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Effects of a Ciprofol-Etomidate Mixture on Intraoperative Hypoxemia and Hypotension in Older Patients Undergoing Gastrointestinal Endoscopy Under Sedation: A Randomized Controlled Trial

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Abstract

Objective

To evaluate the efficacy and safety of a 1:1 ciprofol-etomidate mixture for sedation during combined gastrointestinal endoscopy in older patients and to provide evidence for optimizing clinical sedation strategies.

Methods

This single-center, prospective, double-blind, randomized controlled trial enrolled 203 patients aged 60–80 years who were scheduled to undergo combined gastrointestinal endoscopy under sedation. Patients were randomly assigned to receive either ciprofol alone (Group C, n = 101) or a ciprofol-etomidate mixture (Group CE, n = 102). Patients in Group C received intravenous ciprofol at a dose of 0.3 mg/kg, whereas those in Group CE received a slow intravenous injection of a ciprofol-etomidate mixture comprising ciprofol 0.15 mg/kg and etomidate 0.12 mg/kg over 1 min. The primary outcome was the composite incidence of intraoperative hypotension and hypoxemia. Secondary outcomes included adverse events, sedation onset time, first-dose sedation success rate, recovery time, and satisfaction scores reported by patients, anesthesiologists, and endoscopists.

Results

The incidence of the composite outcome of intraoperative hypotension and hypoxemia was significantly lower in Group CE than in Group C ($P < 0.05$). Group CE also had significantly lower incidences of hypotension (21.2% vs. 42.3%) and vasopressor use (15.4% vs. 34.6%) (both $P = 0.001$). Sedation onset was significantly faster in Group CE than in Group C (61.0 ± 6.1 s vs. 71.1 ± 14.4 s), the first-dose sedation success rate was higher (97.1% vs. 89.4%), and recovery time was shorter (18.3 ± 3.8 min vs. 19.6 ± 4.2 min) (all $P < 0.05$). The incidences of myoclonus and injection pain did not differ significantly between the groups ($P > 0.05$). Anesthesiologist satisfaction was significantly higher in Group CE than in Group C ($P < 0.001$), whereas patient and endoscopist satisfaction scores were comparable between the groups.

Conclusion

A 1:1 ciprofol-etomidate mixture improves hemodynamic stability, accelerates sedation onset, and increases the first-dose sedation success rate in older patients undergoing gastrointestinal endoscopy under sedation, without increasing adverse events. This regimen may enhance the efficiency of anesthesia management and represents a potentially useful clinical sedation strategy.

Trial registration

The trial was registered with the Chinese Clinical Trial Registry (ChiCTR2500103032, https//www.chictr.org.cn/)on 23/05/2025.

1. Background and Objective

With the aging of the population, the need for endoscopic procedures in elderly patients is growing. Sedation- or anesthesia-assisted endoscopy substantially improves patient tolerance [1] and is highly regarded by both the patients and endoscopists [2], thus becoming a common clinical procedure. However, elderly patients often have comorbid conditions like hypertension, cardiovascular, and cerebrovascular diseases, and their low physiological reserves make them susceptible to complications from anesthesia, like hypoxemia and hypotension [3–5]. In critical situations, these complications might become life-threatening. Therefore, optimizing sedation strategies for older patients undergoing gastrointestinal endoscopy is clinically important.

Propofol, one of the most commonly used sedative agents [6], has favorable pharmacokinetic properties, including rapid onset and elimination. However, it is associated with adverse effects such as hypotension, respiratory depression, and injection pain, and its respiratory and cardiovascular depressant effects are more pronounced in older patients [5]. Ciprofol is a novel sedative agent developed in China that has been widely used for gastrointestinal endoscopy under sedation and for the induction of anesthesia. Its sedative efficacy is comparable to that of propofol, but it is associated with lower incidences of hypotension and respiratory depression [7]. Ciprofol also has well-characterized absorption, distribution, metabolism, and excretion profiles and an overall favorable safety profile. Nevertheless, previous studies have reported that the incidence of cardiopulmonary adverse events during ciprofol sedation for gastrointestinal endoscopy ranges from 34.4% to 70% [8, 9]. Etomidate provides greater hemodynamic stability during anesthesia and is associated with lower incidences of respiratory depression and hypoxemia[10–12]. However, when administered alone, it is associated with a high incidence of myoclonus [13]. Previous studies have demonstrated that a propofol-etomidate mixture reduces the incidences of hypotension and hypoxemia during gastrointestinal endoscopy in older patients while also decreasing adverse reactions such as myoclonus[14, 15].

We therefore hypothesized that, compared with ciprofol alone, a ciprofol-etomidate mixture [16] would reduce the incidences of intraoperative hypotension and hypoxemia in older patients undergoing gastrointestinal endoscopy under sedation.

2. Methods

2.1 Study Design

This investigator-initiated, single-center, prospective, double-blind, randomized controlled trial was conducted between June and December 2025 at the Digestive Endoscopy Center of the First Affiliated Hospital of Zhengzhou University, Zhengzhou City,Henan Province, China. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2025-KY-0413-002). The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2500103032, https://www.chictr.org.cn/). Before enrollment, all patients or their family members received detailed information about the study and provided written informed consent.

2.2 Study Participants

Patients were eligible for inclusion if they were 60–80 years of age, had a body mass index (BMI) of 18–30 kg/m^2 and an American Society of Anesthesiologists (ASA) physical status classification of I-III, and were scheduled to undergo combined gastrointestinal endoscopy consisting of esophagogastroduodenoscopy followed by colonoscopy, with or without simple therapeutic procedures such as polypectomy. The exclusion criteria were refusal to participate; BMI ≥ 30 kg/m^2; known allergy to any study drug; severe obstructive sleep apnea; acute upper respiratory tract infection; acute exacerbation of asthma; peripheral oxygen saturation (SpO_2) < 95%; uncontrolled severe hypertension; unstable angina; acute gastrointestinal bleeding; hypotension; severe anemia; gastrointestinal obstruction accompanied by retention of gastric contents; an anticipated procedural duration of > 1 h; or participation in another clinical trial.

