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ORIGINAL RESEARCH

Application of Intravenous Chloroprocaine in Gastrointestinal Endoscopy: A Randomized Controlled Trial

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Background: While propofol is a commonly utilized medication for sedation during gastrointestinal endoscopy, it is associated with adverse effects such as hypotension and injection pain. This trial was conducted to test the hypothesis that chloroprocaine can reduce the requirement for propofol and alleviate injection pain during gastrointestinal endoscopy.

Methods: Sixty patients undergoing gastrointestinal endoscopy were enrolled and randomly divided into study group (Group CP) and control group (Group C). Patients in Group CP received intravenous chloroprocaine 2 mg/kg, followed by continuous infusion at 6 $mg \cdot kg^{-1} \cdot h^{-1}$ until the end of examination. Patients in Group C received the same volume of saline. Subsequently, all patients were intravenously administered sufentanil at a dose of 0.05 μg/kg. Thirty seconds later, propofol was uniformly infused intravenously at a rate of 60 mL/min using an infusion pump. The primary outcome was the consumption of propofol. Secondary outcomes included the incidence of hypoxemia, hypotension, bradycardia, injection pain, and coughing/body movement during examination. The recovery time, PACU stay time, postoperative pain score, and endoscopists' satisfaction score were also recorded.

Results: Group CP demonstrated a significantly lower total requirement for propofol compared to Group C, with means of (119 ±14) mg and (148±18) mg respectively, P<0.001. This trend was also observed for both the first and supplemental doses. There were no significant differences between the two groups regarding intraoperative adverse events. The incidence of injection pain in Group CP was lower than that in Group C (P=0.007). The recovery time [(4.7±1.4) vs (6.6±1.3), P<0.001], PACU stay time [(13.0±2.9) vs (16.7 ±3.0), P<0.001] and postoperative pain score [(1.9±0.7) vs (2.5±0.7), P=0.002] in Group CP were lower than those in Group C.

Conclusion: Intravenous chloroprocaine reduces the requirement for propofol, alleviates propofol injection pain, and improves recovery in patients undergoing gastrointestinal endoscopy.

Keywords: chloroprocaine, endoscopy, propofol, injection pain

Key Summary Points

Propofol is a commonly utilized medication for sedation during gastrointestinal endoscopy, but associated with hypotension and injection pain.

In recent years, various drugs combined with propofol to mitigate these adverse effects and enhance the comfort and safety of painless endoscopic procedures.

Intravenous chloroprocaine could reduce the requirement for propofol, and decrease the incidence of propofol injection pain.

Introduction

Gastrointestinal endoscopy is considered the gold standard for screening digestive tract tumors and for providing diagnosis and treatment.[1,2] Despite its efficacy, non-sedated gastrointestinal endoscopy often results in pain and

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discomfort for over half of the patients undergoing the procedure.[3,4] The mechanical traction and stimulation applied to the esophagus, stomach, and intestines, along with concomitant cardiovascular responses, evoke sensations of anxiety and pain. Moreover, it may lead to severe complications such as perforation, myocardial infarction, and stroke. As a response to these challenges, sedated gastrointestinal endoscopy has become increasingly prevalent in the diagnosis and treatment of digestive diseases.[5] In the United States, more than 98% of gastrointestinal endoscopies are performed under sedation.[6] Sedation not only eliminates patients' painful memories but also enhances their tolerance, enabling endoscopists to perform procedures comfortably and thoroughly.

Propofol, owing to its rapid onset and recovery, is the predominant sedative drug used in gastrointestinal endoscopy.[7] In the United States, the use of propofol increased from 16.7% in 2006 to 58.1% in 2015.[8] However, propofol administration can lead to adverse effects such as body movement, coughing, and injection pain.[9,10] High doses may also significantly depress respiration and circulation, posing challenges to the safety of gastrointestinal endoscopy.[11,12] In recent years, various sedative and analgesic drugs have been introduced in combination with propofol to mitigate these adverse effects and enhance the comfort and safety of painless endoscopic procedures.[13–15] While studies has indicated that opioid drugs combined with propofol can reduce the consumption of propofol, they are also associated with increased risks of hypotension and hypoxemia. Consequently, identifying the ideal adjunct medication to minimize propofol usage is of paramount importance in clinical anesthesia practice.

