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CLINICAL TRIAL REPORT

Adverse Effects of Alfentanil versus Nalbuphine in Decompensated Cirrhotic Patients Undergoing Painless Gastroscopy: A Double-Blind, Randomized Controlled Trial

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Purpose: To compare nalbuphine versus alfentanil combined with etomidate-propofol for safety and efficacy during painless gastroscopy in decompensated cirrhosis patients.

Methods: One hundred and seventy-five advanced cirrhosis patients were randomized to receive Nalbuphine (0.1 to 0.15 mg·kg^{-1} IV bolus) or Alfentanil (5 to 6 μg·kg^{-1} IV bolus). The primary outcome was the incidence of adverse events during and within 48 hours after gastroscopy. Other outcomes included hemodynamic parameters, BIS, adverse events and time during the PACU, first-attempt induction success, etomidate-propofol dosage, induction time, duration of gastroscopy, awakening time, along with the Aldrete score. Additionally, blood samples for ALT, AST, creatinine, and urea nitrogen were drawn within the first 24 hours after gastroscopy.

Results: The complication rates were 37.21% for nalbuphine and 11.24% for alfentanil group within 48 hours, exhibited a significantly difference (P = 0.00). Compared to the nalbuphine group, the RR of the alfentanil group was lower at T_1 (post-induction stabilization, P = 0.03) and T_2 (the end of procedure, P = 0.03). The SpO_2 of the alfentanil group were lower at T_1 (P = 0.01). The recovery time in alfentanil group was shorter (P = 0.01). Additionally, compared to pre-gastroscopy levels, the nalbuphine group showed significant decreases in serum ALT (P = 0.00) and AST levels (P = 0.00) postoperatively while alfentanil group exhibited significant reductions in ALT (P = 0.00) and BUN (P = 0.01) levels, along with a significant increase in Cr (P = 0.00). However, no significant differences existed in intraoperative or PACU complications, first-attempt induction success, dosage of etomidate-propofol, Aldrete score, induction time, operation time and awakening time (P > 0.05).

Conclusion: Alfentanil demonstrates fewer postoperative complications and faster recovery than nalbuphine, potentially making it preferable for painless gastroscopy in decompensated cirrhosis.

Keywords: complication, alfentanil, nalbuphine, decompensated cirrhotic patients, painless gastroscopy

Introduction

Liver cirrhosis is a global health concern, prevalent in both developed and developing countries, and significantly contributes to the global burden of disease.[1] Annually, approximately 1 million deaths worldwide are attributed to cirrhosis.[2] A considerable number of cirrhotic patients without prominent symptoms are classified as having compensatory cirrhosis. This often leads to the neglect of preventive measures and treatment for the progression of the disease. Such negligence may result in the deterioration of the condition over months to decades, culminating in the severe consequences of decompensated cirrhosis. In China, liver diseases affect around 300 million individuals, with cirrhosis-related deaths accounting for 11% of the global total, thereby exerting a substantial impact on the nation's health landscape.[3] At the present, the predominant causes of cirrhosis in China include viral hepatitis (chronic viral hepatitis B and C), alcohol-associated liver disease, metabolic associated liver disease and autoimmune liver disease.[4] Complications such as ascites, esophageal and gastric variceal bleeding, hepatic encephalopathy, or nonobstructive

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jaundice, herald the onset of decompensated cirrhosis,[1] which are associated with high morbidity and mortality. Esophageal and gastric variceal bleeding is the second most frequent complication in patients with decompensated cirrhosis, and typically demands immediate medical attention. Gastroscopy serves as an effective diagnostic tool for esophageal and gastric varices and is the gold standard for assessing the risk of variceal bleeding by gauging the size and location of the varices. The presence of high-risk red signs during endoscopy further escalates the bleeding risk. Consequently, it is recommended that patients with decompensated cirrhosis undergo gastroscopy every six months to a year.[5]

Given the need for comfortable medical treatment and ensuring patient safety during examination and treatment, painless endoscopic therapy emerges as the preferred option for patients with decompensated cirrhosis. The commonly employed clinical protocol involves a combination of sedatives (such as propofol, etomidate, midazolam, etc). and opioid analgesics (such as fentanyl, sufentanil, remifentanil, etc). Etomidate-propofol mixtures demonstrates superior efficacy in reducing postoperative cognitive dysfunction and respiratory depression, suggesting its potential as a preferred anesthetic regimen, particularly for high-risk patients.[6] Liver disease modifies pharmacokinetic profiles, while pharmacological agents themselves may induce hepatic impairment. However, direct comparisons between alfentanil and nalbuphine in clinical trials involving patients with decompensated cirrhosis are scarce.

Nalbuphine is a κ-receptor agonist and partial μ-receptor antagonist, offers certain advantages. By acting as a partial antagonist of the μ-receptor, nalbuphine may avert a range of adverse events associated with μ-receptor activation, including respiratory depression, addiction, euphoria, bradycardia, itching, nausea and vomiting. Previous studies have demonstrated that the intravenous anesthetic dose of nalbuphine for preserving spontaneous respiration ranges from 0.1 to 0.2 $mg{\cdot}kg^{-1}$.[7,8] Nalbuphine has minimal effects on hemodynamics and respiration and exhibits a unique analgesic effect on visceral pain, making it suitable for short outpatient surgical anesthesia.[8] It is typically administered intravenously in clinical practice, providing rapid onset and a duration of action of 3–6 h, with an elimination half-life of 2–5 h.[9] Hepatic metabolism primarily involves UGT2B7, UGT1A3, CYP2C9, and CYP2C19, yielding two hydroxylated derivatives and two conjugated metabolites.[10] The metabolites are predominantly excreted in feces, while approximately 7% of unbound nalbuphine is eliminated renally.[11] It is reported that compared to sufentanil, nalbuphine demonstrates not only a favorable anesthetic effect but also mitigates the risk of respiratory depression and apnea, however, postoperative administration of nalbuphine may elevate the incidence of drowsiness, nausea, and vomiting.[7] In cirrhotic patients, nalbuphine shows significantly altered pharmacokinetics in moderate-to-severe hepatic impairment, with prolonged elimination half-life (t½:+33%) independently associated with elevated total bilirubin, expanded volume of distribution (+85%) attributed to hypoalbuminemia and hyperbilirubinemia increasing unbound drug fractions, and extended mean residence time.[12]

