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CLINICAL TRIAL REPORT

Efficacy and Safety of Ciprofol Alone versus Ciprofol with Fentanyl for Upper Gastrointestinal Endoscopy: A Randomized, Double-Blind, Controlled Trial

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Background: Ciprofol is increasingly used in surgical procedures, and anesthesiologists have observed that it provides deeper sedation compared to propofol. However, it remains unclear whether the use of ciprofol alone, without combining opioids, is sufficient for upper gastrointestinal endoscopy. This study aims to address this question.

Objective: To determine whether ciprofol alone is non-inferior to ciprofol combined with fentanyl regarding sedation success and safety.

Methods: In this randomized, double-blind trial, 344 adult patients (ASA I–II, aged 18–70 years) undergoing elective upper gastrointestinal endoscopy were randomized to receive either ciprofol with saline (CS group) or ciprofol with fentanyl (CF group). Participants in both groups received an initial ciprofol dose of (0.4 mg/kg). The CF group received (1 μg/kg) intravenously before ciprofol administration, while the CS group received an equivalent volume of saline. Additional ciprofol doses (0.15–0.30 mg/kg) were administered as needed. The primary outcome was sedation success, defined as procedure completion with no more than two additional ciprofol doses within any 5-minute interval. Secondary outcomes included the incidence of hypotension and hypoxemia, as well as adverse events.

Results: Sedation success rates were 99.4% for CS and 100% for CF, demonstrating non-inferiority (difference: −0.6%, 95% CI: −0.02, 0.01). The CS group had lower respiratory depression rates and better hemodynamic stability but higher intraoperative coughing (18.1% vs 2.9%, P=0.01). Induction and recovery times were slightly longer in the CS group, and postoperative dizziness was more common (15.2% vs 7%, P=0.03).

Conclusion: Ciprofol alone is non-inferior to ciprofol with fentanyl for sedation in upper gastrointestinal endoscopy and offers advantages in respiratory and hemodynamic stability. However, it is associated with increased coughing, minor delays in induction and recovery, and more postoperative dizziness.

Keywords: ciprofol, upper gastrointestinal endoscopy, sedation, hypotension, hypoxemia, opioid-sparing

Introduction

The demand for gastrointestinal endoscopy has risen steadily in recent years, driven by advancements in endoscopic technology and growing public awareness of health.[1,2] While propofol is a commonly used agent for these procedures,[3] the potential for adverse effects (injection site pain, hemodynamic instability, respiratory depression) has spurred research into alternative drugs.[4,5]

Ciprofol (HSK3486) has emerged as a novel intravenous agent designed for sedation and anesthesia.[6,7] Pharmacologically distinct as a structural analog of propofol, ciprofol exhibits unique properties that have garnered significant clinical interest. One of the most consistently reported characteristics are markedly lower incidence of injection site pain and improved

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compared to traditional agents.[6,8–10] The safety profile of ciprofol is a critical aspect of its evaluation. Current evidence suggests a potentially favorable profile, particularly concerning hemodynamic stability and respiratory effects. Some studies indicate a lower risk of significant hypotension or respiratory depression compared to equipotent doses of propofol, although findings can vary based on dosing regimens and patient populations.[10,11] Reflecting its growing clinical application, ciprofol has been utilized in diverse settings, including gastrointestinal endoscopy,[1,2,4,9,11–14] hip fracture surgery in elderly patients,[15] thoracoscopic surgery,[16] ureteroscopy,[17] pediatric elective surgery,[18] gynecological day surgery,[19] painless hysteroscopy,[20] and cardiac surgery.[21] Furthermore, emerging clinical evidence suggests that ciprofol may induce deeper levels of sedation compared to propofol,[17,22] potentially reducing the need for adjunctive medications.

Opioids are frequently co-administered with sedatives during gastrointestinal endoscopy to enhance analgesia and sedation depth.[23] However, considering the relatively short duration and typically mild stimulation associated with upper gastrointestinal endoscopy, combined with ciprofol's profile—including its potential for effective sedation—the routine necessity of opioid supplementation when using ciprofol is questionable. This raises a clinically important question: could ciprofol, administered as a standalone agent, provide sufficient and safe sedation for patients undergoing upper gastrointestinal endoscopy?

