Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Combined Use of Remimazolam and Ciprofol Reduces Hypoxemia and Shortens Recovery Time During Sedated Gastrointestinal Endoscopy

Hai-Ding Zou[1,2], Cong Luo[1,2], Zhao-Lan Hu[1,2], Pei Zhou[1,2], Ru-Yi Luo[1,2]

[1]Department of Anesthesiology, The Second Xiangya Hospital, Central South University, Changsha, People's Republic of China; [2]Anesthesia Medical Research Center, Central South University, Changsha, People's Republic of China

Correspondence: Ru-Yi Luo, Department of Anesthesiology, The Second Xiangya Hospital, Central South University, Central Ren-Min Road No. 139, Changsha, Hunan, 410011, People's Republic of China, Email luoruyi@csu.edu.cn

Background: Hypoxemia is the most common adverse event during painless gastrointestinal endoscopy (PGIE). This study aimed to evaluate whether the combined use of remimazolam besylate and ciprofol (group RC) reduces the incidence of hypoxemia compared to ciprofol alone (group C) in patients undergoing PGIE under deep sedation.

Methods: A total of 246 patients scheduled for PGIE were recruited from the Second Xiangya Hospital of Central South University and randomly assigned to group C or RC. The primary outcome measured was the incidence of intraoperative hypoxemia. Secondary outcomes included physiological parameters such as blood pressure, heart rate, and oxygen saturation (SpO2) during the procedure, along with time to loss of consciousness (LoC), time to awakening, and major adverse effects (MAEs). Additionally, correlations between minimum SpO2 and factors like body mass index (BMI), age, and preoperative SpO2 were examined.

Results: Group C exhibited a significantly higher incidence and frequency of hypoxemia compared to group RC. Correlation analysis revealed that minimum SpO2 was inversely related to age and BMI, while showing a positive correlation with preoperative SpO2. Additionally, the RC group demonstrated significantly decreased induction and shorter times to LoC and awakening than group C.

Conclusion: The combined administration of ciprofol and remimazolam besylate may enhance the safety profile of deep sedation for PGIE compared to ciprofol alone, offering reduced hypoxemia incidence and improved procedural efficiency.

Trial Registration: www.chictr.org.cn (Registration number: ChiCTR2400092506, Registration date: November 18, 2024).

Keywords: hypoxemia, remimazolam besylate, ciprofol, oxygen saturation, sedation

Key Points

Question: Does the combined use of remimazolam besylate and ciprofol (group RC) reduce the incidence of hypoxemia compared to ciprofol alone (group C) in patients undergoing painless gastrointestinal endoscopy (PGIE) under deep sedation?

Findings: Group RC had a significantly lower incidence and frequency of hypoxemia compared to group C. Additionally, the RC group showed faster induction and shorter times to loss of consciousness (LoC) and awakening than group C.

Meaning: The combination of ciprofol and remimazolam enhances the safety and efficiency of sedation for PGIE, reducing hypoxemia incidence and shortening recovery time.

Introduction

Gastrointestinal endoscopy is the gold standard for diagnosing and treating digestive tract diseases. A national survey reported that approximately 14 million gastrointestinal endoscopies (GIE) are performed annually in China.[1] However, gastroscope insertion often causes significant throat discomfort, leading to adverse effects, such as retching, nausea, and vomiting.[2] Sedation is widely used to mitigate these effects, with over 90% of colonoscopic procedures in Europe

Received: 22 January 2025
Accepted: 22 April 2025
Published: 6 May 2025

employing sedation (91% in Germany) and 98% in the United States.[3,4] The growing emphasis on patient comfort has driven the adoption of painless gastrointestinal endoscopy (PGIE) in clinical practice. PGIE prioritizes safety, patient comfort, and rapid recovery, aligning with modern healthcare trends to enhance the patient experience and optimize postoperative outcomes.

Propofol is the most commonly used anesthetic drug for PGIE but it is frequently associated with hypoxemia, the most prevalent adverse event during the procedure.[5,6] The reported incidence of hypoxemia varies widely, from 1.8% to 69.0%, due to differing definitions and regional variations.[5,7] Addressing hypoxemia requires optimization of anesthesia protocols. Ciprofol, a propofol analog, offers improved pharmacokinetics, providing advantages in hemodynamic and respiratory stability, and reducing adverse effects such as injection pain, nausea, and vomiting.[8,9] Ciprofol is a newly developed agonist targeting the gamma-aminobutyric acid-A (GABA A) receptor, demonstrating enhanced cardiovascular stability and facilitating swift recovery.[10] However, it has not significantly improved wake-up time or recovery quality.[8,9] With the increasing demand for painless gastroscopy, it is essential to study sedation protocols that enhance safety while facilitating faster recovery. Remimazolam besylate, a novel benzodiazepine developed soft drug design, is an ultrashort-acting intravenous sedative with a specific antagonist, flumazenil.[11] Remimazolam exerts its pharmacological effects through selective modulation of gamma-aminobutyric acid (GABA) receptors, with a particular affinity for the GABAA receptor subtype.[12] It has been shown to be safe and effective for sedation during painless gastroscopy[12] and bronchoscopy.[11] Our prior research demonstrated that co-administration of remimazolam and ciprofol maintained a favorable safety profile during painless fiberoptic bronchoscopy.[11] Additionally, the remimazolam-propofol combination has been validated as safe for gastroscopy sedation.[13] Remimazolam undergoes rapid hydrolysis by tissue esterases to inactive metabolites,[14] whereas ciprofol is primarily metabolized via hepatic hydroxylation and glucuronidation,[15] with no evidence of metabolic interaction between the two agents. However, limited research has explored their combined use in gastrointestinal endoscopy.