Chloroprocaine is a short-acting local anesthetic with twice the anesthetic potency of procaine and only half the associated toxicity. Chloroprocaine undergoes rapid hydrolysis by plasma cholinesterase in the blood, with rare occurrences of allergic reactions.[16,17] Clinical evidence has demonstrated that, in comparison to lidocaine, intravenous chloroprocaine results in a lower incidence of dizziness and visual disturbances.[18] Clinical study suggests that intravenous chloroprocaine can significantly inhibit hemodynamic fluctuations and stress-indicator increases associated with tracheal intubation.[19] These properties make chloroprocaine a promising adjunct to propofol sedation, yet there is a lack of similar research in this area. Therefore, this study aims to test the hypothesis that intravenous chloroprocaine can reduce the dosage of propofol, alleviate injection pain, and improve patient recovery following gastrointestinal endoscopy.

Methods

Ethical Statement and Study Setting

The study was conducted at the Second People's Hospital of Wuhu from July to October, 2024, in accordance with the Declaration of Helsinki. The study was approved by the hospital's research ethics committee (the Second People's Hospital of Wuhu, 2024-KY-012) and was registered in the Chinese Clinical Trial Registry (ChiCTR2400085739, Date of registration: 2024-6-17). Written informed consent was obtained from each patient. A total of 60 patients who were American Society of Anesthesiologists (ASA) I–II, aged between 18 and 65, and planned to undergo gastrointestinal endoscopy were recruited for this research. Exclusion criteria comprised hepatic and renal insufficiency, epilepsy, severe cardiac arrhythmia, prolonged use of analgesics, psychotropic drugs, and alcohol abuse, allergy to ester local anesthetics, difficult airway, and individuals experiencing acute upper respiratory tract infection, asthma attacks, or acute and severe laryngeal diseases. Contraindications for the use of chloroprocaine included known hypersensitivity to ester local anesthetics, severe hepatic or renal impairment, severe cardiac arrhythmias, and seizure disorders.

Randomization and Blinding

Patients were randomly divided into the chloroprocaine group (Group CP) and the saline group (Group C) using the computer-generated randomization assignments. The pre-treating agents were prepared in a 20-mL syringe, either with 10 mL of normal saline or with 2 mg/kg of chloroprocaine (diluted to a total volume of 10 mL with normal saline), by an anesthesiologist who was not involved in the investigation. The patients, endoscopists, and anesthesiologists responsible for sedation and data collection remained blinded to the patient's allocation throughout the study.

Study Protocol

Upon entering the room, intravenous access was established, and blood pressure (BP), electrocardiography (ECG), and peripheral oxygen saturation (SpO_2) were continuously monitored. Patients assigned to Group CP received an intravenous injection of chloroprocaine at a dose of 2 mg/kg, administered within 15 seconds, followed by a continuous infusion at a rate of 6 $mg \cdot kg^{-1} \cdot h^{-1}$ until the end of the gastrointestinal endoscopy. Patients in Group C received an equivalent volume of saline. Subsequently, all patients were intravenously administered sufentanil at a dose of 0.05 μg/kg. Thirty seconds later, propofol was uniformly infused intravenously at a rate of 60 mL/min using an infusion pump. The sedation level assessed by the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S),[20] and gastroscopy was performed when the patient's MOAA/S score was ≤ 1.

Throughout the procedure, if patients exhibited signs of discomfort, pain expression, body movement, or a heart rate increase of ≥ 20 beats per minute or a mean arterial pressure increase of ≥ 20 mmHg from baseline, intravenous propofol at a dose of 20~30 mg was administered. Propofol was injected repeatedly if necessary. In the event of a decrease in mean arterial pressure by 20 mmHg from baseline, ephedrine at a dose of 5 mg was administered. If the heart rate dropped below 50 beats per minute, atropine at a dose of 0.25~0.5 mg was administered as needed. In cases where SpO_2 dropped below 90%, jaw lifting was performed for assist ventilation. All patients breathed on their own and received 5 L/min oxygen through nasal catheter.