This study aims to compare the efficacy and safety of ciprofol alone versus ciprofol combined with fentanyl for anesthesia during upper gastrointestinal endoscopy through a randomized controlled trial.

Materials and Methods

Study Design

This study is a randomized, double-blind, controlled trial. The study protocol was approved by the Ethics Committee of the First People's Hospital of Yancheng City (Approval ID: 2024-K-218). Informed consent was obtained from all eligible participants. The study adhered to CONSORT guidelines[24] and was registered at chictr.org.cn (Registration number: ChiCTR2400088300). This study complies with the Declaration of Helsinki. The objective of this study is to compare the efficacy and safety of ciprofol alone versus ciprofol combined with fentanyl for upper gastrointestinal endoscopy under sedation.

Participants

Patients who were scheduled for upper gastrointestinal endoscopy at a tertiary care medical teaching institute from September to December 2024 were enrolled in the study. Inclusion criteria were adults aged 18–70 years, American Society of Anesthesiologists (ASA) physical status I–II, body mass index (BMI) between 18 and 30, and planned elective upper gastrointestinal endoscopy. The exclusion criteria included patients with contraindications to sedation or anesthesia, a history of sedation/anesthesia adverse events, use of sedatives or analgesics before surgery, history of alcohol abuse, participation in any clinical drug trial within the past three months, neurocognitive or psychiatric disorders, endoscopy duration exceeding 30 minutes, pregnancy or lactation, allergies to opioids or ciprofol components (such as soybean oil, glycerin, triglycerides, lecithin, sodium oleate, and sodium hydroxide), or inability to obtain informed consent. Eligible patients were randomized in a 1:1 ratio to either the ciprofol with normal saline (CS) group or the ciprofol combined with fentanyl (CF) group.

Randomization and Blinding

A simple block randomization method was employed in this study to ensure balanced allocation between groups. The randomization process was conducted by a biostatistician prior to the start of the trial using the "blockrand" package in R 4.4.2 (R Core Team, Vienna, Austria), with each block containing four participants, allocating two to the CS group and two to the CF group. Randomization details were concealed in standardized, sealed opaque envelopes to maintain blinding. The biostatistician was not involved in the implementation or evaluation of the trial.

An independent anesthesia nurse, not involved in the procedure itself, opened the sealed envelope shortly before sedation to assign eligible patients in a 1:1 ratio to either the CS group or the CF group. This nurse prepared both fentanyl and saline, ensuring that both solutions were indistinguishable in appearance and filled in identical syringes, thereby maintaining allocation concealment.

Interventions

Upon arrival in the procedure room, patients underwent continuous monitoring of vital signs, including heart rate, peripheral oxygen saturation (SpO_2), and non-invasive blood pressure (NIBP). Baseline measurements of blood pressure, SpO_2, and heart rate were documented prior to the procedure's initiation. SpO_2 levels were monitored via a probe on the left index finger, while blood pressure was recorded every 2 minutes using a cuff positioned on the right upper arm. To maintain sufficient oxygenation, all patients were administered oxygen at a flow rate of 3 L/min through a nasal cannula throughout the procedure. The upper gastrointestinal endoscopy procedures were performed by experienced endoscopists.

All patients were administered 10 mL of Dyclonine Hydrochloride Mucilage (Yangtze River Pharmaceutical Group, Taizhou, China), containing 0.1 g of Dyclonine, orally prior to sedation induction. This topical pharyngeal anesthetic was administered to minimize the gag reflex and patient discomfort during endoscope insertion, thereby facilitating the procedure. Patients in the CF group received fentanyl citrate (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China) at a dose of 1 μg/kg, while those in the CS group received an equivalent volume of normal saline (Shanghai Baxter Healthcare Co., Ltd., Shanghai, China) as a placebo. After 10–30 seconds, all patients were administered ciprofol at a dose of 0.4 mg/kg for sedation induction, given slowly over 20 ± 5 seconds. According to previous research, successful induction was defined as a MOAA/S score of 1 or below,[4,9] assessed every 30 seconds by a blinded investigator until the target score was reached. If the MOAA/S score exceeded 1 at one-minute post-initial ciprofol administration, a supplemental dose (50% of the initial dose) was given. If, after two minutes, the score remained above 1, an additional dose (50% of the initial dose) was administered.

