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Effect of intravenous lidocaine on Ciprofol dose in patients undergoing painless gastrointestinal endoscopy: a double-blinded, randomized, controlled trial

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Abstract

Background Ciprofol (CIP) for procedural sedation and analgesia (PSA) for painless gastrointestinal endoscopy (GE) can cause respiratory or cardiovascular complications. The literature suggests that intravenous (IV) lidocaine infusion can alleviate visceral pain and enhance humans' ventilator response to CO_2. Therefore, it was hypothesized that IV lidocaine could reduce the CIP dose for painless GE and improve recovery time.

Methods This randomized placebo-controlled trial included 40 patients undergoing GE. After CIP titration for unconsciousness, patients in group L were given IV lidocaine (1.5 mg/kg bolus dose, then a 2 mg/kg/h continuous infusion); the same volume saline as placebo was given for N group patients. The primary endpoint was the required CIP dose. Secondary endpoints were: endoscopic examination time, awakening time, post-anesthesia care unit (PACU) discharge time, pain and fatigue after awakening, adverse events, and endoscopist's and patient's satisfaction.

Results Both cohorts had comparable demographic characteristics. Group L's CIP consumption was decreased by 23.0% than the N group (47.38 ± 7.45 mg vs. 61.50 ± 9.44 mg, respectively, $p < 0.001$). Awakening time (P=0.002), PACU discharge time ($P < 0.001$), pain ($P = 0.008$), and fatigue ($P = 0.004$) after awakening were also reduced in group L. Furthermore, group L had higher satisfaction scores than group N ($P = 0.017$). No marked difference was identified in the incidence of unfavorable effects ($P > 0.05$ for all).

Conclusions Lidocaine IV infusion caused a 23.0% reduction in CIP requirements during GE. Furthermore, post-endoscopic pain and fatigue were also improved, thus suggesting that lidocaine is an efficient therapeutic option.

Trial registration This trial has been submitted to the Chinese Clinical Trial Registry (registration number: ChiCTR2300069868, registration date: 28/03/2023).

Keywords Intravenous lidocaine, Ciprofol, Painless gastrointestinal endoscopy

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Introduction

Gastrointestinal endoscopy is an important technique for diagnosing gastrointestinal diseases; however, as an invasive exam, it induces choking, nausea, vomiting, and agitation due to the irritation, and in severe cases, complications such as cardiac arrhythmia can occur. Furthermore, some patients fail the examination due to improper cooperation or self-extraction during the examination [1].

Recently, for painlessness and comfort, anesthesiologists have been substantially involved in elucidating better procedural sedation and analgesia (PSA) for gastrointestinal endoscopy (GE) [2].

Propofol has a short half-life and rapid onset and is increasingly applied for GE sedation [3, 4]. However, has disadvantages, as it produces hypotension, bradycardia [5–7], and pain on injection [8].

Ciprofol (CIP) or HSK3486 is a 2,6-disubstituted phenol analog and novel intravenous (IV) anesthetic. It has structural homology with propofol. CIP interacts with the gamma-aminobutyric acid-A receptor and has been authorized for use by the National Medical Products Administration (China) since 11 December 2020. Compared with propofol, ciprofol can achieve almost the same anesthetic effect in the clinic, but its dosage is only 1/5 to 1/4 of propofol [9]. It has been indicated that CIP has similar effects to propofol during gastroscopy or colonoscopy procedures, with no marked adverse. However, cardiovascular adverse (including transient hypotension) and respiratory adverse (including respiratory depression, apnea, and hypoxemia) events were observed in patients after the CIP administration [10].

A closed malpractice review (2006) indicated that, according to the American Society of Anesthesiologists (ASA) closed-claim database, respiratory depression was a complication observed after over-sedation and was essentially involved in patients' injuries during PSA [11].

Multiple techniques have been carried out to alleviate the occurrence and frequency of adverse effects during PSA. During the colonoscopy, colonic distension and traction cause visceral pain and abdominal discomfort. IV lidocaine has been shown to reduce visceral pain in animal models [12, 13] and substantially relieve pain after colonic surgery [14]. Furthermore, lidocaine infusion increases humans' ventilator response to CO2 [15].