This study aimed to evaluate the safety and sedation profile of ciprofol combined with remimazolam besylate during PGIE. It rigorously assessed their efficacy in maintaining respiratory function and oxygenation, identifying risk factors for hypoxemia, and monitoring for main adverse events (MAEs).

Materials and Methods

Ethics Approval

This prospective, randomized study was carried out at the Second Xiangya Hospital of Central South University, with approval from the institutional ethics committee (approval number: LYF20240096). This trial was registered prior to patient enrollment with the Chinese Clinical Trial Registry (ChiCTR2400092506, https://www.chictr.org.cn). All participants provided written informed consent. The study took place between November and December 2024. This study was performed according to the principles of the Declaration of Helsinki.

Study Population

Eligible participants included adult patients aged 18 to 85 years, of any gender, who were classified as American Society of Anesthesiologists (ASA) Class I to III and had a metabolic equivalent (MET) of 3 or higher. Patients were excluded if they were pregnant, had neuropsychiatric disorders, regularly used benzodiazepines and/or opioids, had severe obstructive ventilatory dysfunction, pre-anesthetic oxygen saturation (SpO2) below 94%, BMI≥28 kg/m², or respiratory failure. All enrolled participants were scheduled to undergo gastroscopy or gastrointestinal endoscopy.

Randomization and Blinding

Patients were randomized in a 1:1 ratio using a random number table to receive either ciprofol (Group C) or a combination of ciprofol and remimazolam besylate (Group RC). Group assignments were concealed from patients, endoscopists, postoperative care providers, outcome assessors, and statisticians.

Anesthesia Protocol

Patients fasted for 8 hours before the procedure and no premedication was administered. Upon arrival, intravenous access was established. Patients were placed in the left lateral decubitus position and standard monitoring, which included electrocardiography (ECG), non-invasive blood pressure (BP), peripheral oxygen saturation (SpO2), and heart rate (HR) was initiated. Oxygen was delivered through a nasal cannula at a rate of 4 L/min.[16]

Group C patients received ciprofol at 0.35–0.7 mg/kg for induction and 2.5–7.5 mg boluses for maintenance. Group RC patients were given remimazolam besylate at 0.05–0.15 mg/kg and ciprofol at 0.2–0.5 mg/kg for induction, followed by additional doses of 1–3 mg of remimazolam besylate or 2.5–7.5 mg of ciprofol were administered as needed. In the RC group, flumazenil (0.3 mg) was administered immediately after the procedure to antagonize remimazolam besylate's effects. Additional medication was administered based on specific intraoperative indications: (1) elevated MOAA/S scores; (2) involuntary movements; (3) physiological parameter fluctuations; (4) endoscopist request; or (5) combined gastroscopy and colonoscopy procedures. Simple gastroscopy, given its short duration, typically requires no further intervention. However, if any of the above criteria were met, ciprofol (2.5–7.5 mg) was administered as necessary. In other cases, remimazolam (1–3 mg) was used to maintain adequate sedation while ensuring rapid recovery in the RC group.

Vital signs were recorded pre-induction and at five-minute intervals after that. Bradycardia (HR <45 bpm) was treated with 0.3–0.5 mg of intravenous atropine, while hypotension (systolic blood pressure <90 mmHg or <80% of baseline) was managed with 0.2–0.5 mg intravenous M-hydroxylamine. Adverse events such as nausea, vomiting, coughing, limb movements, and arrhythmias were monitored. Data collected included total drug consumption, emergence time (from the end of the examination to spontaneous eye opening), and post-anesthesia care unit (PACU) dwell time. All patients were closely monitored in the PACU until discharge.

Management of SpO2 Reduction

Upon admission to the operating room, patients were immediately provided with supplemental oxygen via a nasal cannula at a flow rate of 4 liters per minute. Hypoxemia, defined as a SpO2 value below 94%,[17] is a common complication during PGI endoscopy.[5] The following stepwise protocol was implemented to address hypoxemia: (1) The anesthesiologist closely monitored the patient's oxygen saturation. When it dropped to 90%, the oxygen flow was increased to 6 liters per minute, and a jaw thrust maneuver was performed. (2) If SpO2 fell below 85%, a nasopharyngeal airway was inserted to secure the airway and restore oxygenation. (3) If SpO2 remained below 85% for more than one minute despite these measures, the gastroscope was removed, and positive pressure mask ventilation was initiated. (4) In cases where hypoxemia persisted despite mask ventilation, endotracheal intubation was performed to ensure adequate oxygenation.

Outcome Measurements

Baseline information, including medical history, age, height, weight, MET, body mass index (BMI), and ASA classification, was documented. Vital signs, including mean arterial pressure (MAP), heart rate (HR), and SpO2, were monitored and recorded at specific time points: before anesthesia (T1), after induction (T2), every five minutes during the procedure (T3-T7), and five minutes following transfer to the PACU (T8).

The incidence and frequency of intraoperative hypoxemia, as well as the minimum oxygen saturation (SpO2), were documented. Interventions to improve oxygen saturation were also recorded, including performing a jaw thrust maneuver, applying positive pressure ventilation with a face mask, and endotracheal intubation when necessary. Additional data included hypotension requiring vasopressors, drug consumption, and recovery metrics such as the time to a Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score ≥4 and PACU discharge (MOAA/S = 5). The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale is a validated tool commonly used to measure sedation depth through patient responses to verbal and tactile stimuli. With a range from fully alert (5) to unresponsive (0), it offers a standardized method for sedation assessment. Initially validated using sedatives like midazolam,[18] the MOAA/S scale has become a standard in clinical and research applications.[19]

Primary and Secondary Outcomes

The primary outcome measured was the incidence of intraoperative hypoxemia. Secondary outcomes included the frequency of hypoxemia, minimum SpO2, vital sign parameters, and adverse events.