2.3 Randomization

After eligibility was confirmed, patients were randomly assigned in a 1:1 ratio to either the ciprofol group (Group C) or the ciprofol-etomidate mixture group (Group CE) using block randomization with variable block sizes of four or six. The randomization sequence was generated using a computer program by a statistician who was not involved in the conduct of the study. Treatment assignments were implemented strictly according to the order of patient enrollment.

2.4 Blinding

Treatment allocation was concealed using sequentially numbered, opaque, sealed envelopes. The randomization envelope was opened immediately before anesthesia induction, and the allocation record was returned to the envelope and resealed after completion of the procedure. Ciprofol and etomidate are both milky-white emulsions, and their mixture has the same appearance. Moreover, the total volume administered was identical in both groups (0.12 mL/kg), thereby allowing the study drugs to be visually indistinguishable. Before anesthesia induction, a nurse who was not involved in anesthesia management opened the envelope and prepared the study drug according to the assigned treatment. The attending anesthesiologist who administered the study drug and managed the patient was not involved in randomization and remained blinded to group allocation. Post-anesthesia care unit (PACU) personnel and postoperative follow-up staff were not involved in randomization or intraoperative management and were also blinded to treatment allocation. Patients were unaware of their group assignments.

Investigators responsible for the preoperative assessments were blinded to group allocation and did not participate in perioperative management or postoperative follow-up.

2.5 Sedation Protocol

Patients fasted from solid food for 6–8 h and from clear liquids for 2 h before the procedure. Peripheral venous access was established, and an intravenous crystalloid infusion was initiated. Upon arrival in the endoscopy room, patients were placed in the left lateral decubitus position. Oxygen was administered through a nasal cannula at 4 L/min or a face mask at 6 L/min. Standard monitoring included heart rate, noninvasive blood pressure, and peripheral oxygen saturation (SpO_2).

All patients initially received intravenous alfentanil at a dose of 5 μg/kg over 30 s. Patients in Group C subsequently received intravenous ciprofol at 0.3 mg/kg, whereas those in Group CE received a ciprofol–etomidate mixture containing ciprofol 0.15 mg/kg and etomidate 0.12 mg/kg intravenously over 1 min. The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score was evaluated immediately after the initiation of sedative administration. Endoscopy was initiated once an MOAA/S score of ≤ 1 was achieved. If the MOAA/S score remained > 1, additional 2-mL boluses of the assigned study drug were administered until the score decreased to ≤ 1. Sedation was maintained by continuous intravenous infusion of the study drug at 0.4 mL/kg/h.

Under the rescue sedation protocol, if five supplemental doses of the study drug were administered within 15 min without achieving the target depth of sedation or adequate procedural conditions, further sedative administration was permitted until sufficient sedation was achieved. If the attending anesthesiologist considered analgesia inadequate, supplemental alfentanil was administered at 0.1–0.2 mg per dose as needed. After initiation of the procedure, the MOAA/S score was assessed every minute, and the target depth of sedation was maintained at an MOAA/S score of ≤ 1.

Spontaneous ventilation was maintained throughout the procedure. If airway obstruction or paradoxical thoracoabdominal movement was observed, airway interventions, including a jaw-thrust maneuver, mask-assisted ventilation, or insertion of a nasopharyngeal airway, were performed as clinically indicated. Before anesthesia induction, palonosetron 0.15 mg was administered to prevent postoperative nausea and vomiting. If the mean arterial pressure (MAP) remained < 65 mmHg for more than 1 min, intravenous norepinephrine 8 μg was administered.

After completion of the procedure, patients were transferred to the PACU once two consecutive MOAA/S assessments yielded scores of ≥ 4. Vital signs were continuously monitored in the PACU, and discharge eligibility was determined by the attending anesthesiologist. The discharge criteria were an Aldrete score of ≥ 9 and the absence of clinically significant adverse effects, such as nausea or dizziness.

All anesthesiologists and endoscopists performing the procedures were attending physicians or senior-title physicians with more than three years of clinical experience.

2.6 Data Collection

Baseline characteristics, including sex, age, height, weight, American Society of Anesthesiologists (ASA) physical status classification, and chronic comorbidities, were recorded by the investigator responsible for the preoperative assessment. The duration of clear-liquid fasting, volume of intravenous fluids administered, endoscopic procedure duration, and doses of sedative and analgesic agents were also recorded.

The attending anesthesiologist collected intraoperative data at the following time points: arrival in the examination room(T_0), completion of anesthesia induction(T_1), 1 min after gastroscope insertion(T_2), completion of gastroscopy(T_3), arrival of the colonoscope at the ileocecal junction(T_4), completion of endoscopy(T_5), full recovery of consciousness(T_6), and discharge from the PACU(T_7). The recorded variables included MAP (mmHg), heart rate (beats/min), and SpO_2. MOAA/S scores were assessed at the completion of anesthesia induction, 1 min after gastroscope insertion, completion of gastroscopy, arrival of the colonoscope at the ileocecal junction, and completion of endoscopy.

2.7 Study Outcomes

The primary outcome was the composite incidence of hypotension and hypoxemia, defined as the occurrence of hypotension (MAP < 65 mmHg), hypoxemia (SpO_2 <90%), or both.