Alfentanil, a synthetic opioid analgesic with approximately 20% of fentanyl's potency, demonstrates particularly favorable pharmacological properties for gastroscopic procedures, including rapid onset (1–2 minutes), short duration of action (about 10 minutes), and reduced respiratory depression compared to other opioids. Pharmacokinetically, it exhibits a smaller volume of distribution (Vd) and shorter elimination half-life (t½) than fentanyl or sufentanil, with 92% binding to α1-acid glycoprotein.[13] Its metabolism occurs primarily via CYP3A enzymes,[14] and with an intermediate hepatic extraction ratio (0.3–0.6),[13] its clearance depends on hepatic blood flow, intrinsic CYP3A activity, and protein-binding status.[15] Existing evidence indicates that the effective intravenous anesthetic-dose range of alfentanil is 5 to 10 $\mu g{\cdot}kg^{-1}$.[16] These characteristics potentially confer significant clinical benefits over other opioids and render it a promising candidate for gastroscopy anesthesia.[17–19] In patients with hepatic impairment, alfentanil exhibits significantly altered pharmacokinetics: moderate liver disease prolongs its elimination half-life (219 vs 90 minutes), reduces total clearance by 50%, and decreases unbound drug clearance by 70%, while mild cirrhosis increases AUC 3-fold.[20] These findings collectively indicate that alfentanil requires dose reduction or extended dosing intervals in patients with liver disease.

Previous studies have predominantly focused on general, geriatric, or obese populations, whereas our investigation specifically targets decompensated cirrhotic patients—a distinct subgroup whose responses to anesthetic agents and safety profiles warrant particular scrutiny. Existing evidence suggests that conventional opioids (eg, sufentanil and remifentanil) may induce intraoperative respiratory depression and postoperative nausea/vomiting (PONV). In contrast, both nalbuphine and alfentanil demonstrate significantly reduced incidence of these adverse effects. Notably, nalbuphine

may potentially alleviate post-endoscopic variceal ligation (EVL) visceral discomfort—a clinically relevant yet under-studied benefit. Therefore, we initiated a prospective, double-blinded, randomized controlled trial to comprehensively evaluate and compare the efficacy and safety of alfentanil and nalbuphine when combined with etomidate and propofol for sedation during gastroscopy procedures in patients with decompensated cirrhosis. This trial endeavors to fill the existing void in the literature and furnish evidence-based guidelines to enhance the quality of care and optimize patient outcomes in this vulnerable patient population.

Methods

Ethics and Trial Registration

The trial was conducted at Shaanxi Nuclear Industry 215 Hospital. All the participants provided written informed consent and were free to withdraw from the trial at any time. The study was approved by the Institutional Review Board of Ethics Committee of NO.215 Hospital of Shaanxi Nuclear Industry (approval number: 2023–012) and was registered on clinicaltrials.gov (ChiCTR2300077062). All procedures performed on the patients were in accordance with the Helsinki declaration and its later amendments.

Study Population

Patients were aged 18 to 80 years, with body mass index (BMI) 18–28 $kg \cdot m^{-2}$, decompensated cirrhosis (Child class B and C) and scheduled for gastroscopy under general anesthesia without intubation. The exclusion criteria were as follows: (1) patients with massive hematemesis in the last three days; (2) patients with known general anesthetic allergy before surgery; (3) Mallampatis grade 3 and above; (4) renal function grade 2 and above; (5) American Society of Anesthesiologists (ASA) classification >III.

Randomization and Blinding

Patients were assigned randomly to nalbuphine or alfentanil group at a 1:1 ratio using computer generated randomized numbers. This number list was kept in a sealed envelope and only nursing staff members without any relation to the research could access it.

Double-blind test method was adopted: all the subjects were not clear what group they were in. The designer extracted two transparent water-soluble analgesics and labelled with study numbers only. The investigator did not know the medication, the “analgesic drug” was given to the subjects, and the data of the subjects during the operation was recorded.

Study Interventions

All patients fasted from solids for 8 hours and liquids for 3 hours before the painless gastroscopy operation and placed at the left lateral decubitus position. They were given oxygen inhalation (5 $L \cdot min^{-1}$) with special oxygen mask for gastroscopy while heart rate (HR), pulse oxygen saturation (SpO_2), respiratory rate (RR), non-invasive blood pressure (NIBP) and bispectral index (BIS) were measured by the monitor. An intravenous line was established in the upper limb, and adjust the drip speed of the normal salt solution to 40–60 $drops \cdot min^{-1}$. The patients in nalbuphine group received nalbuphine via intravenous bolus injection at a dose of 0.1 to 0.15 $mg \cdot kg^{-1}$ (Yangtze River Pharmaceutical Group, China), while those in the alfentanil group received alfentanil via intravenous bolus injection at a dose of 5–6 $ug \cdot kg^{-1}$ (Yichang Renfu Pharmaceutical Co., Ltd., China). Propofol (Xi’an Libang Pharmaceutical Co., Ltd., China, 1.0–1.5 $mg \cdot kg^{-1}$) and etomidate (Jiangsu Enhua Pharmaceutical Co., Ltd., 0.1–0.15 $mg \cdot kg^{-1}$) mixture was then administered intravenously at until BIS value decreased to 40–60, and when the patient lost consciousness and showed no response to stimulation, at which point painless gastroscopy was performed. During the operation, if the patients showed any signs of body movement, discomfort, or changes in vital signs and BIS value, additional etomidate-propofol mixture was administered as needed to maintain an appropriate depth of anesthesia.