Sample Size Estimation

Informed by prior studies,[20,21] the sample size was determined based on pilot data. The pilot study prospectively assessed incidence rates, enrolling 55 patients in Group RC and 60 in Group C. Hypoxemia occurred in 9 patients in Group C (15%) and 2 patients in Group RC (3.6%). Using a one-tailed test with a significance level of 0.025 and 80% statistical power, the required sample size was 196 patients (98 per group). Accounting for a 20% dropout rate, 246 patients were enrolled (123 per group). Sample size calculations were performed using PASS 2021 software.

Statistical Analysis

Statistical analyses were conducted using R version 4.3.3 and SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables were represented as mean ± standard deviation (SD) and compared using the independent samples *t*-test. Non-normally distributed variables were summarized as medians with interquartile ranges (IQRs) and evaluated using the Mann–Whitney *U*-test. Categorical variables were presented as counts or percentages and analyzed through $\chi 2$ or Fisher's exact tests. Pearson's correlation coefficient was applied to assess linear relationships between continuous variables. A multivariable logistic regression analysis was performed to evaluate the robustness of the results. Changes in vital signs over time were examined using repeated measures analysis of variance (RM-ANOVA). A P-value of <0.05 was considered statistically significant.

Results

Baseline Characteristics of Participants

A total of 272 patients were screened, of which 246 met the eligibility criteria and were included in this prospective randomized controlled trial, while 26 were excluded due to incomplete perioperative data. The average age of the participants was 50.3 years. Table 1 summarizes the demographic and clinical characteristics of the C and RC groups. The groups showed no significant differences in age, sex, height, weight, BMI, MET, ASA classification, comorbidities, or anesthetic dosages (Table 1).

Analysis of Two Sets of Respiratory Parameters and Respiratory Support

The RC group demonstrated a significantly lower incidence of hypoxemia compared to the C group (11.4% vs 22.8%, $\chi 2 = 5.627$, $P = 0.018$, Table 2), representing a 50% reduction in hypoxemia incidence. Additionally, the frequency of hypoxemia events was lower in the RC group ($P = 0.045$, Table 2). The minimum oxygen saturation (min SpO2) was slightly higher in the RC group (96.1%) compared to the C group (95.2%). In our study, 15 patients in the C group required jaw lifting, and 9 in the RC group necessitated this intervention. Statistical analysis revealed no significant difference between the groups ($P > 0.05$). There were no significant differences between the groups in the management of hypoxemia events, such as the frequency of jaw thrust, mask ventilation, or endotracheal intubation (Table 2).

Analysis of the Correlation Between Min SpO2 and Participants' Physical Parameters

We examined the relationship between hypoxemia and patient characteristics by analyzing correlations between Min SpO2 and body parameters such as BMI, age, and preoperative SpO2. Pearson's correlation revealed no significant relationship between age and Min SpO2 in all patients ($r = -0.097$, $P = 0.130$; Figure 1A) or the RC group ($r = -0.001$, $P = 0.991$; Figure 1C). However, in the C group, there was a weak negative correlation ($r = -0.177$, $P = 0.049$; Figure 1B). BMI was significantly negatively correlated with Min SpO2 across all patients (Figure 1D, $r = -0.225$, $P = 0.0004$). When analyzed separately, this correlation remained significant in the C group ($r = -0.254$, $P = 0.004$; Figure 1E) but was not significant in the RC group ($r = -0.172$, $P = 0.058$; Figure 1F). The preoperative SpO2 was positively corrected with Min SpO2 in all patients, group C and group RC, respectively (Figure 1G–I).

Table 1 Baseline Characteristics of the Study Participants

Variables	Group C	Group RC	*P*-value
Sex (male/female), n	45/78	50 /73	0.513
Age (years)	50.1 ± 13.6	50.5 ± 14.3	0.834
Weight (kg)	59.1 ± 10.9	58.4 ± 9.9	0.571
Body mass index (kg/m^2)	22.6 ± 3.2	22.0 ± 3.0	0.168
Metabolic equivalent	6.7 ± 1.7	6.9 ± 1.9	0.504
ASA 1/2/3	60 /59/4	70/49/6	0.283
Type of procedure			0.701
Gastroscopy	54 (43.9)	57 (46.3)	
Gastrointestinal endoscopy	69 (56.1)	66 (53.7)	
Hypertension (Y/N)	19 /104	21/102	0.73
Diabetes (Y/N)	8/115	6/117	0.582
Coronary artery disease (Y/N)	3/120	5 /118	0.722
History of gastrointestinal surgery (Y/N)	14 /109	11 /112	0.527
Dose of anesthetics			
Total remimazolam, (mg)	0.0 (0.0, 0.0)	6.0 (5.0, 8.0)	/
Total ciprofol, (mg)	38.5 ± 13.6	25.0 ± 10.1	/

Notes: Continuous variables are reported as the mean ± SD and/or median (range). Comparisons between the two groups were performed using an unpaired *t*-test. Categorical data are reported as numbers or frequencies (%) and a χ^2 or Fisher's exact test was used to compare the two groups when appropriate.