Secondary outcomes included the incidences of hypotension (MAP < 65 mmHg), hypoxemia (SpO_2 <90%). Other secondary outcomes included the doses of sedative and analgesic agents; the first-dose sedation success rate, defined as achievement of an MOAA/S score of ≤ 1 after the initial dose; sedation onset time; recovery time, defined as the interval from discontinuation of the sedative infusion to three consecutive MOAA/S scores of 5; and time to PACU discharge, defined as the interval from completion of the procedure to attainment of an Aldrete score of ≥ 9. Satisfaction scores reported by endoscopists, anesthesiologists, and patients were also assessed. Satisfaction was evaluated using a numerical rating scale ranging from 0 to 10, with higher scores indicating greater satisfaction.

2.8 Adverse events

Respiratory depression (90% ≤ SpO_2 <95%), and airway interventions(including a jaw-thrust maneuver, mask-assisted ventilation, and nasopharyngeal airway insertion). Injection pain, myoclonus, nausea and vomiting.

2.9 Sample Size Calculation

Previous studies have reported incidences of hypotension and hypoxemia ranging from 10% to 60% during gastrointestinal endoscopy performed under ciprofol sedation. In our preliminary study, the incidence of the composite outcome was approximately 50% in Group C and 30% in Group CE. Assuming a two-sided significance level (α) of 0.05 and a statistical power of 80%, the required sample size was calculated to be 95 patients per group. Allowing for a potential dropout rate of 10%, we planned to enroll 105 patients in each group.

2.10 Statistical Analysis

The primary and secondary outcomes were analyzed according to the per-protocol principle. All data collection was completed on the day of endoscopic procedures, with no missing data.Continuous variables are presented as the mean (standard deviation) or median (interquartile range), as appropriate, and categorical variables as the number (percentage). Baseline characteristics were compared between the two groups using statistical tests appropriate for the type and distribution of each variable. Continuous variables were compared using the independent-samples t-test or Wilcoxon rank-sum test. Categorical variables were analyzed using the Pearson chi-square test, continuity-corrected chi-square test, or Fisher's exact test, as appropriate. Ordinal variables were compared using the Wilcoxon rank-sum test.

Post hoc subgroup analyses were conducted to explore potential heterogeneity in the effect of the ciprofol-etomidate mixture on the primary outcome according to age, sex, ASA physical status classification, BMI, and procedure duration. Logistic regression models were used for these analyses.

All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 27.0.

2.11 Patient and Public Involvement

Patients and members of the public were not involved in the design, conduct, reporting, or dissemination of this study because of limited financial and organizational resources.

3 Results

3.1 Baseline Characteristics

A total of 210 patients were randomly assigned to Group C (n = 106) or Group CE (n = 104). Two patients in Group C withdrew from the study, and three patients in Group C and two patients in Group CE were excluded because the procedure duration exceeded 60 min. Consequently, 203 patients were included in the per-protocol analysis, comprising 101 patients in Group C and 102 patients in Group CE (Fig. 1).

The mean age of the participants was 67.9 (4.7) years, the mean BMI was 23.8 (2.5) kg/m^2, and 47.3% (96/203) were female. No significant between-group differences were observed in age, height, weight, BMI, duration of clear-liquid fasting, volume of intravenous fluids administered, sex, ASA physical status classification, or the prevalence of hypertension, diabetes mellitus, coronary heart disease, cerebral hemorrhage, cerebral infarction, kidney disease, arrhythmia, or chronic obstructive pulmonary disease (COPD) (all $P > 0.05$).There were no significant between-group differences in the dosage of sedative agents and the duration of the procedure. No significant between-group differences were observed in the time to full recovery of consciousness or in MOAA/S scores at the assessed time points. Baseline characteristics are presented in Table 1.

Table 1
Baseline characteristics

Characteristics	Total (n = 203)	C (n = 101)	CE (n = 102)	*P value*
Age(years)	67.9 ± 4.7	67.3 ± 4.7	68.5 ± 4.6	0.087[a]
Height(m)	1.6 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	0.714[a]
Weight(kg)	64.6 ± 9.6	63.8 ± 8.9	65.3 ± 10.3	0.296[a]
BMI(kg/m^2)	23.8 ± 2.5	23.5 ± 2.4	24.1 ± 2.5	0.083[a]
Duration of clear-liquid fasting(h)	4.8 ± 1.4	4.9 ± 1.4	4.8 ± 1.3	0.594[a]
Volume of intravenous fluids(ml)	360.2 ± 78.5	361.7 ± 74.6	358.6 ± 82.5	0.782[a]
Sex, n(%)				0.947[b]
male	107 (52.7)	53 (52.5)	54 (53.0)	
female	96 (47.3)	48 (47.5)	48 (47.1)	
Previous history				
Hypertension, n(%)	70 (34.5)	30 (29.7)	40 (39.2)	0.154[b]
Diabetes mellitus, n(%)	32 (15.8)	17 (16.8)	15 (14.7)	0.678[b]
Coronary heart disease, n(%)	24 (11.8)	11 (10.9)	13 (12.8)	0.682[b]
Cerebral hemorrhage, n(%)	3 (1.5)	2 (2.0)	1 (1.0)	0.993[b]
Cerebral infarction, n(%)	15 (7.4)	8 (7.9)	7 (6.9)	0.773[b]
Kidney disease, n(%)	1 (0.5)	1 (1.0)	0 (0.0)	0.498[c]
Arrhythmia, n(%)	6 (3.0)	4 (4.0)	2 (2.0)	0.670[b]
COPD, n(%)	8 (3.9)	2 (2.0)	6 (5.9)	0.286[b]
ASA physical status, n(%)				0.373[b]
1	11 (5.4)	5 (5.0)	6 (5.9)	
2	161 (79.3)	84 (83.2)	77 (75.5)	
3	31 (15.3)	12 (11.9)	19 (18.6)	
procedure duration(min)	25.6 ± 9.2	25.3 ± 9.1	25.8 ± 9.3	0.701[a]