All patients were transported to the post anesthesia care unit (PACU) for observation after gastroscopy, and taken back to ward by nurses after no discomfort. Follow-up calls within 48 h after surgery to inquire about adverse events and truthfully recorded. All endoscopic procedures were performed by the same endoscopist and the same anesthesiologist.

Sample Size Estimation

Based on the results of the preliminary trial, we estimated a sample size of 168 patients in this study using G*Power 3.1, which had 95% power to detect a significant difference level of 0.05. Considering a dropout rate of 10%, we enrolled 185 patients.

Statistical Analysis

All the data was analyzed by SPSS software (ver. 27.0; SPSS Inc., Chicago, IL, USA). The data that followed a normal distribution were expressed as mean ± standard deviation (SD) and analyzed using the independent Student's *t*-test. Non-normally distributed variables were summarized as medians with interquartile ranges (IQR) and evaluated via the Mann–Whitney *U*-test. For paired sample comparisons, the Wilcoxon Signed-Rank Test was applied. The statistical data were presented in the form of frequencies and percentages, and the Chi-square test or Fisher's exact test was utilized to assess the differences between groups. $P < 0.05$ was regarded as statistically significant.

Patient Characteristics

The baseline variables of two groups including age, gender, BMI, type of treatment [including diagnostic gastroscopy, endoscopic variceal ligation (EVL), endoscopic injection sclerotherapy (EIS), combined EVL and EIS therapy under gastroscopy], induction time, duration of surgery, medical history [including hypertension, diabetes, coronary heart disease, motion sickness, smoking, alcohol consumption, history of PONV and history of radiotherapy and chemotherapy].

Outcomes

Primary Outcomes

The incidence of adverse events during and within 48 hours after gastroscopy.

Adverse events during the procedure include coughing, movement, hiccups, hypotension, bradycardia, hypoxemia, and respiratory depression. Hypotension is considered to be systolic blood pressure (SBP) <90 mmHg or decreased more than 20% compared with baseline. Dopamine 1–2 mg was administered when hypotension occurs. Bradycardia is defined as HR < 55 beats/minute or a decrease of more than 20% from the baseline, and atropine 0.3–0.5 mg was administered when the HR<50 beats/minute. Hypoxia is defined by SpO_2 <90% for >10 s.[21] Respiratory depression is defined by RR < 6 breaths/minute.[22] When hypoxemia or respiratory depression occurs, we would increase oxygen flow to 8–10 $L{\cdot}min^{-1}$ firstly, and performed head tilt-chin lift and jaw thrust to open the airway at the same time, mask-assisted positive pressure ventilation would be performed in severe cases.

Postoperative adverse events included dizziness, nausea, and vomiting after returning to the ward. When patients experienced mild dizziness, we would not treat immediately but advised them to rest appropriately. If patients exhibited symptoms such as nausea or vomiting, we administered the antiemetic (ie, ondansetron) promptly.

Other Outcomes

Hemodynamic parameters including HR, RR, SpO_2, mean arterial pressure (MAP) and BIS values were systematically documented in both groups at predefined phases: baseline (T_0), post-induction stabilization (T_1), the end of procedure (T_2), return of consciousness (T_3), and pre-discharge assessment (T_4).

Adverse events such as nausea, vomiting, dizziness and lethargy occurring in the PACU were recorded.

The first-attempt induction success at the initial dose, dosage of etomidate-propofol mixture, awakening time, the time to leave the PACU, and the Aldrete score were recorded.

Blood samples for alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and urea nitrogen were drawn from all patients within the first 24 hours after gastroscopy.

Results

One hundred and eighty-five patients were assessed for eligibility, among whom 3 patients were over 80 years old, 3 patients underwent both gastroscopy and colonoscopy, 2 patients had an ASA score greater than III level, 1 patient experienced massive vomiting blood before the examination, and 1 patient refused to participate. Therefore, the study included a total of 175 patients finally, 89 patients in alfentanil group and 86 patients in nalbuphine group, respectively, with no cases lost to follow-up. In the nalbuphine group, 12 patients refused to have blood tests (recheck) for liver and kidney function after 24 hours, and in the alfentanil group, 15 patients refused. Patients who refused to draw blood were also included in the data. All patients had an ASA classification of III level. There were no statistically significant differences observed between the nalbuphine group and the alfentanil group in terms of these baseline variables (Figure 1, Table 1).

Primary Outcomes

The overall incidence of intraoperative complications was compared between two groups. The complication rates were 29.07% for nalbuphine and 29.21% for alfentanil. Chi-square tests revealed no significant difference in complication rates between the groups ($\chi^2 = 0.00$, $P = 0.98$) (Table 2). The distribution of specific complication types (including cough, concurrent cough and body movement, concurrent cough and hypotension, hiccups, body movement, hypoxemia, respiratory depression, bradycardia, and hypotension) during gastroscopy revealed no significant difference ($P > 0.05$) (Table 3).