Table 2 Outcomes in Terms of Peripheral Desaturation Events in the Two Groups

Variables	Group C	Group RC	*P*-value
Hypoxemia (Y/N)	28/95	14/109	0.018
Lowest SpO2, Mean ± SD	95.2 ± 5.8	96.1 ± 4.3	0.169
Frequency of hypoxemia, Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.045
Jaw lifting (Y/N)	15/108	9/114	0.197
Times of jaw lifting, Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.181
Mask pressurized ventilation or endotracheal intubation (Y/N)	0	0	/

Notes: Continuous and categorical (ordinal) variables are reported as the mean ± SD and/or median (range); comparisons between the two groups were performed using an unpaired *t*-test or a Mann–Whitney test.
Abbreviations: HR, heart rate; MAP, mean arterial pressure; SpO2, pulse oxygen saturation; Y, yes; N, no.

Multivariate logistic regression was conducted to assess the association between medication method and hypoxemia, with adjustments for potential confounders including sex and ASA class. In the unadjusted model (Model I), Group RC demonstrated a significantly reduced risk of hypoxemia (Supplemental Table 1, OR = 0.44, P = 0.018). After adjusting for sex (Model II), the association remained significant (Supplemental Table 1, OR = 0.42, P = 0.016), indicating minimal influence of gender. Further adjustment for ASA class (Model III) yielded consistent results (Supplemental Table 1, OR = 0.41, P = 0.015), suggesting limited confounding effects. In the fully adjusted model (Model IV), accounting for both sex and ASA class, the

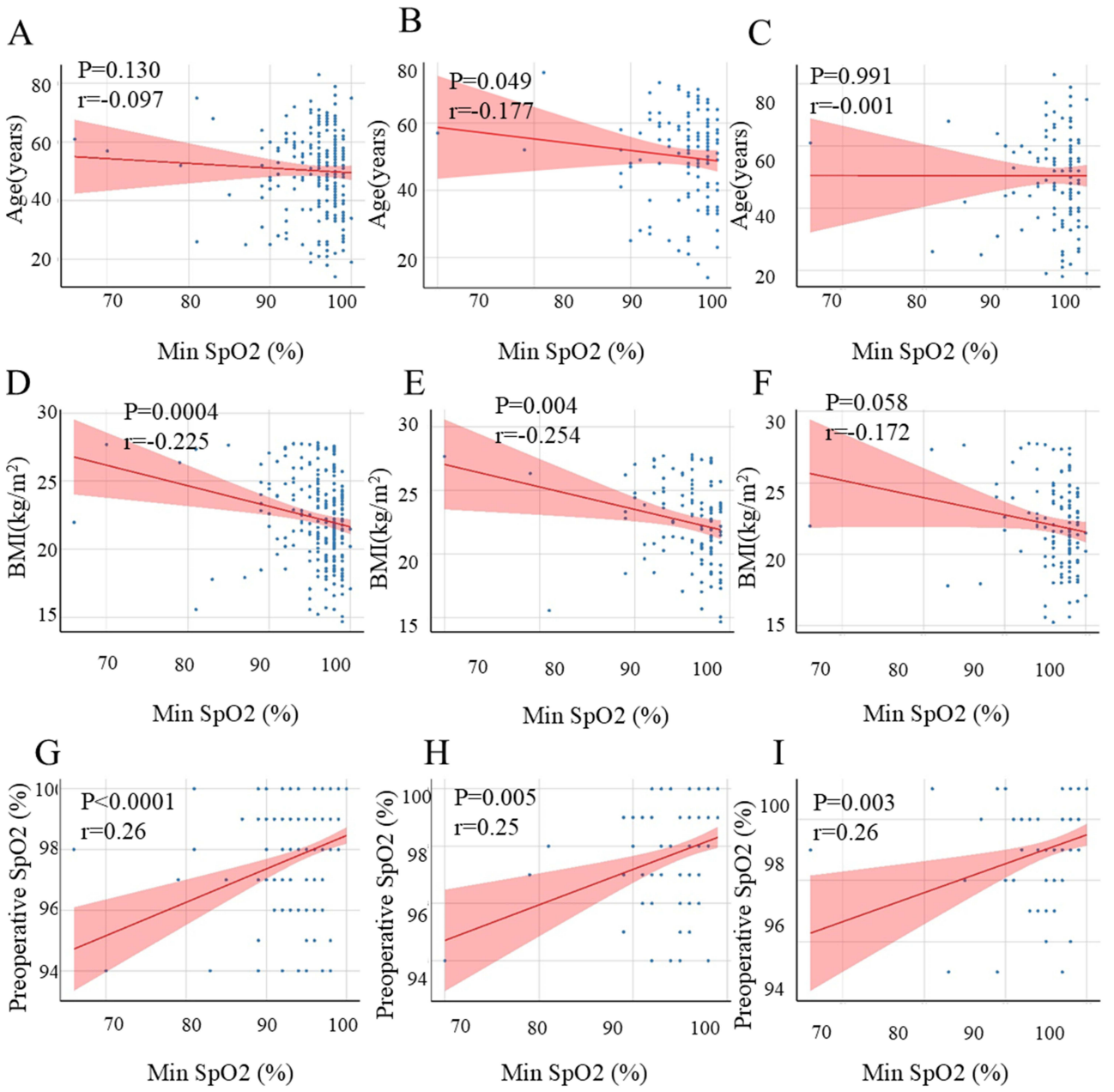

Figure 1 Correlation analysis of Min SpO2 and physical parameters of patients. (**A**) The age of all patients did not correlate with Min SpO2 during the examination. (**B**) The age of patients in group C had a negative correlation with Min SpO2 during the examination. (**C**) The age of patients in group RC did not correlate with Min SpO2 during the examination. (**D**–**F**) The BMI was negatively corrected with Min SpO2 in all patients and group C patients, but not group RC. (**G**–**I**) The preoperative SpO2 was positively corrected with Min SpO2 in all patients, group C and group RC, respectively.
Abbreviations: BMI, body mass index; Min SpO2, minimum pulse oxygen saturation.

protective association of Group RC persisted (Supplemental Table 1, OR = 0.41, P = 0.011), demonstrating that the association between medication method and hypoxemia remained significant after full adjustment. Thus, our results indicate that Group RC is associated with a significantly lower risk of hypoxemia, and this effect remains robust even after controlling for potential confounders. These findings suggest that higher BMI, older age and lower preoperative SpO2 are associated with lower Min SpO2 in the C group, but in group RC lower Min SpO2 are only associated with lower preoperative SpO2.