Characteristics	Total (n = 203)	C (n = 101)	CE (n = 102)	*P value*
Induction Dose of Sedatives (mL)	7.9 ± 1.2	7.9 ± 1.2	7.8 ± 1.2	0.769[a]
Induction Dose of Analgesics (mg)	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.261[a]
Maintenance Infusion Rate of Sedatives	26.1 ± 3.8	25.8 ± 3.5	26.4 ± 4.1	0.263[a]
Total Consumption of Sedatives (mL)	17.6 ± 5.0	17.7 ± 5.0	17.5 ± 5.1	0.797[a]
Total Consumption of Analgesics (mg)	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.955[a]
MOAAS				
Immediate post-induction	0.0 (0.0, 1.0)	0.00 (0.0, 1.0)	0.00 (0.0, 1.0)	0.411[d]
1 min after endoscope insertion	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.425[d]
Completion of gastroscopy	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.217[d]
Reached the ileocecal junction	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	0.937[d]
Completion of the procedure	4.0 (2.0, 5.0)	4.0 (2.0, 5.0)	4.0 (2.0, 5.0)	0.126[d]
COPD Chronic obstructive pulmonary disease				
[a]*t*-test, [b]Chi-square test, [c]Fisher exact,[d]Mann-Whitney *U* test				
p-values < 0.05 were considered statistically significant for all comparisons				

3.2 Primary Outcome

The incidence of the composite outcome of hypotension and hypoxemia was significantly lower in Group CE than in Group C (20.6% vs. 42.6%; risk difference, -22.0%, 95% confidence interval,-35.4%to-8.6%; odds ratio, 0.35; 95% confidence interval, 0.18 to 0.68; $P = 0.002$). In subgroup analyses stratified by sex, age, ASA physical status classification, BMI, and procedure duration, the treatment effect appeared more pronounced among patients aged 60–69 years, those with ASA physical status class II, those who were overweight (BMI, 25.0-29.9 kg/m^2), and those with a procedure duration of ≤ 30 min (all $P < 0.05$). However, no significant interactions were identified between treatment allocation and sex, age group (60–69 vs. 70–79 years), ASA physical status classification, BMI category, or procedure duration (all P for interaction > 0.05). The results are presented in Tables 2 and Fig. 2.

3.3 Secondary Outcomes

The incidences of hypoxemia, respiratory depression, airway intervention, nausea and vomiting, body movement, injection pain, and myoclonus did not differ significantly between the groups (all $P > 0.05$).

Compared with Group C, Group CE had a significantly lower incidence of hypotension (20.6% vs. 42.6%, $P < 0.001$) and a lower rate of vasopressor administration (14.7% vs. 35.6%, $P < 0.001$). The first-dose sedation success rate was significantly higher in Group CE than in Group C (97.1% vs. 89.1%, $P = 0.025$). Sedation onset time was significantly shorter in Group CE than in Group C (60.0 ± 6.1 s vs. 71.4 ± 14.5 s, $P < 0.001$), as was recovery time (18.2 ± 3.7 min vs. 19.4 ± 4.1 min, $P = 0.026$). Anesthesiologist satisfaction was significantly higher in Group CE than in Group C [10.00 (9.00–10.00) vs. 9.00 (8.00–10.00), $P < 0.001$]. Endoscopist and patient satisfaction scores did not differ significantly between the groups (both $P > 0.05$).

Table 2
Primary and Secondary outcomes

Characteristics	**Total (n = 203)**	**C (n = 101)**	**CE (n = 102)**	***P value***
Primary Outcome, n(%)	64 (31.5)	43 (42.6)	21 (20.6)	< .001[b]
Secondary Outcomes				
hypotension,n(%)	64 (31.5)	43 (42.6)	21 (20.6)	< .001[b]
Vasopressor administration,n(%)	51 (25.1)	36 (35.6)	15 (14.7)	< .001[b]
First-dose sedation success, n(%)	189 (93.1)	90 (89.1)	99 (97.1)	0.025[b]
Sedation onset time(s)	66.2 ± 12.3	71.4 ± 14.5	61.0 ± 6.1	< .001[a]
Fully alert(min)	7.4 ± 1.9	7.6 ± 2.0	7.2 ± 1.8	0.141[a]
Recovery time(min)	18.8 ± 4.0	19.4 ± 4.1	18.2 ± 3.7	0.026[a]
Patient satisfaction	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	0.596[d]
Anesthesiologist satisfaction	10.00 (9.00, 10.00)	9.00 (8.00, 10.00)	10.00 (9.00, 10.00)	< .001[d]
Endoscopist satisfaction	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	0.077[d]
COPD Chronic obstructive pulmonary disease				
[a]*t*-test, [b]Chi-square test, [c]Fisher exact,[d]Mann-Whitney *U* test				
p-values < 0.05 were considered statistically significant for all comparisons				

Figure 2 Subgroup analyses

3.4 Adverse events

The incidences of respiratory depression, airway intervention, nausea and vomiting, body movement, injection pain, and myoclonus did not differ significantly between the groups (all P > 0.05).The results are presented in Tables 3.