The overall incidence of a postoperative complications within 48 hours after gastroscopy were 37.21% for nalbuphine and 11.24% for the alfentanil group, respectively. Chi-square tests indicated a significant difference between the groups ($\chi^2 = 16.18$, $P = 0.00$) (Table 2). However, among patients who developed complications, the distribution of specific complication types (including dizziness, nausea, vomiting, concurrent nausea and vomiting, and concurrent dizziness, nausea, and vomiting) within 48 hours after gastroscopy revealed no significant difference ($P > 0.05$) (Table 3).

Other Outcomes

Hemodynamic Parameters Changed in Two Groups

Heart rate did not show statistically significant changes across the time points ($P > 0.05$) (Figure 2A). At time point T_2, the RR of the alfentanil group was lower than that of the nalbuphine group ($Z = 2.18$, $P = 0.03$) (Figure 2B). At time

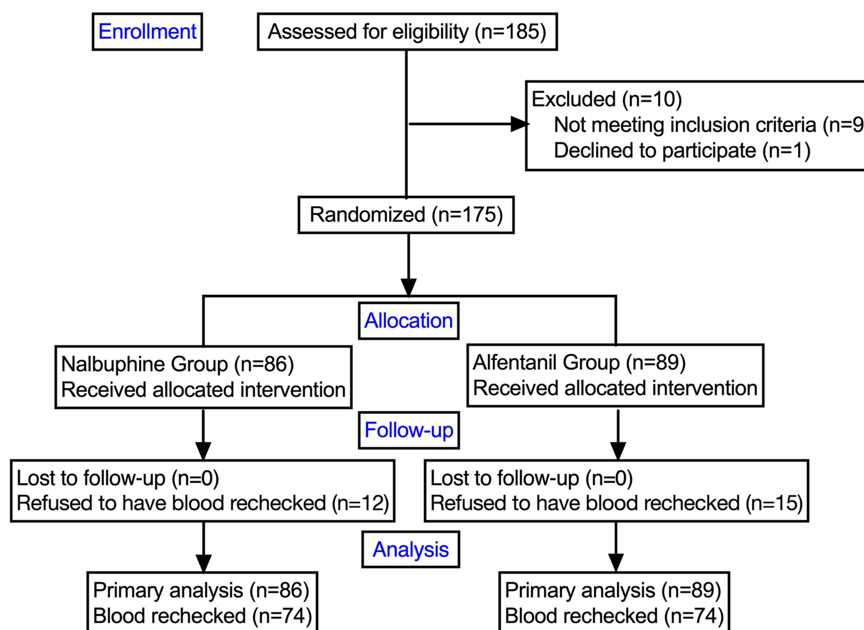

Figure 1 Flow diagram of the study.

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Table 1 Baseline Demographic and Clinical Characteristics of Two Groups

	Nalbuphine Group (n=86)	Alfentanil Group (n=89)	t / Z / χ^2	*P* Value
Age (years), $\bar{x}$ (SD)	59.58 (11.26)	56.97 (11.16)	t (1.54)	0.13
Gender (%)			χ^2(0.11)	0.74
Male	52 (60.47%)	56 (62.92%)		
Female	34 (39.53%)	33 (30.08%)		
BMI (kg/m^2), $\bar{x}$ (SD)	23.24 (2.90)	23.12 (3.01)	t (0.26)	0.79
Type of treatment (%)			χ^2(0.90)	0.72[a]
DG	46 (53.49)	53 (61.80)		
EVL	39 (45.35)	35 (39.33)		
EIS and EVL+EIS	1 (1.16)	1 (1.12)		
Medical history (%)				
Hypertension	10 (11.63)	11 (12.36)	χ^2(0.02)	0.88
Diabetes	21 (24.42)	16 (17.98)	χ^2(1.09)	0.30
Coronary heart disease	5 (5.81)	3 (3.37)	χ^2(0.60)	0.44
Motion sickness	4 (4.65)	7 (7.87)	χ^2(0.77)	0.38
Smoking	22 (25.58)	31 (34.83)	χ^2(1.77)	0.18
Alcohol consumption	15 (17.44)	13 (14.61)	χ^2(0.26)	0.61
History of PONV[b]	2 (7.14)	4 (12.90)	–	0.67[c]
History of radiotherapy and chemotherapy	1 (1.16)	2 (2.25)	–	1.00[c]

Notes: The data that followed a normal distribution were expressed as mean ± standard deviation (SD) and analyzed using the independent Student's *t*-test. The statistical data were presented in the form of frequencies and percentages, and the Chi-square test or Fisher's exact test was utilized to assess the differences between groups. P< 0.05 is considered statistically significant. a: Due to computational limitations in SPSS, Fisher's exact test was replaced with a Monte Carlo simulation (10,000 replicates) for sparse data analysis. b: Nalbuphine group: 31 patients with general anesthesia history (4 PONV); Alfentanil group: 28 patients (2 PONV). c: Statistical significance was assessed using Fisher's exact test.

Abbreviations: DG, Diagnostic gastroscopy; EVL, endoscopic variceal ligation; EIS, endoscopic injection sclerotherapy; PONV, postoperative nausea and vomiting.