Pain at the injection site was assessed using a Visual Analog Scale (VAS) at the time of initial administration and before the patient lost consciousness. A second assessment of injection site pain was conducted after the patient was transferred to the post-anesthesia care unit (PACU).

After induction, the ciprofol dose was adjusted as needed, with supplemental doses ranging from 0.15 to 0.3 mg/kg to maintain the desired level of sedation. The target sedation level at the initiation of upper gastrointestinal endoscopy was set to an MOAA/S score of 1.

Airway support was provided if oxygen saturation fell below 95%, initially with a jaw thrust maneuver. If SpO2 continued to drop below 90%, the oxygen flow rate was increased to 6 L/min. If SpO2 dropped below 90% for more than 10 seconds, the endoscope was withdrawn from the patient's mouth, and positive pressure ventilation was provided via a mask, with further airway support measures, such as the use of an oropharyngeal airway or tracheal intubation, implemented if necessary.

Hypotension was defined as a systolic blood pressure < 90 mmHg or a decrease of >30% from baseline. If hypotension occurred, it was promptly managed with an intravenous bolus of ephedrine 5 mg or phenylephrine 50 μg, repeated as necessary to maintain hemodynamic stability.

Outcomes

The primary outcome of this study was the sedation success rate, defined by successful completion of the procedure and the administration of no more than two additional doses of ciprofol within any 5-minute interval following the initial induction dose. To clarify the rationale for this endpoint, it is important to note that the administration of supplemental doses was strictly guided by objective assessment using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score, with doses given only when the score exceeded 1. This approach, focusing on the need for minimal, objectively triggered rescue medication, serves as a pragmatic indicator of the initial regimen's efficacy and aligns with methodologies used in previous procedural sedation studies.[4,9,11,14,25]

Secondary outcomes included induction time, defined as the interval from the start of ciprofol administration to the point at which the MOAA/S score reached 1, and recovery time, defined as the time from arrival in the post-anesthesia care unit (PACU) to discharge, with discharge permitted after three consecutive Aldrete scores of ≥9, assessed every 5 minutes.

The rate of airway intervention was assessed, including procedures such as jaw thrust, positive pressure mask ventilation, and endotracheal intubation. Hypoxemia was defined as SpO2 < 90% for ≥10 seconds, while hypotension was defined as a systolic blood pressure < 90 mmHg or a decrease of >30% from baseline. Additional secondary outcomes included the occurrence of gagging, the total dose of ciprofol administered, injection pain (VAS score >3), and

postoperative adverse events, such as nausea, vomiting, dizziness, headache, hallucinations or nightmares, pruritus, dry mouth, and urinary retention. Furthermore, satisfaction levels of the anesthesiologist, endoscopist, and patient were assessed using a 100-point numerical rating scale, where 0 indicated "very dissatisfied" and 100 indicated "very satisfied". The assessments for the anesthesiologist and endoscopist were conducted immediately following the procedure. Patient satisfaction was assessed upon full recovery in the post-anesthesia care unit.

Statistical Analysis

The sample size calculation was based on a non-inferiority trial design to ensure sufficient statistical power. The event rate in the CF group was expected to be 99%, with a non-inferiority margin set at 5%. This margin was determined based on clinical judgment, considering the high expected success rate of sedation for upper gastrointestinal endoscopy and the desire to ensure that any potential reduction in efficacy with the ciprofol-alone regimen compared to the ciprofol-fentanyl regimen would be clinically minimal. This chosen margin of 5% represents a stringent threshold, narrower than the 10% margin sometimes employed in non-inferiority studies, reflecting our conservative approach to establishing non-inferiority while evaluating the potential benefits of an opioid-sparing technique. A one-sided alpha level of 0.0125 and a power (1-β) of 90% were used. The sample size calculation, performed using PASS (NCSS, Kaysville, UT, USA), indicated that 154 participants were required per group, for a total of 308 participants. Considering a potential 10% dropout rate, we planned to recruit a total of 344 participants (172 per group) to ensure sufficient statistical power for a robust analysis.