An investigation revealed that IV lidocaine infusion caused a 50% alleviation of the required propofol dose for colonoscopy and improved immediate post-colonoscopy fatigue and pain [2]. However, the impact of IV lidocaine infusion for painless GE with CIP remains to be elucidated. Therefore, this investigation hypothesized that IV lidocaine reduces CIP requirements during GE and improves post-endoscopic pain and fatigue. This was assessed by conducting a trial to provide a basis for optimizing the CIP application.

Methods

Ethics

This single-center, prospective, randomized, controlled investigation was performed at Jinling Hospital, a large Chinese tertiary-level teaching hospital. The ethical board of the hospital authorized this trial (2023DZKY-010-01), which was then submitted to the Chinese Clinical Trial Registry (registration number: ChiCTR2300069868, registration date: 28/03/2023). The research followed the CONSORT recommendations [16]. Before inclusion, all the participants and their legal guardians were informed about the trial, and their consent was acquired.

Study design and population

This trial included 46 patients with ASA physical status I or II. The patient's age ranged between 18 and 65 years, and the BMI was $18 \leq BMI < 30$ kg/m2. These individuals were prearranged for painless GE during April 2023 and May 2023. The patients:1) those who refused to sign informed consent; 2) those with contraindications to painless GE; 3) those with a history of drugs allergies related to the study; 4) those with communication disorder; 5) those with a central nervous system or neuropsychiatric disorders; 6) those who received general anesthesia or superficial IV anesthesia within the last three months; 7) those who participated in other clinical trials as a subject within the last three months; 8) those who had taken sedative-hypnotics, anxiolytics, or antidepressants within the last three months; 9) those who were deemed unsuitable for this clinical study by the investigators were excluded.

Randomization and blinding

The participants were randomly categorized into group L (lidocaine) and group N (0.9% saline) in equal ratios via a computer-produced sequence before GE. A nurse carried this randomization sequence in an opaque envelope. After admitting the patient, another anesthesiologist not associated with any part of the investigation was asked to open the envelope and prepare the drugs based on group allocation. The lidocaine and saline syringes were identical; the solutions were colorless and non-identifiable by appearance, color, or smell. The endoscopists, patients, and anaesthesiologists were blinded to the group allocation. To avoid blinding interference, the trial infusions were administered after the unconsciousness in both cohorts, as the initial lidocaine bolus may cause a specific reaction, indicating to the researchers that lidocaine was administered.

Study design

Prior to the procedure, all the participants fasted as advised without preoperative medication. The participants were brought into the preparation room 15 min before the examination. On the right upper limb, a peripheral venous channel was prepared. Upon the participant's entrance into the operating room, heart rate (HR), electrocardiography, blood pressure (BP), and pulse oxygen saturation (SpO_2) were assessed. Then the patient was positioned on the left lateral side for anesthesia administration. All patients received IV CIP (0.4 mg/kg) for 30 s. Then, each participant received either an IV lidocaine bolus (1.5 mg/kg) followed by a continuous 2 mg/kg/h infusion or the same volumes of saline. This 30 min lidocaine dose does not cause toxic plasma levels [17]. The sedation levels were measured every minute with the MOAA/S scale (Modified Observer's Assessment of Alertness/Sedation Scale: Level 5: readily response in a normal tone to name called; Level 4: lethargic response in a normal tone to name called; Level 3: only responds after the name is called loudly or repeatedly; Level 2: only responds after mild shaking or prodding; Level 1: only responds after painful trapezius squeeze; Level 0: no response after painful trapezius squeeze). The endoscopist inserted the gastroscopy after the participant's MOAA/S score was ≤1. A supplemental CIP bolus (0.1 mg/kg) was induced for adequate sedation level after administration every time the MOAA/S score > level 1. Furthermore, the anesthesiologist adds more drugs depending on the duration and the patient's response (e.g., body movements, eye-opening, speech, and other signs of lightening anesthesia). All patients breathed voluntarily during the procedure and were induced with O_2 (4 L/min) via a nasal catheter to maintain oxygen saturation > 90%. The anesthesiologist lifted the participant's jaw when the SpO_2 < 90%; if it was still < 90% or continued to decrease, assisted ventilation was provided.