Table 2 The Incidence of Adverse Events During the Peri-Examination Period

Adverse Events (%)	Nalbuphine Group (n=86)	Alfentanil Group (n=89)	χ^2	*P* Value
Intraoperative	25 (29.07)	26 (29.21)	0.00	0.98
Postoperative	32 (37.21)	10 (11.24)	16.18	0.00
PACU-related	28 (32.56)	22 (24.72)	1.32	0.25

Notes: The statistical data were presented in the form of frequencies and percentages, and the Chi-square test or Fisher's exact test was utilized to assess the differences between groups. P< 0.05 is considered statistically significant.

point T_1, the RR (Z = 2.22, *P* = 0.03) (Figure 2B) and SpO_2 (Z = 2.48, *P* = 0.01) (Figure 2C) of the alfentanil group were lower than those of the nalbuphine group. No statistically significant differences in mean arterial pressure were observed across the time points (*P* > 0.05) (Figure 2D). At time points T_0 and T_4, the BIS values of the alfentanil group were higher than those of the nalbuphine group (Z = 3.08, *P* = 0.00) (Figure 2E).

The Incidence of AdversEvents in PACU

The results of complications in PACU indicated that the incidence of complications in PACU was comparable between the nalbuphine and alfentanil groups, with no significant difference observed (χ^2 = 1.32, *P* = 0.25) (Table 2). There were no statistically significant differences between two groups in the occurrence of various complications (including dizziness, nausea, and concurrent nausea and vomiting) in PACU (*P* > 0.05) (Table 3).

There were no statistically significant differences in induction time, operation time and awakening time between two groups (*P* > 0.05) (Figure 3A–C). However, the time to leave the PACU was significantly shorter in the alfentanil group compared to the nalbuphine group (Z = 2.75, *P* = 0.01) (Figure 3D). No significant difference in first-attempt induction

Table 3 Distribution of Specific Complication Types Among Patients Who Developed Complications During the Peri-Examination Period

	Adverse Events (%)	Nalbuphine Group	Alfentanil Group	χ^2	P
		n=25	n=26		
Intraoperative	Cough	13 (52.00)	7 (25.92)	3.36	0.07
	Cough and body movement	1 (4.00)	1 (3.85)	–	1.00[c]
	Cough and hypotension	1 (4.00)	0 (0)	–	0.49
	Hiccups	2 (8.00)	4 (15.38)	–	0.67 [c]
	Body movement	1 (4.00)	0 (0)	–	0.49 [c]
	Hypoxemia	0 (0)	2 (7.69)	–	0.49 [c]
	Respiratory depression	1 (4.00)	4 (15.38)	–	0.35 [c]
	Bradycardia	0 (0)	2 (7.69)	–	0.49 [c]
	Hypotension	6 (24.00)	6 (23.08)	0.01	0.94
		n=32	n=10		
Postoperative	Dizziness	1 (3.13)	1 (10.00)	–	0.42 [c]
	Nausea	4 (12.50)	4 (40.00)	3.74	0.05
	Vomiting	2 (6.25)	0 (0)	–	1.00 [c]
	Nausea and vomiting	23 (71.88)	5 (50.00)	1.64	0.20
	Dizziness, nausea and vomiting	2 (6.25)	0 (0)	–	1.00 [c]
		n=28	n=22		
PACU-related	Dizziness	26 (92.86)	21 (95.45)	-	1.00 [c]
	Nausea	1 (3.57)	1 (4.55)	-	1.00 [c]
	Nausea and vomiting	1 (3.57)	0 (0)	-	1.00 [c]

Notes: The statistical data were presented in the form of frequencies and percentages, and the Chi-square test or Fisher's exact test was utilized to assess the differences between groups. P< 0.05 is considered statistically significant. c: Statistical significance was assessed using Fisher's exact test.

success at the initial dose ($P = 0.27$), dosage of etomidate-propofol mixture [including induction sedation dose ($P > 0.05$) and total sedation dose ($P > 0.05$)], and the Aldrete score (T_2: Z = 1.54, $P = 0.12$; T_4: Z = 0.04, $P = 0.97$) between the two groups (Table 4).

Compared to pre-gastroscopy levels, the nalbuphine group showed significant decreases in serum ALT (Z = 4.22, P = 0.00) and AST levels (Z = 3.04, P = 0.00) postoperatively, while no significant changes were observed in Cr (Z = 1.77, P = 0.08) and BUN (Z = 1.80, P = 0.07) levels. However, alfentanil group exhibited significant reductions in ALT (Z = 3.06, P = 0.00) and BUN (Z = 2.68, P = 0.01) levels, along with a significant increase in Cr (Z = 0.76, P = 0.00) (Table 5).

Discussion

Patients with decompensated cirrhosis undergoing painless gastroscopy or therapeutic interventions require careful selection of analgesic and sedative agents, as impaired hepatic function may significantly alter drug metabolism and increase the risk of hepatotoxicity associated with certain medications.

The primary objective of this study was to compare the incidence of complications during and after painless gastroscopy in patients with cirrhosis receiving either nalbuphine combined with an etomidate-propofol mixture or alfentanil combined with an etomidate-propofol mixture. The research revealed that among patients with decompensated cirrhosis undergoing painless gastroscopy, the incidence of adverse events post-procedure was higher in the nalbuphine group than in the alfentanil group. Although nalbuphine group exhibited a higher overall complication rate, the spectrum of complications among affected patients was comparable to alfentanil group, suggesting the observed variance stems from differential adverse effect liability profiles of the medications, not from fundamental differences in clinical complication phenotypes. Nausea and vomiting were the most common reactions after the endoscopic procedure, necessitating the administration of antiemetic drugs for relief. However, during the painless gastroscopy procedure and PACU, there was no significant difference in the incidence of adverse events between the two groups. Cough and