Continuous variables were first assessed for normality using the Kolmogorov–Smirnov test. Comparisons of data with a normal distribution between groups were conducted using an independent samples *t*-test, while the Mann–Whitney *U*-test was employed for non-normally distributed data. Categorical variables were analyzed using the chi-square test, or Fisher's exact test when expected frequencies were below 5. Differences in success rates and confidence intervals were determined using the Farrington-Manning method, applying a non-inferiority margin of −5%.

Statistical significance was defined as a p-value below 0.05. All data analyses were conducted using R software (version 4.4.2; R Core Team, Vienna, Austria).

Results

A total of 537 patients were screened, of which 344 were enrolled in the trial (Figure 1). Three patients were excluded due to procedure durations exceeding 30 minutes, resulting in 341 patients included in the final per-protocol analysis (171 in the CS group and 170 in the CF group).

Patient demographics and baseline clinical parameters are presented in Table 1, showing no significant differences between the two groups. The median age ranged from 53 to 55 years, with the majority of participants being female (male proportion: 36.8–37.6%). Approximately 85% of patients were classified as ASA II, and the proportion of patients with treated hypertension ranged from 17.6% to 18.1%.

Primary Outcome

The sedation success rate was 99.4% in the CS group and 100% in the CF group (Table 2). The difference in proportions, calculated using the Farrington-Manning method, was −0.6% (95% CI: −0.02, 0.01), which did not exceed the predefined non-inferiority margin of 5%. The lower bound of this 95% CI (−0.02) is above the pre-specified non-inferiority margin of −5%, thus demonstrating that cisprofol alone (CS group) is non-inferior to cisprofol combined with fentanyl (CF group) for sedation success. Therefore, the primary outcome was achieved. Only one patient in the CS group failed sedation due to a high dose requirement of ciprofol in a short period.

Secondary Outcomes

Table 3 shows that induction time was significantly longer in the CS group, with a median of 60 seconds (IQR: 50, 60) and a mean of 59 seconds, compared to a median of 50 seconds (IQR: 40, 50) and a mean of 48 seconds in the CF group (P=0.01). Recovery time was also slower in the CS group, with a mean of 19.59 minutes and a median of 20 minutes, compared to a mean of 17.44 minutes and a median of 15 minutes in the CF group (P=0.01).