Study endpoints

The primary outcome was the total CIP consumption. The secondary outcomes were: mean artery pressure (MAP), HR, and SpO_2 at the following time points: (T0) prior to administration, (T1) post-anesthesia administration but pre-procedure, (T2) post-endoscopic insertion, (T3) post-endoscopic removal, and (T4) at awaking.

Definition

Endoscopic examination time: the time from the endoscope insertion to complete retraction. Awakening time: the time from the procedure end to patients answering their name accurately. PACU discharge time: the time between the end of the examination and the patient's Aldrete score > 9. Pain and fatigue scores: visual analog scale (VAS) with 0 to 10 scores [2]; the greater the score, the higher the pain intensity. Recorded after awaking and 15 and 30 min later). The prevalence of adverse events: hypoxia, choking and coughing, belching, body movement, nausea, and vomiting). Endoscopist's and patient's satisfaction: elucidated using VAS from 0 to 10; the greater the score, the higher the satisfaction.

Sample size and statistical analysis

Local pilot research indicated CIP dose during GE as: 107.65 ± 30.67 mg/ 30 min. Therefore, it was estimated as 16 patients/group sample size would allow 80% power to elucidate a 30% difference in CIP dose in the cohorts at an 0.05 alpha level using PASS 15.0 (NCSS, USA). After including a 20% dropout rate, 40 participants were finally selected.

Data was collected in Microsoft Excel (v 2202, USA), and the normality was elucidated via the Shapiro-Wilk test. The normally distributed values were depicted as means ± standard deviation (x ± s) and compared by the independent sample T-tests. The non-normally distributed values were presented as the median [interquartile range] and compared using Mann-Whitney U tests. Chi-square or Fisher's exact tests were applied for comparing categorical data that were then reported as numbers (%).

The two groups' total CIP consumption, MAP, HR, SpO2, endoscopic examination time, recovery time, and PACU discharge time were compared via independent sample T-tests. A mixed model analysis of variance (ANOVA) compared post-surgical pain score and fatigue. The Mann-Whitney U test compared the endoscopist's and patient's satisfaction [median]. Bivariate Spearman correlation compared the correlation between the overall adverse event rate and patient age, the total amount of cyclopentol, BMI, and endoscopic examination time. All statistical measurements were performed on SPSS 25.0 (IBM, USA). The statistical P-value < 0.05 was deemed significant.

Results

Patient data

A total of 58 patients were reviewed for trial participation. 12 were excluded after assessing the inclusion criteria. Of the 46 selected patients, 6 were further removed, including 3 L group patients, 2 due to operation time over 30 min and 1 due to loss of CIP data and 3 N group patients, 1 due to operation time over 30 min, and 2 due to loss of CIP data. Finally, 40 patients were selected for this investigation (Fig. 1). The participant's demographic characteristics were comparable in groups L and N (n = 20, respectively) (Table 1).

CIP consumption and adverse events

CIP dose decreased by 23.0% in group L than in group N (47.38 ± 7.45 mg vs. 61.50 ± 9.44 mg, respectively,

