	14/115	6/42	17/47^{cc,dd}	12/85	11/68	14/51	15/106	22/98
CR group	8/120	3/43	8/54^{aa}	5/88	5/66	9/63	8/99	11/118^{aa}
C group	6/92	4/49	7/79^{aa}	3/91^{a}	6/66	8/63	7/117	10/103^{a}
P	0.228	0.541	<0.001	0.018	0.235	0.084	0.098	0.008
Severe hypoxia								
P group	5/115	1/42	14/47^{cc,dd}	10/85	7/68	3/51	12/106	8/98
CR group	3/120	3/43	4/54^{a}	3/88^{a}	4/66^{a}	3/63	4/99	6/118
C group	3/92	1/49	5/79^{aa}	2/91^{a}	2/66	5/63	5/117^{a}	4/103
P	0.693	0.522	<0.001	0.016	0.247	0.803	0.049	0.399
Nausea after surgical operation								
P group	10/115	3/42	3/47	7/85	4/68	5/51	4/106	12/98^{g}
CR group	8/120	1/43	2/54	4/88	3/66	4/63	1/99	10/118^{g}
C group	6/92	1/49	7/79	7/91	4/66	3/63	4/117	10/103
P	0.786	0.446	0.512	0.579	1.000	0.571	0.479	0.65
Vomiting after surgical operation								
P group	4/115	1/42	0/47	3/85	1/68	1/51	0/106	5/98^{g}
CR group	2/120	0/43	0/54	1/88	0/66	1/63	1/99	1/118
C group	3/92	1/49	2/79	2/91	0/66	2/63	0/117	4/103^{g}
P	0.696	1.00	0.505	0.533	1.000	1.000	0.307	0.136

Notes: Data are presented as Numbers (Percentage). Compared to group P, ^{a}indicates $P < 0.05$, ^{aa}indicates $P < 0.01$; Compared to group CR, ^{b}indicates $P < 0.05$; Compared with the subgroup with BMI < 23 kg/m^2, ^{cc}indicates $P < 0.01$; Compared with the subgroup with 23 < BMI < 25 kg/m^2, ^{dd}indicates $P < 0.01$; Compared with the subgroup with age < 45 years old, ^{e}indicates $P < 0.05$, ^{ee}indicates $P < 0.01$; Compared with the subgroup with age 45~59 years old, ^{f}indicates $P < 0.05$; Compared with the male subgroup, ^{g}indicates $P < 0.05$.
Abbreviation: BMI, body mass index.

Table 6 Subgroup Analysis of Sedative Drug Dosage

	P Group: Dosage of Propofol (mg)			Cr Group: Dosage of Remimazolam (Mg)			C Group: Dosage of Ciprofol (mg)		
	<100	100-120	≥120	<4.5	4.5–5.5	≥5.5	<22.5	22.5–30	≥30
Hypotension	3/83	15/57$^{\#\#}$	26/64$^{\#\#}$	10/74	4/75	3/68	2/30	16/91	9/99
Bradycardia	7/83	8/57	9/64	5/74	3/75	0/68	2/30	12/91	7/99
Mild hypoxia	9/83	13/57	15/64	9/74	7/75	3/68	1/30	5/91	11/99
Severe hypoxia	1/83	6/57$^{\#}$	13/64$^{\#\#}$	3/74	2/75	5/68	1/30	2/91	6/99
Nausea after surgical operation	7/83	2/57	7/64	4/74	3/75	4/68	2/30	6/91	6/99
Vomiting after surgical operation	3/83	1/57	1/64	1/74	0/75	1/68	1/30	2/91	1/99

Notes: Data are presented as Numbers (Percentage). In group P, compared with the subgroup with a propofol < 100 mg, $^{\#}$indicates $P < 0.05$, $^{\#\#}$indicates $P < 0.01$.

In both the male and female subgroups, the incidence of hypotension in the CR group was significantly lower than that in the P group ($P = 0.033$ and $P = 0.004$, respectively). In the male subgroup, the incidence of bradycardia in both the CR and C groups was lower than that in the P group ($P = 0.022$), with the CR group showing the lowest incidence of bradycardia. Additionally, the C group had the lowest incidence of severe hypoxia. In the female subgroup, the incidence of mild hypoxia in both the CR and C groups was significantly lower than that in the P group ($P = 0.008$). No statistically significant differences were observed in the incidence of post-examination nausea and vomiting among the three groups in either the male or female subgroups (Table 5).