Observation of Vital Signs During PGI

Vital signs during PGIE are presented in Figure 2. Both groups exhibited a slight decrease in blood pressure (SBP and DBP) within 5 minutes of drug administration (T1 to T2). No significant differences in SBP, DBP, MAP, HR, or SpO2

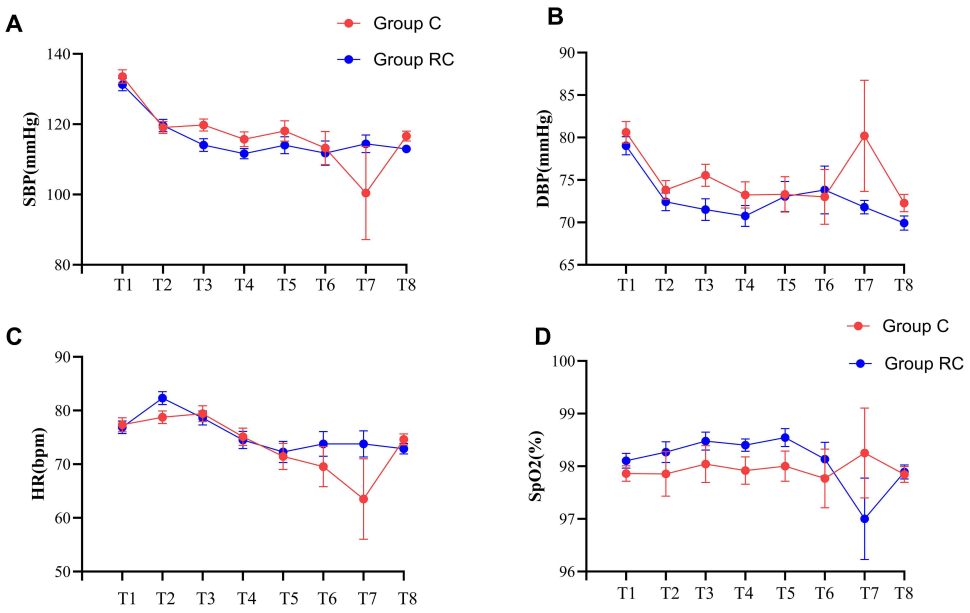

Figure 2 Vital signs at different time points in two groups. (**A**–**D**) Vital signs, including SBP (**A**), DBP (**B**), HR (**C**), and SpO2 (**D**), showed no statistically significant differences between the two groups at different time points. Data are presented as mean (standard error of the mean). T1, entering the operating room; T2, after induction; T3-T7, at the time of 5, 10, 15, 20, 25 minutes post T2, T8, at the time of PACU.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SpO2, oxygen saturation.

were found between the groups at baseline (T1), post-anesthesia induction (T2), during the procedure (T3-T7), or five minutes after PACU admission (T8).

Sedation Profile and Post-Procedural Outcomes of Different Groups

No significant differences in operation time were observed between the two groups (Figure 3A). However, group C exhibited a significantly longer time to loss of consciousness (Figure 3B, LoC, $P < 0.001$, $t = 94.992$) and time to awakening ($P = 0.02$, $t = 5.177$, Figure 3C) compared to the RC group. The RC group had a shorter PACU stay time (8.9 ± 3.4 minutes) compared to the C group (11.6 ± 6.6 minutes), but the difference was not statistically significant ($P = 0.1$, $t = 2.68$; Figure 3D).

The Occurrence of MAEs in Both Groups

Table 3 indicates that the incidence of adverse events, including hypertension, hypotension, bradycardia, tachycardia, nausea, and vomiting, was similar in both groups. Coughing ($P = 0.005$, $\chi2 = 7.857$) and involuntary movements ($P < 0.001$, $\chi2 = 15.064$) were significantly less frequent in the RC group, while hiccups occurred more often in the RC group than in the C group (Table 3).

Discussion

The study shows that using a combination of remimazolam and ciprofol (RC group) during PGIE leads to higher minimum SpO2 levels and a reduced incidence of hypoxemia compared to ciprofol alone (C group), highlighting the improved safety of RC in preserving oxygenation. Additionally, the RC combination significantly reduced LoC time and wake-up times, offering clear advantages for clinical application.

Ensuring perioperative normoxia remains critical responsibility and challenge of anesthesiologists during PGIE diagnosis and treatment.[11] Hypoxemia, a common complication of gastrointestinal endoscopy, is reported in 15–30.8% of cases.[22,23] Although high-flow nasal oxygen therapy can mitigate hypoxemia during sedation,[24] such equipment is not universally available in operating rooms. Obesity and aging further exacerbate the risk of hypoxemia, as evidenced by a 30.8% incidence during painless gastroscopy among obese individuals.[23] In our study, the RC group exhibited a lower