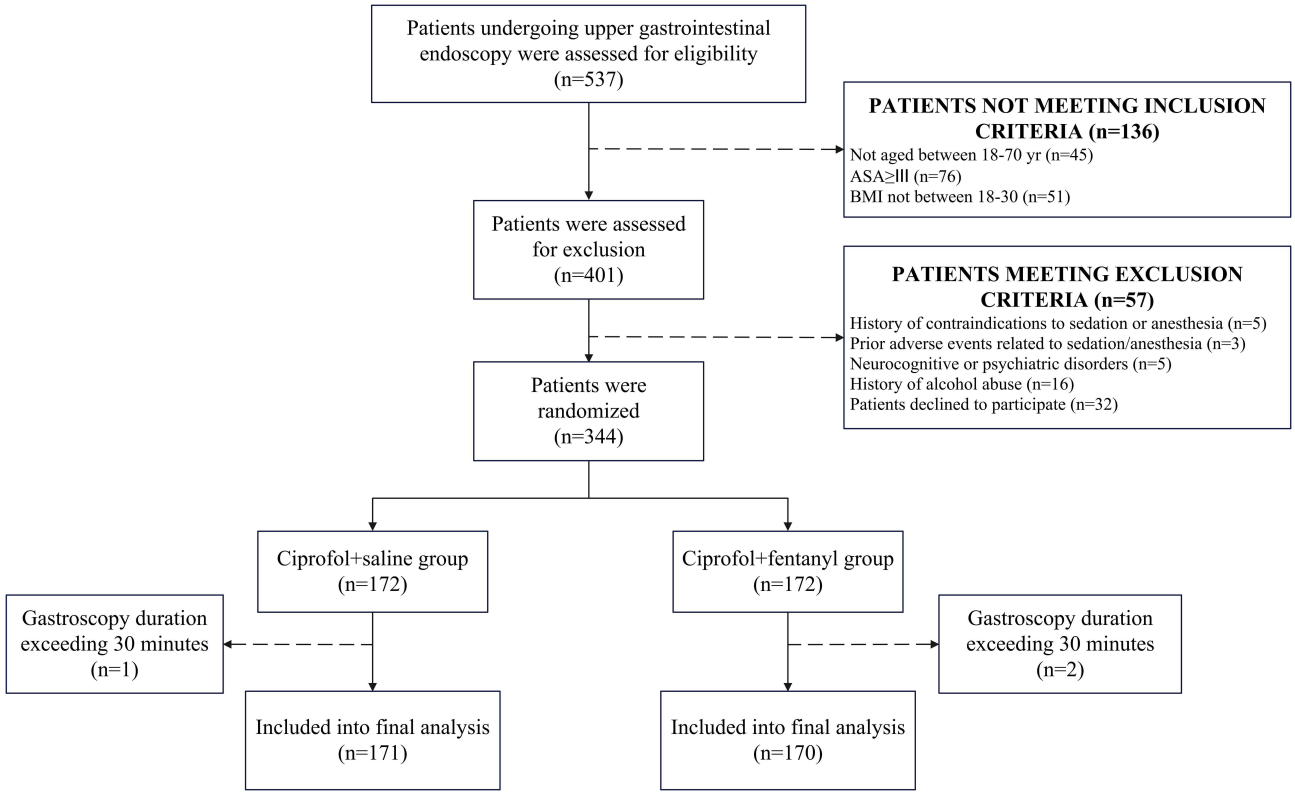

Figure 1 CONSORT flow chart of subject enrollment.

The rate of airway intervention was significantly lower in the CS group (10.5%) compared to the CF group (31.3%) (P=0.01). Similarly, the incidence of hypoxemia was lower in the CS group (4.1%) compared to the CF group (12.9%), with a statistically significant difference. Hypotension occurred in 7.6% of the CS group compared to 42.3% in the CF group (P=0.01). These results collectively indicate better hemodynamic stability and reduced respiratory depression in the CS group.

Table 1 Patient Demographics and Baseline Clinical Parameters

	CS Group (n=171)	CF Group (n=170)	P values
Age, year	53.00 (45.00, 59.00)	55.00 (41.00, 61.00)	0.56
Sex (Male)	63 (36.8)	64 (37.6)	0.97
Height, cm	163.85 ± 7.49	164.56 ± 8.16	0.41
Weight, kg	64.06 ± 11.26	64.57 ± 11.02	0.68
BMI, kg/m2	23.76 ± 3.14	23.74 ± 2.89	0.93
ASA physical Status group			0.96
Class I	24 (14.0)	25 (14.7)	
Class II	147 (86.0)	145 (85.3)	
Modified Mallampati score			0.83
Class I	29 (17.0)	31 (18.2)	
Class II	141 (82.4)	139 (81.8)	
Class III	1 (0.6)	0 (0)	
Treated hypertension	31 (18.1)	30 (17.6)	1.00
Diabetes mellitus	7 (4.1)	5 (2.9)	0.77
Smoking history	11 (6.4)	13 (7.6)	0.68

(*Continued*)

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Table 1 (Continued).

	CS Group (n=171)	CF Group (n=170)	P values
Pre-induction vital signs			
SBP, mmHg	128.05 ± 17.71	127.86 ± 15.05	0.92
DBP, mmHg	72.04 ± 11.14	72.88 ± 10.64	0.48
Heart rate, bpm	82.07 ± 13.29	79.79 ± 13.01	0.11
SpO_2, %	100.00 (99.00, 100.00)	100.00 (99.00, 100.00)	0.79

Notes: Values are presented as mean ± SD, median (interquartile range), or n (%).
Abbreviations: CS, Ciprofol + Saline group; CF, Ciprofol + fentanyl group; BMI, body mass index; ASA, American Society of Anesthesiologists; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, pulse oxygen saturation.