Table 3
Adverse events

Characteristics	**Total (n = 203)**	**C (n = 101)**	**CE (n = 102)**	***P value***
respiratory depression, n(%)	9 (4.4)	6 (5.9)	3 (2.9)	0.486[b]
airway intervention,n(%)	7 (3.5)	5 (5.0)	2 (2.0)	0.434[b]
body movement, n(%)	44 (21.7)	27 (26.7)	17 (16.7)	0.082[b]
nausea and vomiting, n(%)	1 (0.5)	0 (0.00)	1 (1.0)	1.000[c]
injection pain, n(%)	1 (0.5)	1 (1.0)	0 (0.0)	0.498[c]
myoclonus, n(%)	1 (0.5)	0 (0.0)	1 (1.0)	1.000[c]
[b]Chi-square test, [c]Fisher exact				
p-values < 0.05 were considered statistically significant for all comparisons				

3.5 Vital Signs at Different Time Points

No significant between-group differences were observed in MAP upon arrival in the examination room or immediately after completion of anesthesia induction. Heart rate and peripheral oxygen saturation did not differ significantly between the groups at any assessed time point (all $P > 0.05$).

Compared with Group C, Group CE had significantly higher MAP values at 1 min after endoscope insertion (78.2 ± 11.1 vs. 74.7 ± 9.7 mmHg, $P = 0.017$), at the completion of gastroscopy (78.5 ± 10.3 vs. 73.0 ± 9.1 mmHg, $P < 0.001$), when the colonoscope reached the ileocecal junction (81.3 ± 11.0 vs. 75.9 ± 11.1 mmHg, $P < 0.001$), at the completion of the procedure (83.7 ± 11.0 vs. 77.0 ± 10.9 mmHg, $P < 0.001$), upon full recovery of consciousness (85.1 ± 9.7 vs. 79.3 ± 9.7 mmHg, $P < 0.001$), and at discharge from the PACU (87.9 ± 9.2 vs. 84.6 ± 8.0 mmHg, $P = 0.007$). The results are shown in Fig. 3.

Time points: $T_{0,}$ arrival in the examination room; T_1, completion of anesthesia induction; $T_{2,}$ 1 min after gastroscope insertion; $T_{3,}$ completion of gastroscopy; T_4, arrival of the colonoscope at the ileocecal junction ;T_5, completion of endoscopy; T_6, full recovery of consciousness; T_7, discharge from the PACU.*$P < 0.05$

4 Discussion

This study demonstrated that, compared with ciprofol alone, a 1:1 ciprofol-etomidate mixture significantly reduced the composite incidence of hypotension and hypoxemia during gastrointestinal endoscopy in older patients, primarily by decreasing the incidence of hypotension. The mixture also provided a more rapid onset of sedation, a shorter recovery time, a higher first-dose sedation success rate at an administration volume of 0.12 mL/kg, and greater hemodynamic stability.

The induction dose of ciprofol used in this study was selected on the basis of previous research. Ciprofol at a dose of 0.3 mg/kg has been shown to be safe and effective for anesthesia induction in older patients undergoing gastrointestinal endoscopy under sedation, with a low incidence of adverse events[17, 18]. Patients in Group C received ciprofol 0.3 mg/kg, whereas those in Group CE received ciprofol 0.15 mg/kg combined with etomidate 0.12 mg/kg. This dosing regimen ensured that the total volume of induction sedatives administered per unit of body weight was identical in the two groups, thereby facilitating blinding.

Hypoxemia risk factors in sedated gastrointestinal endoscopy patients include having age above 60 years, underlying heart or respiratory conditions, American Society of Anesthesiologists physical status above I, obesity, and obstructive sleep apnea [19]. In the present study, participants of age range 60–80 years have been selected, whereas those with obesity and obstructive sleep apnea have been excluded. Baseline demographics, along with other underlying conditions, were similar in both groups. One participant in group CE had hypoxemia; however, this patient was excluded from the study as he remained in the procedure room for more than 1 hour. Consequently, the hypoxemia frequency registered in the current study was noticeably lower compared to those revealed in previous researches [8, 9]. The above disparity may largely be explained by different approaches to oxygen administration. While in previous studies the use of oxygen in sedated patients during gastroscopy was performed via a nasal cannula, in the current research all patients received oxygen using a face mask for about 2 minutes before gastroscopy procedure.

In China, sedation or anesthesia for gastrointestinal endoscopy is administered by anesthesiologists. Given routine clinical practice and evidence that preoxygenation can substantially prolong the safe apnea period[20, 21], oxygen is commonly administered through a face mask before endoscopy. Although complete preoxygenation may not be feasible because of the rapid turnover of gastrointestinal endoscopy procedures, face-mask oxygen administration before the examination may nevertheless increase oxygen reserves and reduce the incidence of hypoxemia, as demonstrated in previous studies[22–24]. This approach may be particularly beneficial for older patients.

With respect to the sedative agents, clinically relevant doses of etomidate have minimal effects on respiratory function, including spontaneous ventilation, tidal volume, and airway responsiveness[10, 11]. Ciprofol also causes less respiratory depression than propofol [8, 17]. In the present study, the ciprofol–etomidate mixture was associated with minimal respiratory depression and a low incidence of hypoxemia. The relatively slow administration of the study drugs [25] may also have contributed to the low incidence of hypoxemia.