Outcomes

The primary outcome was the consumption of propofol. Secondary outcomes included: The incidence of injection pain, hypoxemia (defined as SpO_2<90%), hypotension, bradycardia, coughing, and body movement. The recovery time (defined as time from end of examination to patient being able to provide their name), PACU stay time (discharge criteria: vital signs returned to preoperative levels, clear consciousness, lucid response, able to walk normally, no discomfort complaint), postoperative pain score (visual analogue scale, VAS, 0–10 scale), and endoscopists' satisfaction score (1 point is dissatisfied, 2 points is not very satisfied, 3 points is quite satisfied, and 4 points is very satisfied) were also recorded.

Statistical Analysis

Based on the results of our previous study involving 20 patients, the consumption of propofol for gastrointestinal endoscopy was 154±40 mg in Group C and 123±34 mg in Group CP. With a significance level of 0.05 (two-sided) and power of 80%, 24 patients were required in each group. Considering a 20% dropout rate, a total of 60 patients were finally included.

Statistical analysis was performed using SPSS 24.0 software (SPSS Inc., USA). Continuous variables are expressed as mean (standard deviation) or median (interquartile range), and compared using *t*-test or Mann-Whitney *U*-test. Categorical variables were described as frequencies and percentages and compared using chi-squared test. $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

A total of 66 patients were recruited for this study. However, 6 patients were excluded due to meeting the exclusion criteria (4 patients) and refusing to participate (2 patients). 60 patients were enrolled and randomly allocated into two groups in this study. The groups consisted of 30 patients in each group for analysis (Figure 1). No significant differences were observed in the demographic characteristics of the two groups. Additionally, no significant differences were noted in the intraoperative variables, including endoscopy time, between the two groups (Table 1).

Outcomes

Group CP demonstrated a significantly lower total requirement for propofol compared to Group C, with means of (119 ±14) mg and (148±18) mg respectively, $P < 0.001$. This trend was also observed for both the first and supplemental doses. (Table 2).