Table 2 Primary Outcome

	CS Group(n=171)	CF Group (n=170)
Success of sedation, n (%)	170 (99.4)	170 (100)
Difference of proportions, %	−0.6	
95% CI	(−0.02, 0.01)	
Failure to complete procedure, n (%) More than two additional doses of ciprofol administered within any 5-minute interval following the induction dose, n (%)	0 (0) 1 (0.6)	0 (0) 0 (0)

Notes: Values are presented as n (%). Success of sedation is defined as meeting all of the following criteria: successful completion of the procedure, and no more than two additional doses of ciprofol administered within any 5-minute interval following the induction dose. The differences in success rates and confidence intervals are determined using the Farrington–Manning method, applying a noninferiority margin of −5%.
Abbreviations: CS, Ciprofol + Saline group; CF, Ciprofol + fentanyl group; CI, Confidence interval.

Table 3 Secondary Outcomes

	CS Group (n=171)	CF Group (n=170)	P values
Intraoperative parameter			
Induction time, s	60 (50, 60)	50 (40, 50)	< 0.01
Procedure duration, min	9 (7, 9)	9 (7, 9)	0.63
Recovery time, min	20 (15, 25)	15 (15, 20)	< 0.01
Airway intervention, n (%)	18 (10.5)	53 (31.3)	< 0.01
Hypoxemia, n (%)	7 (4.1)	22 (12.9)	< 0.01
Hypotension, n (%)	13 (7.6)	72 (42.3)	< 0.01
Gagging, n (%)	4 (2.3)	0 (0)	0.12
Cough, n (%)	31 (18.1)	5 (2.9)	< 0.01
Total dose of ciprofol injected, mg/kg	0.4 (0.4, 0.6)	0.4 (0.4, 0.4)	< 0.01
0.4 mg/kg, n (%)	98 (57.3)	153 (90.0)	< 0.01
0.6 mg/kg, n (%)	65 (38.0)	15 (8.8)	
> 0.6 mg/kg, n (%)	8 (4.7)	2 (1.2)	
Injection pain, n (%)	1 (0.6)	0 (0)	1
Patient satisfaction	97.31 ± 6.76	98.39 ± 6.82	0.14
Endoscopist satisfaction	95.26 ± 10.19	96.53 ± 8.30	0.21
Anesthesiologist satisfaction	83.38 ± 14.88	79.56 ± 16.04	0.02

(*Continued*)

Table 3 (Continued).

	CS Group (n=171)	CF Group (n=170)	P values
Postoperative adverse events			
Pruritus, n (%)	0 (0)	2 (1.2)	0.25
Nausea, n (%)	1 (0.6)	0 (0)	1
Vomiting, n (%)	0 (0)	0 (0)	1
Dizziness, n (%)	26 (15.2)	12 (7.1)	0.03
Headache, n (%)	0 (0)	0 (0)	1
Hallucinations or nightmares, n (%)	1 (0.6)	0 (0)	1
Dry mouth, n (%)	58 (33.9)	64 (37.6)	0.54
Uroschesis, n (%)	0 (0)	0 (0)	1

Notes: Values are presented as mean ± SD, median (interquartile range), or n (%).
Abbreviations: CS, Ciprofol + Saline group; CF, Ciprofol + fentanyl group.

The occurrence of intraoperative gagging showed no significant difference between the groups (2.3% vs 0%). In contrast, coughing was markedly more common in the CS group (18.1%) compared to the CF group (2.9%), with a statistically significant difference (P = 0.01). This finding indicates improved procedural tolerance in the CF group.

The total ciprofol dose administered was notably higher in the CS group, with statistical significance (P = 0.01). The median dose in the CS group was 0.4 mg/kg (IQR: 0.4–0.6), compared to 0.4 mg/kg (IQR: 0.4–0.4) in the CF group. The mean doses were 0.50 mg/kg and 0.42 mg/kg for the CS and CF groups, respectively. The addition of fentanyl in the CF group reduced the required dose of ciprofol, with 90% of patients in the CF group requiring only a single induction dose (0.4 mg/kg), whereas over 40% of patients in the CS group required at least one additional dose. Fisher's exact test confirmed a significant difference in overall dosing between the groups (P=0.01).

Injection pain was rare, occurring in only one patient in the CS group. Patient satisfaction scores were high in both groups, with mean scores of 97.31 ± 6.76 for CS and 98.39 ± 6.82 for CF. Endoscopist satisfaction was similarly high, with mean scores of 95.26 ± 10.19 for CS and 96.53 ± 8.30 for CF (P=0.21). Anesthesiologist satisfaction, however, was significantly higher in the CS group (83.38 ± 14.88) compared to the CF group (79.56 ± 16.04, P=0.02).