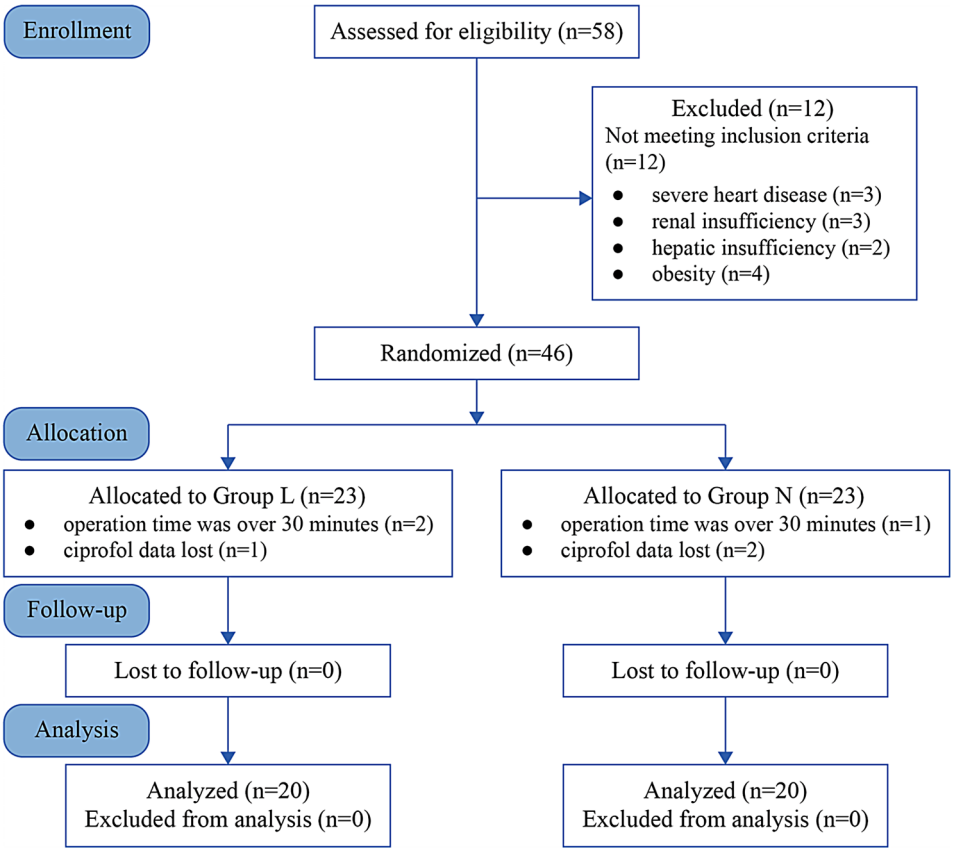

Fig. 1 The flow diagram of the Study population

Table 1 The demographic characteristics

	Group L (*n* = 20)	Group N (*n* = 20)	*P*
Age (y)	44.20 ± 10.56	43.60 ± 10.93	0.861
Height (cm)	167 ± 7	167 ± 7	0.726
Weight (kg)	65.25 ± 8.41	63.73 ± 8.01	0.561
BMI (kg/m^2)	23.23 ± 1.81	23.00 ± 2.61	0.749
Male sex (%)	12 (60)	11 (55)	0.749
ASA			0.749
I	8	9	
II	12	11	
Hypertension	4	5	1.000
Diabetes	0	0	
History of smoking	1	2	1.000
History of drinking	6	8	0.507
Academic qualifications			0.722

Notes: Data are presented as x ± s or numbers (%)

Abbreviations: ASA: American Society of Anesthesiologists, BMI: body mass index

$p < 0.001$). No marked difference was identified in the CIP induction dose in the two cohorts; however, the supplemental dose was notably smaller in the L group than in the N group (21.28 ± 8.18 mg vs. 36.01 ± 9.36 mg, respectively, $p < 0.001$). The data indicated no notable difference between the prevalence of hypoxia, choking and coughing, belching, and body movement ($P > 0.05$ for all) (Table 2).

Heart rate, mean artery pressure, and pulse oxygen saturation

The intergroup comparison at the same time points revealed that the difference in MAP at the T4 was markedly significant. Furthermore, the difference in HR at T2, T3, and T4 time points was also notably significant; however, none of the differences in SpO2 were substantially significant (Fig. 2).

Post-procedure pain and fatigue evaluation

Pain scores after GE were marked alleviated in Group L [ANOVA: drug effect (df = 1, F = 7.247): $P = 0.008$, time effect (df = 2, F = 18.492): $P < 0.001$, and interaction (df = 2, F = 3.023): $P = 0.053$] (Fig. 3). Group L revealed markedly reduced postoperative fatigue [ANOVA: drug effect (df = 1, F = 8.646): $P = 0.004$, time effect (df = 2, F = 10.99): $P < 0.001$, and interaction (df = 2, F = 1.651): $P = 0.196$] (Fig. 3).