Hypotension is another major concern during anesthesia in older patients. Advanced age is a risk factor for hypotension[26], and intraoperative hypotension may contribute to multiorgan dysfunction and adverse clinical outcomes[27]. In a similar study[17], the incidence of hypotension among older patients receiving ciprofol for gastroscopy under sedation was 36.4%, which was lower than the 42.6% observed in the present study. This difference may be attributable to the longer duration of sedation in our study[28], because patients underwent colonoscopy after gastroscopy, as well as to preprocedural bowel preparation. Bowel preparation has also been identified as a risk factor for intraoperative hypotension[29]. In the present study, the incidence of hypotension was significantly lower in Group CE than in Group C (20.6% vs. 42.6%, $P < 0.001$), as was the rate of vasopressor use (14.7% vs. 35.6%, $P < 0.001$). These findings may be attributable to the reduced dose of each individual agent when the two drugs were administered in combination. Etomidate has minimal hemodynamic effects and is particularly suitable for older patients and those with cardiovascular disease, severe trauma, or other conditions associated with hemodynamic instability[30]. Evidence regarding the mechanisms underlying ciprofol-induced hypotension remains limited. Ciprofol is structurally and pharmacologically similar to propofol; however, it is associated with a lower incidence of hypotension, potentially because of its lower plasma concentration at equipotent doses. In the present study, combining ciprofol with etomidate reduced the administered dose of ciprofol and provided greater hemodynamic stability.

Also, the combination of ciprofol and etomidate was linked to a shorter onset time and the higher probability of effective sedation at first administration. Etomidate is characterized by the onset time ranging from 30 to 60 seconds which is similar to the onset time of propofol. Previous research found that ciprofol is characterized by the slower onset time than propofol[9]. The reduction of onset time of the ciprofol-etomidate mixture compared to the ciprofol administration only may be explained by the synergism of the γ-aminobutyric acid type A ($GABA_a$) receptors activation by both drugs [31, 32] and enhancement of sedation. Recovery time was also shorter in Group CE than in Group C. The reason for such results may lie in the difference in the metabolic pathways of the drugs. Ciprofol is metabolized mostly through glucuronidation in liver[33], while etomidate is metabolized by esterases of the liver and blood plasma[32]. Because the two agents do not compete for the same metabolic pathway, their combined use may permit rapid elimination and reduce the risk of sedative accumulation.

Previous studies have shown that injection pain associated with etomidate emulsion and ciprofol is substantially less frequent than that associated with propofol[9, 34]. In the present study, alfentanil was administered before induction, and no cases of injection pain were observed. Etomidate may induce myoclonus [13]; however, its incidence can be reduced by pretreatment with low doses of opioids, benzodiazepines, lidocaine, or etomidate [35–37]. In this study, the combination of alfentanil and ciprofol may have contributed to the low incidence of myoclonus in Group CE (0.96%). Clinical doses of etomidate may cause transient adrenocortical suppression lasting approximately 12–36 h. However, this effect generally has no clinically significant consequences in patients with normal preoperative adrenal function [38].

The overall sedation success rate was 100% in both groups, and satisfaction among anesthesiologists, endoscopists, and patients was high. Anesthesiologist satisfaction was higher in Group CE than in Group C, which may have been related to the faster onset of sedation, reduced need for supplemental sedative doses during induction, and lower rate of vasopressor use. Endoscopist and patient satisfaction scores were comparable between the groups.

5 Limitations

This study has several limitations. First, it was conducted at a single center and included a relatively limited sample size. Because the emergency equipment available in the endoscopy center was less comprehensive than that available in the operating room, only relatively healthy older patients were enrolled to ensure patient safety. The generalizability of the findings may therefore be limited, and further validation is required in older patients with obesity, critical illness, or other high-risk conditions.

Second, the sedation effectiveness and side effects of the medications were evaluated just on the day of performing gastrointestinal endoscopy without any follow-ups later. Furthermore, only 1:1 ratio of ciprofloxacin and etomidate was analyzed; therefore, it is not known how different ratios of these two medicines would impact patients.

Third, it is known that only the time of pre-procedural fasting was evaluated in the study; hence, there might be some bias caused by the patients' memory. Although all patients used polyethylene glycol electrolyte powder for bowel preparation before the procedure, different times and bowel cleansing efficiency differed in each patient. Moreover, total fasting duration and fluid intake were not recorded, potentially affecting the assessment of intravascular volume status.

Fourth, all participants received oxygen via a facemask for about 2 minutes before anesthetic induction. There were no cases of hypoxemia among the 203 patients analyzed, limiting the ability to assess the effect of the intervention on hypoxemia outcomes. However, the process of giving oxygen conforms to normal practice in the clinical setting.

Fifth, objective monitoring methods such as the bispectral index were not used to assess sedation depth. Sedation depth was evaluated solely using the MOAA/S scale, which is subject to observer variability. Satisfaction was assessed at discharge from the PACU. Because sedative agents may cause amnesia, patients may have recalled their experiences in the PACU more clearly than those during the procedure, potentially influencing their satisfaction scores.

Sixth, a per-protocol analysis was performed, excluding patients who withdrew or had missing data (n = 2) and those whose procedures lasted > 60 min (n = 5). However, excluded patients accounted for < 5% of the enrolled population, and their exclusion was unlikely to have materially affected the results.

Finally, the subgroup analyses were conducted post hoc and may have had insufficient statistical power. These findings should therefore be considered exploratory and interpreted cautiously.

Despite these limitations, the present study provides indications that the use of a ciprofol–etomidate combination would yield clinical benefits over using ciprofol alone, especially concerning hemodynamic stability, without compromising safety and applicability.

6 Conclusion

The results indicate that compared to the use of ciprofol alone, a 1:1 ciprofol–etomidate solution substantially reduced the occurrence of hypotension and hypoxemia among older patients receiving gastrointestinal endoscopy under sedation, mainly by reducing hypotension. Thus, the combination can be regarded as a promising option for this patient population. Further studies involving larger and more diverse populations, including patients with obesity, critical illness, or other high-risk conditions, are warranted before widespread clinical implementation.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2025-KY-0413-002) on 30 April 2025

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest.