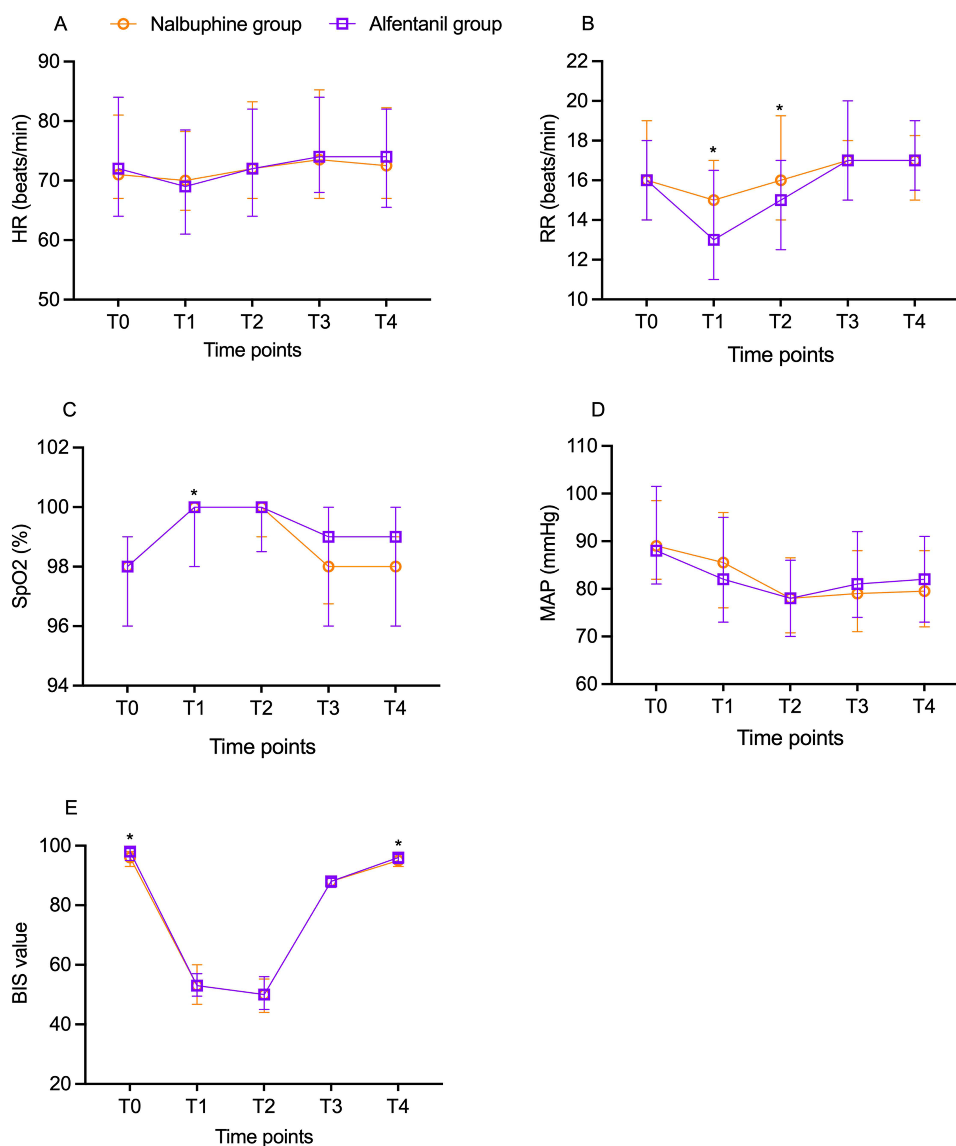

Figure 2 Hemodynamic parameters, including HR (**A**), RR (**B**), SpO_2 (**C**), MAP (**D**) and BIS value (**E**), at different time points in two groups. Data are presented as medians with interquartile ranges (IQR) and evaluated via the Mann–Whitney *U*-test. * means compared with nalbuphine group. $P < 0.05$ was regarded as statistically significant.
Abbreviations: T_0, baseline; T_1, post-induction stabilization; T_2, the end of procedure; T_3, return of consciousness; T_4, pre-discharge assessment. HR, heart rate; RR, respiratory rate; SpO_2, saturation of peripheral oxygen; MAP, mean arterial pressure; BIS, bispectral index.

hypotension were more common among patients during the procedure, and dizziness was more common in PACU. During PACU care, dizziness predominated as the primary complication (attributable to residual sedative effects), while positional stability and fasting status suppressed nausea and vomiting. Following ward transfer, resumption of oral intake and physiological changes (eg, orthostatic hypotension) triggered gastrointestinal responses, unmasking latent side effects. Nalbuphine's prolonged elimination half-life and potent κ-opioid receptor agonism resulted in significantly higher 48-hour adverse event incidence compared to alfentanil. Overall, these side effects were manageable and did not significantly impact the recovery process. Respiratory depression and hypoxemia during painless gastroscopy remain a challenge for anesthesiologists.[23] Studies indicated that the incidence of hypoxemia in painless gastrointestinal endoscopy ranges from approximately 15% to 30.8%.[24,25] Compared with the nalbuphine group, patients in the alfentanil group exhibited significant reductions in oxygen saturation and respiratory rate following anesthesia induction, indicating that alfentanil exerts more pronounced respiratory depression than nalbuphine. Notably, six patients in the alfentanil group required mask-assisted manual ventilation during painless gastroscopy due to oxygen desaturation events.