Table 2 Intergroup Comparisons of Intraoperative Outcomes

	Group L (*n* = 20)	Group N (*n* = 20)	*P*
Operation duration (min)	16.49 ± 4.46	18.45 ± 5.51	0.224
Lidocaine induction dose (mg)	97.88 ± 12.61	/	/
Lidocaine maintenance dose (mg)	35.46 ± 8.97	/	/
Total lidocaine consumption (mg)	133.33 ± 17.28	/	/
CIP induction dose (mg)	26.10 ± 3.36	25.49 ± 3.20	0.561
Supplemental CIP (mg)	21.28 ± 8.18	36.01 ± 9.36	< 0.001
Total CIP consumption (mg)	47.38 ± 7.45	61.50 ± 9.44	< 0.001
Polypectomy	2	6	0.236
Biopsy	2	1	1.000
Pressing the abdomen	9	11	0.527
Choking and coughing	1	3	0.598
Belching	0	1	1.000
Body movement	2	2	1.000
Hypoxia	1	3	0.598

Notes: Data are presented as x ± s or numbers (%)

Table 3 Intergroup comparisons of postoperative outcomes during PACU

	Group L (*n* = 20)	Group N (*n* = 20)	*P*
Time to awakening (min)	4.88 ± 3.60	10.09 ± 6.05	0.002
time to PACU discharge (min)	16.07 ± 6.17	26.07 ± 7.44	< 0.001
Nausea/Vomiting	1	0	1.000
Patients' satisfaction	9.00 (9.00–10.00)	8.00 (7.00–9.00)	0.758
Endoscopists' satisfaction	10.00 (9.00–10.00)	10.00 (8.25-10.00)	0.017

Notes: Data are depicted as x ± s or numbers (%)

Abbreviations: PACU: post-anesthesia care unit

Time to awakening, time to PACU discharge, and comparison of patient and endoscopist satisfaction

Group L participants had a shorter awakening ($P = 0.002$) and out-of-the-room time ($P < 0.001$) than group N; both differences were statistically essential (Table 3). The L group participant's satisfaction score was increased than the N group ($P = 0.017$), while those of the endoscopists

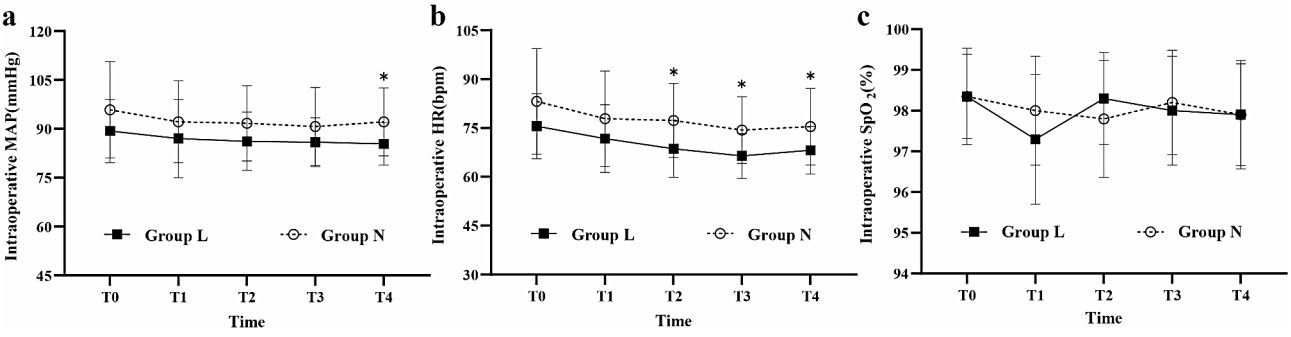

Fig. 2 MAP, HR, and SpO_2 in both groups. Notes: T0 = prior to administration; T1 = post-anesthesia administration but pre-procedure; T2 = post-endoscopic insertion; T3 = post-endoscopic removal; T4 = at awaking. * $P < 0.05$ Group N vs. Group L. Abbreviations: MAP: mean artery pressure, HR: heart rate, SpO_2: pulse oxygen saturation