In group P, patients with BMI ≥ 25 kg/m² exhibited significantly higher incidences of mild and severe hypoxia compared to those with BMI < 25 kg/m² ($P < 0.001$). Additionally, hypotension was more prevalent in patients aged ≥ 45 years than in those aged < 45 years ($P < 0.01$). Furthermore, bradycardia occurred more frequently in patients aged ≥ 60 years compared to those aged 45–59 years ($P = 0.011$). Lastly, female patients demonstrated higher incidences of PONV than male patients ($P = 0.025$ and 0.024, respectively). In group CR, patients aged ≥ 60 years exhibited a significantly higher incidence of hypotension compared to those aged < 60 years ($P = 0.002$). Additionally, female patients demonstrated a higher incidence of postoperative nausea than male patients ($P = 0.013$). In group C, patients aged ≥ 60 years showed a markedly increased incidence of hypotension relative to those aged < 45 years ($P < 0.001$), and female patients experienced postoperative vomiting more frequently than male patients ($P = 0.047$) (Table 5).

Finally, we conducted an analysis of adverse reactions in relation to dosage levels across the three groups of sedative drugs. In group P, the incidences of hypotension and severe hypoxia were significantly higher in patients receiving a propofol dosage of ≥100 mg compared to those receiving <100 mg ($P < 0.01$). No such differences were observed in groups CR and C (Table 6).

Discussion

The skills and expertise of gastroenterologists in performing gastroscopy may result in varying levels of pain and discomfort for patients. Meanwhile, anesthesiologists may differ in their assessment of the depth of sedation required. Therefore, this study was conducted consistently by the same team of experienced gastroenterologists and anesthesiologists throughout the entire process to minimize errors arising from human factors. Studies have demonstrated that the combination of sedative agents, such as propofol, with low-dose opioid drugs for painless gastroscopy can effectively decrease the required dosage of sedatives, minimize the incidence of complications, and enhance the satisfaction of both patients and gastroenterologists.[18–20] Consequently, in our study, all patients were administered 0.1 μg/kg of sufentanil and 2 mg of tropisetron to ensure both their safety and comfort during the painless gastroscopy examination. At present, a dose of 0.4 mg/kg of ciprofol has been demonstrated to be safe and effective for painless gastroscopy in clinical practice.[21,22] However, a study conducted by Duan G et al[12] revealed that the incidence of hypotension and bradycardia was significantly higher in the high-dose ciprofol group, particularly among elderly patients. Meanwhile, several studies have demonstrated that an initial sedation dose of 5 mg (0.07–0.1 mg/kg) of remimazolam exhibits the highest safety and efficacy during internal diameter examinations.[14,23] Through preliminary experimental observations, the final selected

dose of ciprofol in the group CR was set at 0.25 mg/kg, while the dose of remimazolam was determined to be 0.08 mg/kg.

The Influence on the Circulatory System

Propofol, a classic sedative drug, has an inhibitory effect on the cardiovascular system. The incidence of hypotension is positively correlated with both the infusion dose and rate.[6,24] In group P, patients with older age, higher BMI, and larger doses of propofol are more likely to experience hypotension during the examination. In this study, regardless of age, weight, and gender, the incidence of hypotension was significantly lower in both group CR and group C compared to group P (CR vs P: 7.8% vs 21.6%, $P < 0.001$; C vs P: 12.3% vs 21.6%, $P < 0.001$). Notably, group CR demonstrated a significantly lower incidence, suggesting that the combined medication regimen had a lesser impact on the circulatory system. The possible reasons for this result may include the following: (1) The inhibitory effect of ciprofol itself on circulation is less pronounced compared to propofol; (2) The administration of remimazolam decreased the required dosage of ciprofol, a finding that aligns with the research outcomes reported by Xiao et al.[25]

The Impact on the Respiratory System

Painless gastroscopy often requires efficient and rapid patient turnover. The respiratory depressant effects of propofol are dose- and injection rate-dependent. Although rapid or excessive injection can quickly achieve the desired level of sedation, it may also result in a decreased respiratory rate and tidal volume, thereby leading to hypoxia.[26] In group P, patients with a higher BMI or who received a larger dosage of propofol exhibited a significantly higher incidence of respiratory depression, while no similar trend was observed in group CR and group C. If severe hypoxia cannot be alleviated by a chin lift, it may become necessary to pause the procedure, apply pressure via a mask for oxygen delivery, assist ventilation as needed, and this could potentially prolong the operation time and reduce turnover efficiency. In extreme cases, tracheal intubation might be warranted. Existing studies have demonstrated that ciprofol and remimazolam have a relatively minor effect on the respiratory system.[27–29] In this study, the incidences of mild hypoxia in group CR and group C (CR vs P: 8.8% vs 18.1%, $P = 0.005$; C vs P: 7.7% vs 18.1%, $P = 0.001$) and severe hypoxia (CR vs P: 4.6% vs 9.8%, $P = 0.038$; C vs P: 4.1% vs 9.8%, $P = 0.020$) were significantly lower than those in the group P. Similarly, the proportions of patients requiring chin lift and assisted ventilation were lower in the groups CR and C compared to group P, although no significant difference was observed between the groups CR and C. These findings indicate that the combined medication regimen offers certain advantages. Meanwhile, ciprofol has less impact on the respiratory system compared to propofol, making it particularly suitable for patients with higher body weight.