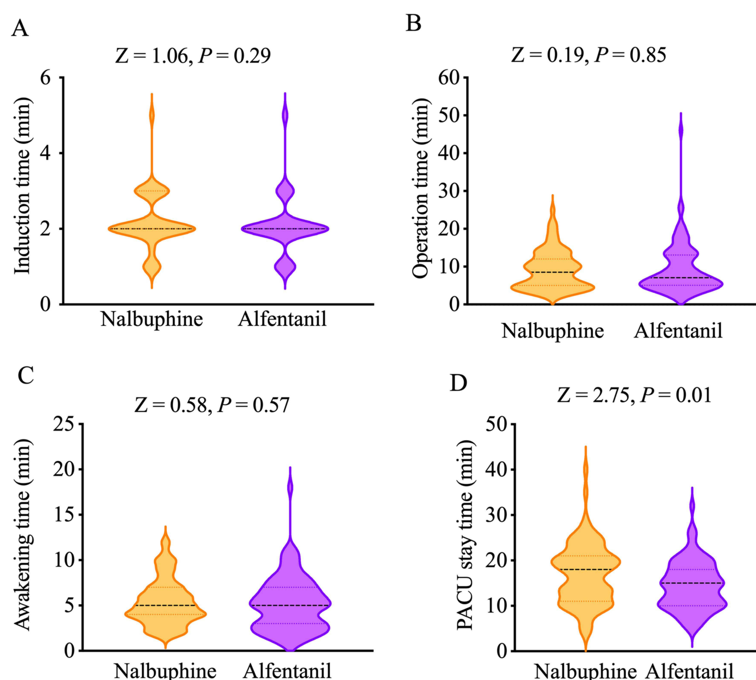

Figure 3 Comparison of sedation profile and post-procedural recovery between the two groups. Induction time (**A**), operation time (**B**), awakening time (**C**) had no difference between the two groups. The PACU stay time (**D**) was significantly shorter in patients of alfentanil group.

Although there is a statistically significant difference in BIS, this difference may not necessarily translate to a clinically meaningful difference in patient outcomes or anesthetic management. No significant differences were observed between the two groups in sedative consumption, Aldrete scores, or PACU complications, suggesting that both anesthetics were well tolerated during the painless gastroscopy operation. Patients in the alfentanil group demonstrated a more favorable recovery time compared to nalbuphine group. This disparity may be linked to differential hepatic metabolism profiles: hepatic impairment may result in prolonged nalbuphine metabolism. Evidence from pharmacokinetic studies indicates that patients with hepatic impairment undergoing abdominal surgery exhibit a prolongation of nalbuphine's elimination half-life, which may be attributed to reduced albumin synthesis capacity associated with compromised liver function.[12] The faster discharge time observed in the alfentanil group suggests that this analgesic may offer a more efficient recovery profile post-procedure.

Table 4 Comparison of Anesthetic Outcomes and Recovery Metrics Between Two Groups

	Nalbuphine Group (n=86)	Alfentanil Group (n=89)	χ^2/*Z* Value	*P* Value
First-attempt induction failed (%)	5 (5.81)	2 (2.25)	-	0.27[c]
Induction sedation (mg), Median (IQR)				
Etomidate	5.00 (5.00–6.00)	5.00 (4.00–6.00)	*Z* (1.66)	0.10
Propofol	50.00 (48.75–60.00)	50.00 (40.00–60.00)	*Z* (1.27)	0.21
Total sedation (mg), Median (IQR)				
Etomidate	9.00 (7.00–11.00)	8.00 (6.00–11.00)	*Z* (1.37)	0.17
Propofol	90.00 (70.00–110.00)	80.00 (60.00–105.00)	*Z* (1.22)	0.22
Aldrete score				
T_2	6.00 (6.00–8.00)	7.00 (6.00–10.00)	*Z* (1.54)	0.12
T_4	10.00 (10.00–10.00)	10.00 (10.00–10.00)	*Z* (0.04)	0.97

Notes: The statistical data were presented in the form of frequencies and percentages, and the Chi-square test or Fisher's exact test was utilized to assess the differences between groups. Non-normally distributed variables were summarized as medians with interquartile ranges (IQR) and evaluated via the Mann–Whitney *U*-test. $P < 0.05$ is considered statistically significant. c: Statistical significance was assessed using Fisher's exact test. T_2: the end of procedure; T_4: pre-discharge assessment.

Table 5 Comparison of Serum ALT, AST, Creatinine, and BUN Levels Between the Two Groups

	Nalbuphine Group (n=74)	Z Value	P Value	Alfentanil Group (n=74)	Z/t Value	P Value
ALT baseline (U/L)	24.00 (16.00–33.00)	4.22	0.00	24.50 (17.00–37.25)	Z (3.06)	0.00
ALT post-treatment	20.50 (15.00–27.25)			22.00 (15.00–33.25)		
AST baseline (U/L)	29.50 (22.00–42.25)	3.04	0.00	28.50 (23.00–42.50)	Z (0.87)	0.38
AST post-treatment	26.00 (17.00)			29.00 (23.00–44.00)		
Cr baseline (μmol/L)	59.00 (50.00–68.25)	1.77	0.08	58.93 (13.12)	t (0.76) [a]	0.00
Cr post-treatment	61.00 (50.75–73.00)			62.55 (15.66)		
BUN baseline (mmol/L)	5.00 (4.10–7.03)	1.80	0.07	5.10 (4.07–6.23)	Z (2.68)	0.01
BUN post-treatment	4.75 (4.07–6.23)			4.50 (3.80–5.60)		

Notes: Wilcoxon signed-rank test was conducted to assess differences within four paired groups in each group. Non-normally distributed variables were summarized as medians with interquartile ranges (IQR) and evaluated via the Mann–Whitney *U*-test. a: The data that followed a normal distribution were expressed as mean ± standard deviation (SD) and analyzed using the independent Student's *t*-test. $P < 0.05$ was regarded as statistically significant.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; BUN, urea nitrogen.