Postoperative adverse events, such as pruritus, nausea, vomiting, headache, hallucinations, nightmares, and urinary retention, were rare and showed no significant differences between the groups. The incidence of dry mouth was comparable, affecting 33.9% of patients in the CS group and 37.6% in the CF group. However, dizziness was significantly more prevalent in the CS group (15.2%) than in the CF group (7.1%) (P = 0.03).

Discussion

This randomized, double-blind, controlled trial demonstrated that ciprofol alone is non-inferior to ciprofol combined with fentanyl for sedation in upper gastrointestinal endoscopy. Ciprofol alone provided significant advantages in terms of hemodynamic stability and reduced respiratory depression. However, it was associated with a higher incidence of intraoperative coughing, required greater ciprofol dosages, and resulted in a higher frequency of postoperative dizziness.

Regarding patient selection, this study included ASA I–II patients aged 18–70 years, excluding high-risk and elderly individuals. Consequently, caution must be exercised when generalizing these findings to broader populations. In elderly patients, the use of ciprofol alone might potentially offer benefits, as maintaining hemodynamic stability and minimizing respiratory depression are particularly crucial for this population, and ciprofol has shown advantages in these aspects in our study population aged 18–70 years. However, we acknowledge that our study excluded patients over 70 years of age, and thus, this discussion remains speculative. Specific studies focusing on ciprofol sedation in the elderly are still emerging,[15,26–29] and tailored dosing strategies are likely necessary for this group,[7,26] given potential altered pharmacokinetics and pharmacodynamics. Furthermore, only patients undergoing upper gastrointestinal endoscopy were included, which involves shorter procedure times and less surgical stimulation. For patients undergoing more invasive procedures, the addition of fentanyl may yield different outcomes, potentially providing superior analgesia and enhancing procedural success.

The incidence of injection pain was reported at 5.9% in the ciprofol package insert, while Gan et al[6] reported a rate of 6% for NRS >4. In our study, however, only one patient experienced injection pain. This discrepancy may be attributed to differences in the definition of injection pain across studies. In our study, injection pain was defined as either a clear verbal expression of pain at the injection site or a painful facial reaction (VAS >4), consistent with findings by Zhong and Man.[9,19] Injection pain may also be influenced by factors such as injection technique and the placement of intravenous cannulas—higher injection rates and smaller veins increase the likelihood of pain. Currently, the application of ciprofol in various surgical sedations shows a significant reduction in injection pain, as indicated by numerous literature sources.[6,12,15,30–34] Sneyd et al recently suggested that, while injection pain can occur, it may not be a major clinical concern, as it can be effectively mitigated by administering lidocaine.[35]

The higher anesthesiologist satisfaction observed in the CS group suggests this regimen's preferability, likely attributed to the associated benefits of reduced respiratory depression, fewer required airway interventions, and improved hemodynamic stability. This finding is consistent with previous studies by Zhang et al[31] Lan et al[33] Gao et al[11] and Ortegal et al.[36] It is important to note, however, that these findings are based on a fixed dosing regimen. In clinical practice, some anesthesiologists may favor the addition of fentanyl, allowing for more flexible dose adjustments of ciprofol to minimize hypoxemia and coughing. Therefore, individualized induction dosing remains a critical consideration. Dose-finding studies with ciprofol have indicated variability in patient response, supporting the need for tailored approaches rather than rigid protocols to optimize sedation while minimizing adverse effects.[7,12,37–39]

Although induction was faster in the CF group, the difference did not reach clinical significance. Similarly, the CF group demonstrated a shorter recovery time, likely due to reduced ciprofol consumption; however, this difference was also not clinically meaningful. From a pharmacoeconomic perspective, the additional ciprofol used in the CS group did not translate into increased costs, as most patients required only a single 20 mL:50 mg vial of ciprofol. Moreover, reducing opioid use aligns with current anesthesia practices favoring opioid-sparing techniques. This trend is driven by efforts to mitigate opioid-related side effects, such as respiratory depression, postoperative nausea and vomiting, and potential for misuse, concerns highlighted even in the context of procedural sedation.[23,40–44]