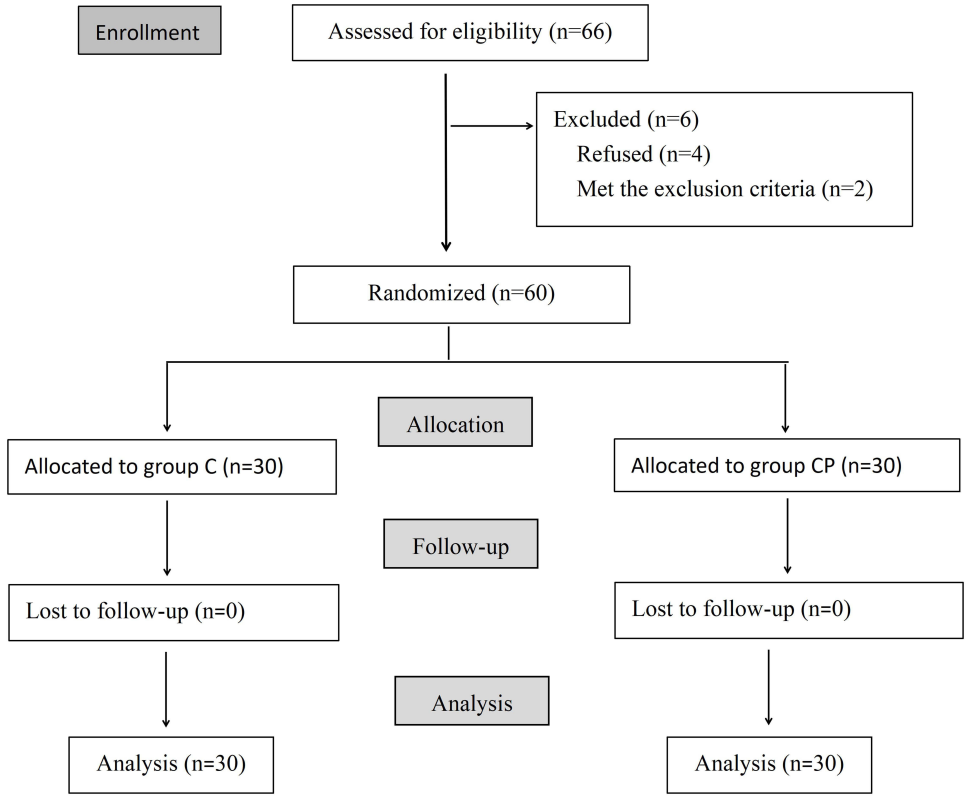

Figure 1 Flow chart of the present study.

No significant difference between the two groups in the incidences of coughing/body movement, hypotension, hypoxemia, bradycardia and intraoperative awareness. Statistical analysis revealed that the incidence of injection pain in Group CP was significantly lower than that in Group C (P = 0.007), with respective rates of 10.0% and 40.0% as detailed in Table 3.

The recovery time in Group CP was significantly shorter than in Group C, with means of (4.7±1.4) minutes compared to (6.6±1.3) minutes (P < 0.001). Similarly, the post-anesthesia care unit (PACU) stay time was (13.0±2.9) minutes for

Table 1 Demographic Data of the Patients and Endoscopy Time in Two Groups

	Age (yr)	Gender (M/F)	ASA (I/II)	BMI (kg/m^2)	Endoscopy Time (min)
Group C (n=30)	52.8.±9.4	18/12	5/25	22.5±1.8	24.0±5.8
Group CP (n=30)	54.1±6.7	17/13	6/24	22.2±2.0	24.6±4.9
t/x^2	0.632	0.069	0.111	0.601	0.386
p	0.530	0.793	0.739	0.550	0.701

Table 2 The Consumption of Propofol in Two Groups

	First Dose (mg)	Supplement Dose (mg)	Total Dose (mg)
Group C (n=30)	111±13	36±10	148±18
Group CP (n=30)	95±12[a]	24±8[a]	119±14[a]
t	5.017	5.316	6.908
p	<0.001	<0.001	<0.001

Note: [a] P < 0.05 vs Group C at the same time.

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Table 3 Comparison of Intraoperative Adverse Events

	Injection Pain [n(%)]	Coughing/Body Movement [n(%)]	Hypotension [n(%)]	Hypoxemia [n(%)]	Bradycardia [n(%)]	Intraoperative Awareness [n(%)]
Group C (n=30)	12(40.0)	6(20.0)	4(13.3)	4(13.3)	3(10.0)	0(0)
Group CP (n=30)	3(10.0)[a]	3(10.0)	5 (16.7)	3(10.0)	2(6.7)	0(0)
X^2	7.200	1.176	0.131	0.162	0.218	/
p	0.007	0.278	0.718	0.688	0.640	/

Note: [a]P < 0.05 vs Group C at the same time.

Table 4 Comparison of Recovery Period in Two Groups

	Recovery Time (min)	PACU Stay Time (min)	Postoperative Pain Score
Group C (n=30)	6.6± 1.3	16.7±3.0	2.5±0.7
Group CP (n=30)	4.7±1.4[a]	13.0±2.9[a]	1.9±0.7[a]
t	5.727	4.660	3.290
p	<0.001	<0.001	0.002

Note: [a]P < 0.05 vs Group C at the same time.

Table 5 Endoscopists' Satisfaction Score in Two Groups

	Endoscopists' Satisfaction Score [n(%)]					
	1	2	3	4	Z	*p*
Group C (n=30)	0(0.0)	2(6.6)	13(32.5)	15(50.0)	0.596	0.551
Group CP (n=30)	0(0.0)	1(3.3)	12(40.0)	17(56.7)		

Group CP versus (16.7±3.0) minutes for Group C (P < 0.001). Additionally, the postoperative pain score was lower in Group CP, with a mean of (1.9±0.7) compared to (2.5±0.7) in Group C (P = 0.002). (Table 4).