Currently, there is limited research on the rational use of medications for painless gastroscopy in patients with liver cirrhosis. In normal patients, Li[8] noted that within the studied dosage range (0.5–2.0 mg·kg^{-1}) of nalbuphine, no significant increase in postoperative adverse events was observed when combined with propofol. In the Tang's study,[26] the incidence of PONV of 0.10 mg·kg^{-1} nalbuphine group was lower (3.23%), as well as propofol dosage, incidence of hypotension, and shorter recovery time compared to the 0.15 mg·kg^{-1} nalbuphine group. A prospective study on painless hysteroscopy demonstrated that[27] the alfentanil group exhibited a PONV incidence of 4.8% when co-administered with propofol. In our study, the incidence rates of PONV in the nalbuphine and alfentanil groups were 37.21% and 11.24%, respectively, which is higher than previous findings. This discrepancy may be attributed to two factors. First, prior studies primarily involved patients without cirrhosis, whereas our study population consisted of individuals with liver disease, whose altered drug metabolism may significantly influence the incidence of complications. Second, the use of an etomidate-propofol mixture in our protocol may have contributed to nausea and vomiting in some patients. Based on the receptor pharmacology and clinical evidence presented,[28,29] we propose the following hypothesis to explain the difference in PONV incidence rates between the two groups: (1) Direct stimulation of κ-receptors in the chemoreceptor trigger zone (CTZ), and (2) Induction of dysphoria (a κ-receptor-associated adverse effect), which synergistically exacerbates nausea perception; (3) Nalbuphine's longer elimination half-life prolongs exposure to KOR-mediated emetic stimuli. In contrast, alfentanil's rapid redistribution limits sustained CTZ activation and lacks significant κ-activity, thereby reducing its emetogenic potential. Absence of this κ-mediated dysphoric component likely contributes to its lower overall incidence of nausea compared to nalbuphine, despite shared central emetic pathways with other opioids. Propofol and etomidate are short-acting intravenous anesthetics known for their rapid onset and quick recovery. Tang et al[30] reported that compared to propofol alone, a 1:10 dose ratio mixture of etomidate and propofol is associated with a 7.4% incidence of PONV during painless gastroscopy.

Given the significant difference in the overall incidence of postoperative complications between the two groups, we further investigated the occurrence of various complications. Comparative analysis revealed no significant differences in these specific complications, indicating that the severity of adverse events was generally consistent between the two groups, PONV is the most frequently reported adverse events. Although there were no statistically significant differences in intraoperative complications or PACU complications between the two groups, we conducted a detailed analysis of each complication type. The results indicated no notable differences in the incidence or severity of complications between the groups, suggesting that the overall burden of adverse events was similar.

Alfentanil, chemically related to fentanyl, is characterized by rapid onset of action and holds regulatory approval for adjunctive administration in general anesthesia, and metabolized in the liver largely by the P450 enzyme system. Opioids are rarely associated with drug-induced liver injury (DILI), with hepatotoxicity primarily occurring under specific circumstances such as overdose or pharmacokinetic interactions, particularly in the context of concomitant acetaminophen administration. The majority of patients underwent gastroscopy on the second day to hospital and under fasting conditions, potentially inducing hemoconcentration. Both groups exhibited decreases in specific biochemical parameters

(ALT, AST and blood urea nitrogen), which may be attributable to standardized fluid resuscitation protocols after gastroscopy. Notably, the alfentanil group demonstrated a statistically significant elevation in serum creatinine (0.67 $mg \cdot dL^{-1}$ [55.93 $\mu mol \cdot L^{-1}$] to 0.71 $mg \cdot dL^{-1}$ [62.55 $\mu mol \cdot L^{-1}$]; Δ=0.04 mg/dL), though this increment remained below the threshold for clinical significance as defined by a serum creatinine increase $\geq$0.3 $mg \cdot dL^{-1}$.[31] In our study, neither nalbuphine nor alfentanil had a statistically significant impact on hepatic and renal functions. Nevertheless, further research is needed to explore their effects in other surgical anesthesia contexts.

Limitations

There are several limitations to our trial. Firstly, as it was a single-center study, the results might not be applicable to other settings, more multi-center, prospective studies may be necessary. Secondly, we only selected patients with liver function classified as Child-Pugh B and C, without conducting statistics and stratification for patients with Child-Pugh B and C liver function. Thirdly, we did not complete blood concentration measurements for each group. Future study is needed to find strategies for mitigating postoperative nausea and vomiting, as well as other discomforts in patients.

Conclusion

This study suggests that both nalbuphine and alfentanil, in combination with etomidate-propofol, are safe and effective options for sedation during painless gastroscopy in decompensated cirrhotic patients. However, it is important to note that both analgesics were safe and well-tolerated, as evidenced by the stable vital signs recorded throughout the procedure. It should be acknowledged that alfentanil was associated with a higher incidence of respiratory depression compared to nalbuphine, though all events were transient and resolved without intervention. In conclusion, while both alfentanil and nalbuphine are viable choices for analgesia during painless gastroscopy, the fewer adverse events associated with alfentanil may make it a more preferable option in clinical practice. Further studies are warranted to confirm these findings and to explore any potential long-term benefits of using alfentanil in this setting.

Data Sharing Statement

The data are available from the corresponding author Liuqin Jiang (jlq215hp@163.com) on reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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