The significantly higher incidence of coughing observed in the CS group compared to the CF group (18.1% vs 2.9%, P=0.01) is likely attributable to inadequate sedation depth or insufficient suppression of airway reflexes when using ciprofol alone at the doses administered in this study. While many studies define successful sedation by achieving a MOAA/S score of ≤1,[6,9,11,14,19,25] our findings reveal that patients in the CS group frequently presented with an MOAA/S score of 1. This indicates they did not respond to verbal commands or light shaking but still reacted to painful stimuli, such as the insertion of the endoscope, often manifesting as coughing. This observation suggests that the painful stimulus of endoscope insertion is a key trigger for coughing in patients sedated only with ciprofol at this level. Therefore, adopting a stricter definition for successful sedation, perhaps requiring an MOAA/S score of <1 (indicating no response even to painful stimuli), could potentially reduce the incidence of coughing in patients receiving ciprofol alone. However, achieving this deeper level of sedation would likely necessitate higher induction doses of ciprofol, which must be carefully balanced against the potential increased risks of respiratory depression or hemodynamic instability, warranting further investigation.

Several factors likely contributed to the observed differences between the CS and CF groups. While the addition of fentanyl in the CF group reduced the required ciprofol dosage (median dose: 0.4 mg/kg, IQR: 0.4–0.4 vs 0.4 mg/kg, IQR: 0.4–0.6 in CS group; P=0.01) and may have contributed to trends toward faster induction and recovery, it was associated with a higher incidence of respiratory depression (evidenced by increased airway interventions and hypoxemia) and hemodynamic instability (increased hypotension). However, other variables also likely played a role in these outcomes. For instance, the use of topical pharyngeal anesthesia, though standardized in our protocol, may variably influence patient responses such as coughing, which was significantly higher in the CS group (18.1% vs 2.9%, P=0.01). Additionally, the higher ciprofol doses required in the CS group could impact sedation depth and associated adverse events like coughing. Variations in the operational habits of anesthesiologists (eg, timing and technique of injection) and endoscopists (eg, procedural stimulation intensity) may further contribute to differences in outcomes, despite efforts to standardize the procedure through training and protocol adherence. Lastly, while randomization aimed to balance patient-specific factors (eg, age, ASA status), inherent variability in individual responses to sedation likely influenced the spectrum of results observed. It is also worth noting that our

findings are based on a relatively fixed dosing protocol; individualized titration in clinical practice might modulate these outcomes and warrants further exploration.

This study has several limitations. First, it was conducted at a single center, and potential biases may have arisen due to variability in patient demographics, anesthesiologist practices, and endoscopist expertise. Second, the study included only patients classified as ASA II or lower and excluded those over 70 years of age, which limits the generalizability of the findings. Future studies should consider including a broader population, such as elderly and obese patients, to validate these results. Lastly, the dosing regimen used was based on existing guidelines and previous studies. Future research should explore individualized dosing strategies in different patient populations, as outcomes may vary with personalized approaches.

Based on our findings, clinicians can consider utilizing ciprofol alone for sedation during upper gastrointestinal endoscopy in appropriately selected patients (ASA I–II, aged 18–70 years). This strategy offers improved respiratory and hemodynamic profiles, aligning with opioid-sparing initiatives. However, the increased potential for intraoperative coughing and postoperative dizziness must be anticipated and managed. Therefore, the decision to use ciprofol monotherapy should involve a careful risk-benefit assessment for the individual patient, weighing the advantages of opioid avoidance against these potential side effects.

Conclusion

In upper gastrointestinal endoscopy, the use of ciprofol alone is non-inferior to ciprofol combined with fentanyl in terms of sedation success, and offers advantages in terms of respiratory and hemodynamic stability. However, it is associated with a higher incidence of intraoperative coughing, a slight delay in induction and recovery times, and an increased incidence of postoperative dizziness.

Data Sharing Statement

The authors do not intend to share individual deidentified participant data generated or analyzed during this study. Therefore, details regarding specific data to be shared, other study documents, data accessibility, or timelines for availability are not applicable.

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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

No competing interests declared.

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