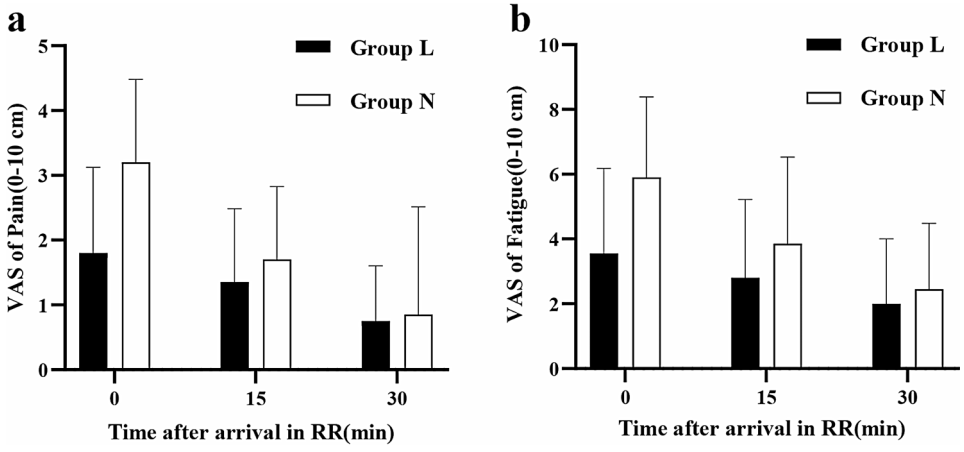

Fig. 3 Pain and fatigue score after gastrointestinal endoscopy. Notes: Data are presented as x ± s. Pain and fatigue scores were recorded after waking and 15 and 30 min later. Group L's pain scores were notably reduced than Group N's (ANOVA: $P = 0.008$). Group L's fatigue scores were notably reduced than Group N's (ANOVA: $P = 0.004$)

did not notably different in the two cohorts. ($P > 0.05$) (Table 3).

Correlation analysis of the incidence of overall adverse events

The bivariate Spearman correlation analysis revealed a positive correlation between the overall adverse event rate with patient age ($P = 0.001$) and the total amount of CIP ($P = 0.03$) and no significant correlation with BMI and operation time ($P > 0.05$) (Table 4).

Table 4 Correlation analysis of overall adverse event rates

	Correlation coefficient	*P*
Age (y)	0.517	0.001
BMI (kg/m^2)	0.279	0.081
Operation duration (min)	0.153	0.347
Total CIP consumption (mg)	0.344	0.030

Notes: Overall adverse events were defined as intraoperative, including choking and coughing, belching, body movement, and hypoxia

Abbreviations: BMI, body mass index

Discussion

This trial revealed that IV lidocaine addition to CIP PSA reduces CIP dose by 23% for GE without any severe adverse reactions. It also improves post-endoscopic pain and fatigue. The sedative dose was affected by various factors, including the type of procedure, ASA status, patient's age, procedure time, and comorbidities. These factors did not reveal any marked difference between the two cohorts. Therefore, the procedure time might be the primary factor affecting the sedative dose, indicating that it might have been too short to assess the CIP-sparing effect of IV lidocaine. This might partly elaborate why 23% CIP dose reduction might not be meaningful clinically, although it was statistically essential.

Abdominal pain is a frequent colonoscopy complication linked with intestinal cavity swelling due to water and gas injection or mechanical stretching of the intestinal wall by the endoscope. The VAS score of group L during the recovery time was reduced than the N group, suggesting the analgesic effect of IV lidocaine. A meta-analysis of 12 randomized controlled studies revealed that IV lidocaine infusion (1.5 mg/kg/h) inhibits pain after cholecystectomy [18]. Koppert et al. [19] indicated that this analgesic effect could be extended to 72 h post-surgery. Lidocaine is an amide-type local anesthetic that suppresses the production and conduction of nerve action potentials by inhibiting sodium channels, thereby exerting analgesia at peripheral and central levels [20, 21]. The literature suggests that IV lidocaine inhibits neurotransmission of injured nervous tissue, suppresses granulocytes and lysosome migration, and reduces pro- and anti-inflammatory cytokine production, thereby exerting an anti-hyperalgesia [22, 23].

Although the CIP dose decreased in group L, the procedure duration was less prolonged than in the N group. Furthermore, endoscopists' satisfaction scores did not markedly differ for the two groups, suggesting that the drug dose reduction did not affect GE. These results are consistent with the study of Forster and colleagues [2]. In group L, the consciousness recovery and PACU stay duration were shortened, indicating reduced sedation during recovery time. Therefore, perioperative lidocaine administration could avoid the over-sedation caused by high CIP dose.