The Impact of Sedative Effects on Recovery Time

There are variations in how nurses awaken patients. In our study, nurses consistently awakened patients by gently patting their shoulders to minimize human error. Teng Y et al[30] reported that the sedative or anesthetic effects of ciprofol at doses of 0.4–0.6 mg/kg were comparable to those of propofol at doses of 1.5–2.5 mg/kg. Additionally, a dose of 0.4 mg/kg of ciprofol was found to provide effective sedation for gastroscopy and enteroscopy procedures. Through pre-experiment observations, we found that the induction time of ciprofol at doses lower than 0.4 mg/kg was prolonged, and some patients were more likely to exhibit an excited state. In this study, both the induction time and recovery time were longer in group CR and group C compared to group P (induction time: P vs CR: 1.24 vs 1.37 min, $P = 0.003$; P vs C: 1.24 vs 1.62 min, $P < 0.001$; recovery time: P vs CR: 10.97 vs 12.79 min, $P < 0.001$; P vs C: 10.97 vs 13.73 min, $P < 0.001$), which might differ from the study by Gao SH et al.[10] This may be explained by the fact that in actual clinical practice, efforts to expedite procedural throughput, including loud verbal stimuli or forceful physical actions (eg, shouting or slapping), might lead to earlier patient arousal. However, the induction time (1.37 vs 1.62 min, $P < 0.001$) and recovery time (12.79 vs 13.73 min, $P < 0.05$) were significantly shorter in group CR than in group C, suggesting that the combined medication regimen offers greater benefits. This finding suggests that the addition of remimazolam effectively reduces the induction and recovery times associated with ciprofol-based anesthesia.

The Influence on Nausea and Vomiting After the Examination

Due to the effects of anesthetic drugs and the gastroscopy procedure itself, postprocedural nausea and vomiting are common complications. Low-dose propofol has been shown to possess antiemetic properties.[31] In this study, there was no statistically significant difference in the incidence of nausea ($P = 0.632$) or vomiting ($P = 0.480$) among the three groups, which may be attributed to the use of ondansetron during the examination. Notably, a subgroup analysis revealed that female patients demonstrated a higher incidence of postoperative nausea and vomiting, consistent with findings from our previous study[24] and possibly associated with hormonal influences.[32]

Other Influences

The injection pain associated with propofol has consistently been a primary cause of dissatisfaction for both patients and anesthesiologists.[10,19] The incidence of injection pain with ciprofol is markedly lower than that with propofol.[10,21,28] In this study, the incidence of injection pain in group CR (0.9%) and group C (4.5%) was significantly lower than that in group P (20.6%, $P < 0.001$). It is noteworthy that the incidence of hiccups was higher in group CR than in group C (4.1% vs 0.5%, $P = 0.041$), potentially attributable to remimazolam, although the underlying mechanism remains unclear.[33,34] Given the limited number of reports on this association, further investigation is warranted to confirm this finding in future studies.

The Article Has Certain Limitations

The limitations of this study are as follows: (1) This was a single-center clinical trial, which might limit the generalizability of the findings to broader patient populations. (2) To prioritize patient safety and comfort, a low dose of sufentanil was used. The synergistic interaction between opioids and sedatives could introduce confounding into the results. (3) Side effects of sedatives after discharge were not evaluated. Future studies could incorporate longer-term follow-up assessments to better evaluate prolonged adverse effects.

Conclusion

The combined use of ciprofol and remimazolam for procedural sedation during gastroscopy appears to be safe and effective. Compared with the administration of propofol alone or ciprofol alone, this combination causes less compromise of circulatory and respiratory function, is associated with fewer drug-related adverse events, and increases satisfaction among both gastroenterologists and anesthesiologists. This combined regimen is particularly advantageous for high-risk patients, such as those who are obese or elderly. Future studies are warranted to investigate the optimal dosage of this combination.

Abbreviations

$GABA_A$, γ-aminobutyric acid type A; BMI, body mass index; ASA, American Society of Anesthesiologists; OSAHS, obstructive sleep apnea-hypopnea syndrome; SpO_2, oxygen saturation of blood; BIS, Bispectral Index; MOAA/S, Modified Observer's Assessment of Alertness/Sedation; ANOVA, one-way analysis of variance; PONV, postoperative nausea and vomiting; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, Respiration Rate.

Data Sharing Statement

The data collected and/or analyzed in this study can be obtained in electronic form from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of the General Hospital of Central Theater Command of PLA (approval number: [2023]046-1). Written informed consent was obtained from all participants. The clinical trial is registered with the number ChiCTR2400079998. http://www.chictr.org.cn.

Consent for Publication

Informed consent was obtained from all participating patients and researchers involved in the study.

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Author Contributions

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

Lin Li, Yusi Zhu, Pengfei Cheng, Jie Zhu, Mingyue Zeng, Yu Duan, Xiang Zhou have no conflicts of interest or financial ties to disclose.

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