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Author Contribution

Concept and design:PL and JZAcquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript,Statistical analysis:PL and XW Critical review of the manuscript for important intellectual content: NX and XWObtained funding: NX Administrative, technical, or material support: NX and PL

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Data Availability

Deidentified participant data and relevant study documents are available from the corresponding author on reasonable request.

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Figures

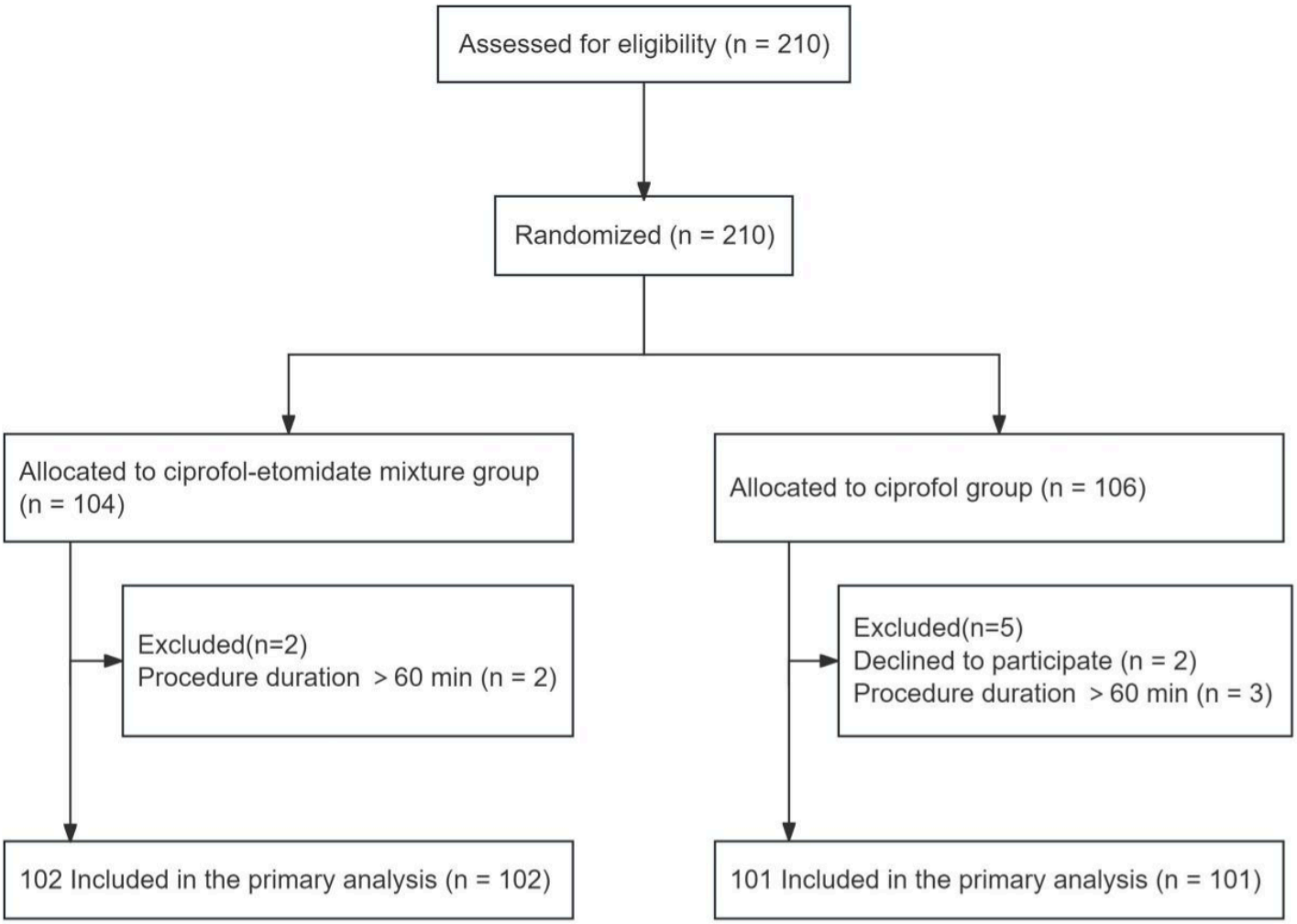


Figure 1

Flow diagram of the study.