Hypoxia and apnea, secondary to airway obstruction and respiratory depression, are endoscopy's most frequent cardiopulmonary PSA complications. One of the objectives of this trial was to decrease the CIP dose and, consequently, the incidence of its adverse effects. The CIP effects on hemodynamics and respiratory depression are dose-dependent, and reducing the dose could alleviate cardiopulmonary adverse events. Although the L group indicated notable CIP synergistic effects, there were non-significant differences in the reduced SpO_2 between the two groups. The hypoxemia incidence in this trial was about 10%; however, research on adults revealed a greater value of 25% [2]. This may be because CIP produces weaker respiratory depression than propofol [10]. The number of hypoxia cases in the L group was less than in the N group, with no statistical difference. The duration of SpO_2 episodes was not assessed, which could have allowed the elucidation of lidocaine's beneficial effects. At T4, the HR and MAP indicated a reduction in group L than in the N group. This difference can be (partially) because of the analgesic effect of lidocaine. Whereas no difference was observed for SpO_2 in the two groups at all time points. These results were highly expected as the recruited participants were relatively healthy (ASA I and II), although they only received small CIP doses for induction and continuous sedation. However, Chen et al. [24] validated that despite using increased lidocaine, no marked difference in MAP was observed between the two cohorts. Whether patients benefit from reduced adverse events caused by CIP after IV lidocaine induction requires a larger sample size and multicenter trial.

Limitation

The limitations of this research are as follows: (1) The plasma lidocaine concentration after administration was not measured. (2) The IV lidocaine safety profile was assessed via the patient's clinical manifestations, and no patient indicated any signs of local anesthetic intoxication. Therefore, future pharmacokinetics investigations are required in patients to confirm IV lidocaine safety for endoscopy. (3) Objective indicators, including BIS or End-expiratory CO_2 monitoring, were not assessed

peri-procedure. Although no difference was indicated in the SpO_2 between the two cohorts, timely monitoring of CO_2 accumulation may help early detection of respiratory depression. There might be slight variation in the judgment of the sedation depth among the individual patients when the MOAA/S score, the subjective observation technique, was applied. To minimize the potential bias, we tried to standardize the personal assessment skill to a single anesthesiologist blinded to the patient's grouping. (4) This trial mostly comprised relatively healthy participants (ASA I ~ II) and lacked high-risk, more CIP-vulnerable patients (ASA III ~ IV). (5) The post-colonoscopy intestinal function recovery was not assessed as the patients were discharged from the PACU immediately after recovery. Therefore, further trials are needed to validate these results.

Conclusion

Overall, IV lidocaine reduced the CIP dose by 23% during PSA for a colonoscopy without affecting the endoscopist's procedure. It also improved post-colonoscopy fatigue and pain. However, this investigation could not assess a reduction in the incidence of O_2 desaturation despite the CIP-sparing effect.

Abbreviations

ASA	American Society of Anesthesiologists physical status
BMI	Body mass index
MAP	Mean arterial pressure
HR	Heart rate
SpO_2	Oxygen saturation
CO_2	Carbon dioxide
PACU	Post-anesthesia care unit

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Author contributions

Manlin Duan, Qiang Sun and Xinyu Cao designed the study. Xinyu Cao, Guangli Zhu and Chongya Yang collected data. Bin Wang, Yang Ang analysed data. Manlin Duan, Qiang Sun and Xinyu Cao contributed to manuscript writing. Kangli Hui, Jingwei Xiong and Jiejie Zhou contributed to manuscript revision. All authors read and approved the final version of the manuscript.

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Data availability

All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The ethical board of Jinling hospital authorized this trial (2023DZKY-010-01), which was then submitted to the Chinese Clinical Trial Registry (registration number: ChiCTR2300069868, registration date: 28/03/2023).The protocol of the study was performed in accordance with the Declaration of Helsinki. The quality control of this study was conducted by GCP guidelines. Written informed consent was obtained from all patients before enrollment.

Consent for publication

Not application.

Competing interests

The authors declare no competing interests.

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