https://doi.org/10.2147/DDDT.S515783

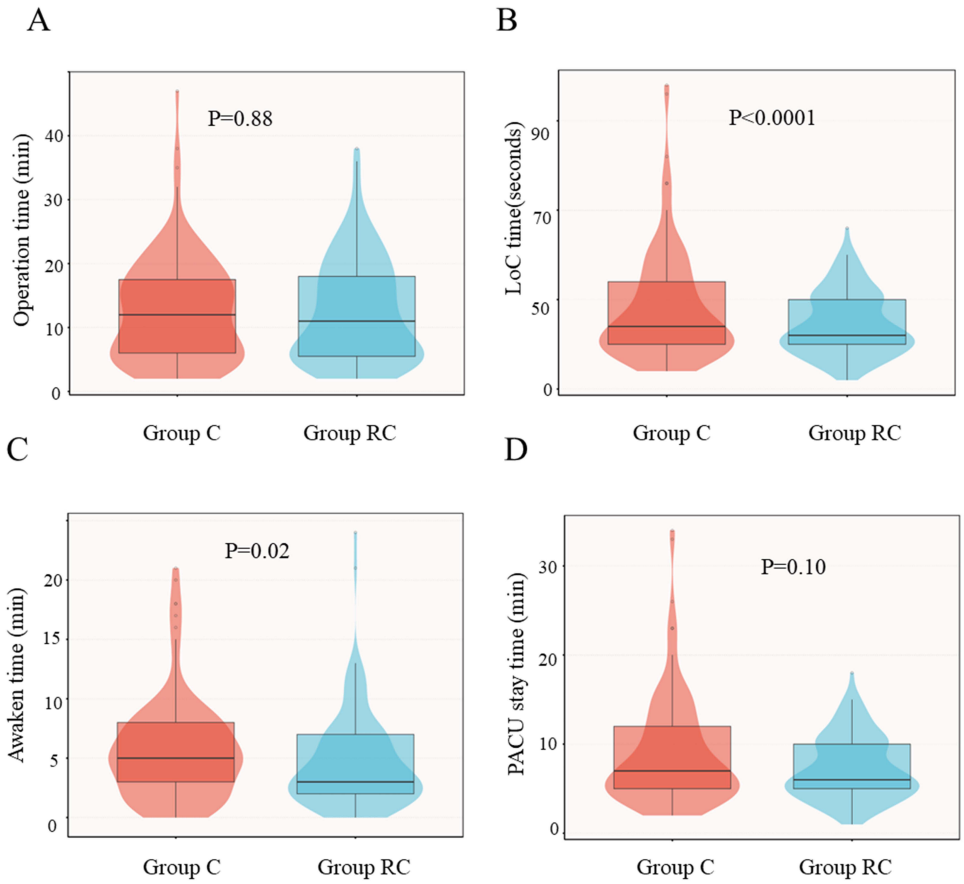

Figure 3 Sedation profile and post-procedural outcomes of different groups. (**A**) There was no statistically significant difference in operation time between the two groups. (**B**) The duration of LoC was shorter in group RC group. (**C**) The time of awakening was significantly shorter in patients of group RC. (**D**) The PACU stay time has no difference between the two groups.
Abbreviations: LoC, loss of conscience; min, minutes.

incidence of hypoxemia (11.3%) compared to typical rates reported in the literature. During painless gastrointestinal endoscopy, high BMI and older age are important risk factors for the development of hypoxemia.[25] Furthermore, higher BMI and older age correlated with reduced oxygen saturation in the C group but not in group RC group, highlighting the benefits of RC in populations such as the elderly and individuals with higher BMI. Further studies with larger sample sizes are needed to validate this finding.

Table 3 Incidence of Adverse Effects in the Two Groups

Variables	Group C	Group RC	*P*-value
Hypotension (Y/N)	0/123	5 /118	0.06
Hypertension (Y/N)	6 /117	3/120	0.5
Bradycardia (Y/N)	1 /122	1/122	1
Tachycardia (Y/N)	5/118	10 /113	0.183
Nausea (Y/N)	0/123	0/123	/
Vomit (Y/N)	1/122	1/122	1
Hiccup (Y/N)	8/115	27/96	< 0.001

(*Continued*)

Table 3 (Continued).

Variables	Group C	Group RC	*P*-value
Involuntary movement (Y/N)	30/93	8/115	< 0.001
Muscle twitch (Y/N)	6 /117	6/117	1
Dizzy (Y/N)	12/111	9/114	0.494
Cough (Y/N)	39 /84	20 /103	0.004

Note: Categorical data were described as numbers and a $\chi 2$ or Fisher's exact tests were used for comparison between the two groups when appropriate.

As the prevalence of minimally invasive diagnostic and therapeutic procedures increases, there is a growing demand for sedation protocols that optimize induction and recovery times. For example, remimazolam has been shown to reduce the effective dose (EC50) of propofol required for hysteroscopic procedures in women without prolonging anesthesia emergence or recovery times.[26] However, a previous study reported a delayed awakening in the remimazolam-alone group compared to the propofol group.[27] It is important to note, however, that remimazolam was not antagonized by flumazenil in that study. And increased sedation upon admission to the post-anesthesia care unit (PACU) has also been observed.[28] Ciprofol, in contrast, has demonstrated superior hemodynamic and respiratory stability compared to propofol during PGIE.[8] In the present study, the RC combination not only maintained oxygenation more effectively but also shortened induction and awakening times, demonstrating its clinical superiority over ciprofol alone. The synergistic sedative effect of remimazolam and ciprofol enables a faster onset of deep sedation compared to ciprofol alone, as evidenced by the shorter induction time. Additionally, the RC group routinely received flumazenil post-surgery to antagonize the effect of remimazolam. Once the remimazolam effect was reversed by flumazenil, only the sedative effect of ciprofol remained, allowing for a quicker recovery due to the reduced dosage of ciprofol.