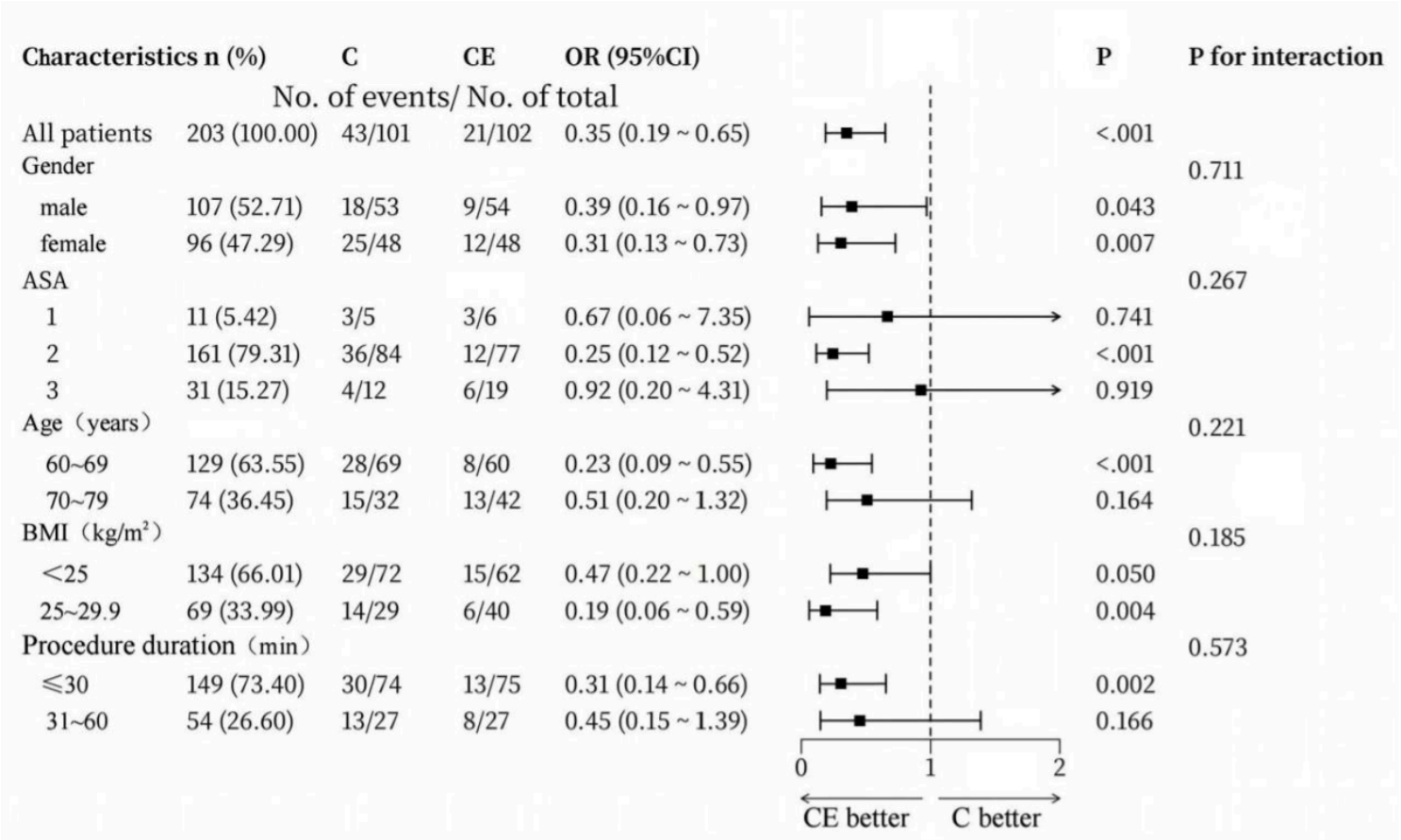


Figure 2

Subgroup analyses

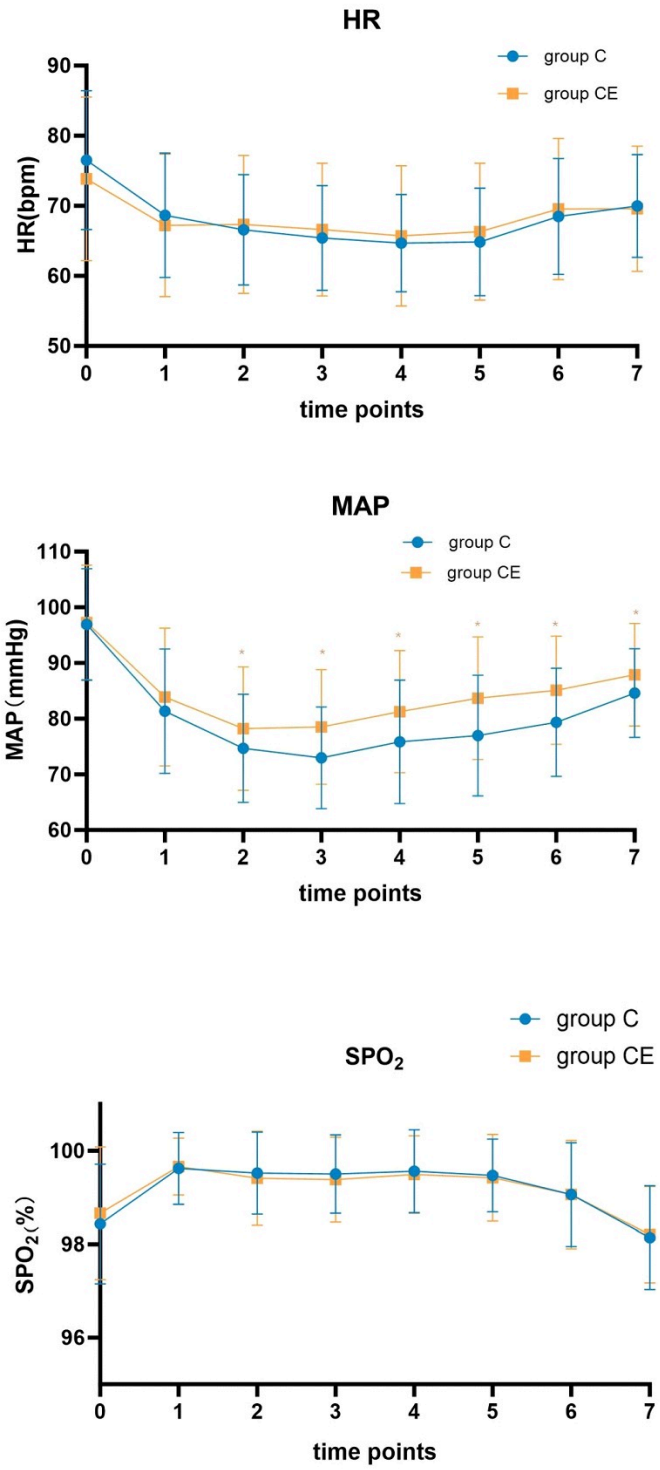


Figure 3

Vital Signs at Different Time Points

Supplementary Files

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