Regarding adverse reactions, the RC group exhibited markedly reduced incidences of involuntary movements and cough, indicating a more favorable safety profile with minimal respiratory interference. Nevertheless, the incidence of hiccups was higher in the RC group (21.95%) compared to the C group (6.5%), with an absolute difference of 15.45%. Previous research by Zhang et al identified an adverse hiccup incidence of 13%.[29] Liu et al further demonstrated that midazolam administration significantly elevated hiccup risk in endoscopic patients, with incidences of 20.5% in the sedation group versus 5.1% in the non-sedation group, revealing statistically significant difference.[30] Hiccups during painless gastrointestinal endoscopy arise from multiple factors, including diaphragmatic spasm, gastric distension, vagus nerve stimulation, anesthetic effects, and patient positioning.[30,31] Targeted investigation into anesthetic-induced hiccups, particularly those associated with benzodiazepines, remains necessary. In the present study, blood pressure measurements at eight time points revealed no statistically significant intergroup differences. However, the RC group exhibited a consistent trend toward increased hypotension incidence compared to the C group, though without statistical significance ($P > 0.05$). Reported hypotension incidences with remimazolam sedation during painless gastrointestinal endoscopy range from 13.04% to 15%.[32,33] Collectively, the evidence indicates that for patients with unstable hemodynamics, employing a single sedative agent may offer a safer approach.

Limitation

This study has some limitations. Firstly, being a single-center study, its findings may lack generalizability. Multicenter randomized controlled trials are necessary to confirm and expand upon these results. Secondly, our observations were restricted to the perioperative period, spanning from the time patients entered the operating room to their discharge from the PACU. Long-term follow-up assessments were not conducted, and future studies should include extended monitoring to evaluate the durability of the observed benefits. Lastly, hiccups, a common adverse event during gastroscopic procedures,[34] were notably more frequent in the RC group than in the C group. Further research is needed to explore effective strategies for minimizing hiccup occurrence in patients undergoing sedation with the RC combination.

Conclusion

In conclusion, this study demonstrates that the combined use of remimazolam besylate and ciprofol reduces the incidence of hypoxemia, optimizes time management, and accelerates turnover processes, offering significant advantages for clinical practice. Combined use of remimazolam besylate and ciprofol may represent a novel sedation protocol in PGIE.

Data Sharing Statement

The data are available from the corresponding author (luoruyi@csu.edu.cn) on reasonable request.

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.

Funding

This trial was funded by the Scientific Project of Hunan Health Commission (Grant No. B202304116531 to RYL), the Natural Science Foundation of Hunan (Grant No. 2024JJ5503 to RYL), and the Natural Science Foundation of Changsha (Grant No. kq2403082 to RYL).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Zhou S, Zhu Z, Dai W, et al. National survey on sedation for gastrointestinal endoscopy in 2758 Chinese hospitals. *Brit J Anaesth*. 2021;127:56–64. doi:10.1016/j.bja.2021.01.028
2. Wang Y, Yang H, Cai W, Ni H. Effects of propofol combined with sufentanil on painless gastroscopy and hemodynamics in children under general anesthesia. *Am J Transl Res*. 2023;15:4942–4950.
3. Cohen LB, Wecsler JS, Gaetano JN, et al. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol*. 2006;101:967–974. doi:10.1111/j.1572-0241.2006.00500.x
4. Riphaus A, Geist F, Wehrmann T. Endoscopic sedation and monitoring practice in Germany: re-evaluation from the first nationwide survey 3 years after the implementation of an evidence and consent based national guideline. *Z Gastroenterol*. 2013;51:1082–1088. doi:10.1055/s-0033-1335104
5. Wang S, Ji J, Xiong C, et al. Comparing oxygen therapies for hypoxemia prevention during gastrointestinal endoscopy under procedural sedation: a systematic review and network meta-analysis. *J Clin Anesth*. 2024;98:111586. doi:10.1016/j.jclinane.2024.111586
6. Memtsoudis SG, Cozowicz C, Nagappa M, et al. Society of anesthesia and sleep medicine guideline on intraoperative management of adult patients with obstructive sleep apnea. *Anesth Analg*. 2018;127:967–987. doi:10.1213/ANE.0000000000003434
7. Gouda B, Gouda G, Borle A, Singh A, Sinha A, Singh PM. Safety of non-anesthesia provider administered propofol sedation in non-advanced gastrointestinal endoscopic procedures: a meta-analysis. *Saudi J Gastroenterol*. 2017;23:133–143. doi:10.4103/sjg.SJG_501_16
8. Chen L, Xie Y, Du X, et al. The effect of different doses of ciprofol in patients with painless gastrointestinal endoscopy. *Drug Des Dev Ther*. 2023;17:1733–1740. doi:10.2147/DDDT.S414166
9. 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;131:138–148. doi:10.1111/bcpt.13761
10. Ding G, Wang L, Zhao W, Diao Y, Song D. Comparison of the efficacy and safety of ciprofol and propofol for ERCP anesthesia in older patients: a single-center randomized controlled clinical study. *J Clin Anesth*. 2024;99:111609. doi:10.1016/j.jclinane.2024.111609
11. Zhou P, Fu D, Luo C, Dai R-P, Luo R-Y. Unveiling the impact of airways: a comparative analysis of oropharyngeal and nasopharyngeal airways in painless fiberoptic bronchoscopy. *Heliyon*. 2024;10:e35053. doi:10.1016/j.heliyon.2024.e35053
12. Zhang H, Li H, Zhao S, Bao F. Remimazolam in general anesthesia: a comprehensive review of its applications and clinical efficacy. *Drug Des Devel Ther*. 2024;18:3487–3498. doi:10.2147/DDDT.S474854
13. Xiao X, Xiao N, Zeng F, Chen H, Zhang L, He X. Gastroscopy sedation: clinical trial comparing propofol and sufentanil with or without remimazolam. *Minerva Anestesiol*. 2022;88:223–229. doi:10.23736/S0375-9393.21.15917-6
14. Freyer N, Knöspel F, Damm G, et al. Metabolism of remimazolam in primary human hepatocytes during continuous long-term infusion in a 3-D bioreactor system. *Drug Des Devel Ther*. 2019;13:1033–1047. doi:10.2147/DDDT.S186759
15. Petkar S, Bele A, Priya V, Bawiskar D. Pharmacological insights and clinical applications of ciprofol: a narrative review. *Cureus*. 2024;16:e68034. doi:10.7759/cureus.68034
16. Hao L, Hu X, Zhu B, Li W, Huang X, Kang F. Clinical observation of the combined use of propofol and etomidate in painless gastroscopy. *Medicine*. 2020;99:e23061. doi:10.1097/MD.0000000000023061

17. Terblanche NCS, Middleton C, Choi-Lundberg DL, Skinner M. Efficacy of a new dual channel laryngeal mask airway, the LMA®gastro™ airway, for upper gastrointestinal endoscopy: a prospective observational study. *Br J Anaesth*. 2018;120:353–360. doi:10.1016/j.bja.2017.11.075
18. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the observer's assessment of alertness/sedation scale: study with intravenous midazolam. *J Clin Psychopharmacol*. 1990;10:244–251.
19. Kim TK, Niklewski PJ, Martin JF, Obara S, Egan TD. Enhancing a sedation score to include truly noxious stimulation: the Extended Observer's Assessment of Alertness and Sedation (EOAA/S). *Br J Anaesth*. 2015;115:569–577. doi:10.1093/bja/aev306
20. Schulz KF, Grimes DA. Sample size calculations in randomised trials: mandatory and mystical. *Lancet*. 2005;365:1348–1353. doi:10.1016/S0140-6736(05)61034-3
21. Wang X, Ji X. Sample size estimation in clinical research: from randomized controlled trials to observational studies. *Chest*. 2020;158:S12–20. doi:10.1016/j.chest.2020.03.010
22. Coté GA, Hovis RM, Ansstas MA, et al. Incidence of sedation-related complications with propofol use during advanced endoscopic procedures. *Clin Gastroenterol Hepatol*. 2010;8:137–142. doi:10.1016/j.cgh.2009.07.008
23. Wang Y, Zhu J, Wang X, et al. Comparison of high-flow nasal cannula (HFNC) and conventional oxygen therapy in obese patients undergoing cardiac surgery: a systematic review and meta-analysis. *In Vivo*. 2021;35:2521–2529. doi:10.21873/invivo.12533
24. Nay M-A, 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). *Brit J Anaesth*. 2021;127:133–142. doi:10.1016/j.bja.2021.03.020
25. Qadeer MA, Rocio Lopez A, Dumot JA, Vargo JJ. Risk factors for hypoxemia during ambulatory gastrointestinal endoscopy in ASA I-II patients. *Dig Dis Sci*. 2009;54:1035–1040. doi:10.1007/s10620-008-0452-2
26. Zhou Y-H, Li S-X, Li L, et al. Effect of remimazolam supplementation on propofol requirements during hysteroscopy: a double-blind, dose-response study. *Anesth Analg*. 2024;139:1309–1316. doi:10.1213/ANE.0000000000006921
27. Zhang X, Li S, Liu J. Efficacy and safety of remimazolam besylate versus propofol during hysteroscopy: single-centre randomized controlled trial. *BMC Anesthesiol*. 2021;21:156. doi:10.1186/s12871-021-01373-y
28. Wu Q, Xu F, Wang J, Jiang M. Comparison of remimazolam-flumazenil versus propofol for recovery from general anesthesia: a systematic review and meta-analysis. *J Clin Med*. 2023;12:7316. doi:10.3390/jcm12237316
29. Zhang Q, Zhao R, Wu Y, Zhang L, Feng Y. Etomidate combined with propofol versus remimazolam for sedation in elderly patients during gastrointestinal endoscopy: a randomized prospective clinical trial. *Drug Des Devel Ther*. 2024;18:2681–2692. doi:10.2147/DDDT.S454314
30. Liu CC, Lu CY, Changchien CF, Liu PH, Perng DS. Sedation-associated hiccups in adults undergoing gastrointestinal endoscopy and colonoscopy. *World J Gastroenterol*. 2012;18:3595–3601. doi:10.3748/wjg.v18.i27.3595
31. He J, Guan A, Yang T, et al. Pathogenesis and treatment of perioperative hiccups: a narrative review. *Ann Med*. 2025;57:2474173. doi:10.1080/07853890.2025.2474173
32. Chen S-H, Yuan T-M, Zhang J, et al. Remimazolam tosilate in upper gastrointestinal endoscopy: a multicenter, randomized, non-inferiority, Phase III trial. *J Gastroenterol Hepatol*. 2021;36:474–481. doi:10.1111/jgh.15188
33. Zhang K, Bao Y, Han X, et al. Effects of opioid-free propofol or remimazolam balanced anesthesia on hypoxemia incidence in patients with obesity during gastrointestinal endoscopy: a prospective, randomized clinical trial. *Front Med*. 2023;10:1124743. doi:10.3389/fmed.2023.1124743
34. Yu W-Q, Zhu Y-H, Yang -X-X, et al. Study on painless gastroscopy and POCD of smoking patients under general anesthesia. *Ibrain*. 2022;8:276–284. doi:10.1002/ibra.12041