No significant difference in the satisfaction of endoscopists between the two groups (Table 5).

Discussion

This study demonstrates that Intravenous chloroprocaine reduces the requirement for propofol, alleviates propofol injection pain, maintains respiratory and circulatory stability during examination, and improves post-gastroscopy pain and discomfort in patients undergoing gastrointestinal endoscopy, without affecting the working conditions of endoscopists.

Among the various opioids and non-opioid drugs (eg, esketamine, dexmedetomidine, etomidate) used in endoscopic sedation, lidocaine is commonly used for its analgesic, anti-inflammatory, and anti-stress effects.[21,22] However, lidocaine carries certain cardiovascular risks, including effects on cardiac conduction. Chloroprocaine has 2-fold greater anesthetic potency than procaine, yet its plasma cholinesterase hydrolysis rate is increased 4–5 times, with rare allergic reactions and half the toxicity of procaine. Compared to lidocaine and other ester local anesthetics, chloroprocaine demonstrates superior antiarrhythmic effects. Recent studies have suggested that intravenous chloroprocaine may cause fewer side effects such as dizziness and visual impairment compared to lidocaine.[16,19,23] A case report indicates that high doses of intravenous chloroprocaine (up to 30 mg/kg) in chronic pain patients resulted in only mild mental symptoms.[18] A 4 kg infant given accidental 120 mg intravenous chloroprocaine during epidural anesthesia developed 30-second bradycardia (30 beats/minute) that spontaneously resolved with chest compressions and atropine.[24] These cases demonstrate chloroprocaine has a wide safe dosage range for intravenous infusion.

Studies have shown that intravenous injection of 1.5 mg/kg lidocaine during a painless colonoscopy reduces the need for propofol during colonoscopy and improves immediate pain and fatigue after colonoscopy.[21,22,25] In studies examining chloroprocaine's inhibition of tracheal intubation stress response, intravenous doses of 3.0~4.5 mg/kg were administered. These doses avoided local anesthetic toxicity and significantly inhibited hemodynamic fluctuations and related stress marker increases caused by intubation. Given that the in vitro plasma half-life of chloroprocaine is 11 to 21 seconds,[26] although certain substrates in the body interfere with cholinesterase metabolism, but whether the in vivo half-life of epidural administration is 3.1±1.6 minutes or the plasma half-life of intraperitoneal administration is 5.3 minutes,[27] suggesting a single intravenous bolus may be insufficient for entire gastroscopy procedures. Additionally, the ratio of procaine to lidocaine is generally considered to be 1:2, and gastroscopy insertion induces less stimulation than tracheal intubation. Based on the literature and preliminary experiments, this study utilized an intravenous bolus of 2 mg/kg 3% chloroprocaine, followed by 6 $mg \cdot kg^{-1} \cdot h^{-1}$ continuous infusion until examination completion.

This study showed that the incidence of injection pain was lower in Group CP (10.0%) compared to Group C (40.0%). With reduced propofol dosing compared to the control group, the experimental group exhibited significantly decreased postoperative pain and discomfort, without impacting the endoscopist's operations. Propofol injection pain comprises immediate and delayed pain, the former from phenols or lipids directly stimulating vessels, the latter from pain mediator release induced by drug-endothelium contact.[28,29] Chloroprocaine binds vessel inner pain receptor sites and block membrane voltage-gated sodium channels, achieving anesthesia. Like lidocaine, it may also inhibit pain mediator conduction, causing local venous blockade. The improved postoperative pain and comfort scores in the experimental group may stem from chloroprocaine blocking Na^+ inflow and K^+ outflow, thereby inhibiting neuronal discharge conduction, stabilizing cell membranes, and reducing intracellular biochemical-energy metabolism reactions to exert central sedative and analgesic effects. Circulating chloroprocaine also mildly blocks peripheral nerve endings. Additionally, a visceral pain theory holds that many fibers are "silent" until inflamed. Local anesthetics such as chloroprocaine reduce inflammatory mediator and free radical release from neutrophils, alleviating visceral pain.[27] Because of the analgesic and anti-inflammatory effects of procaine, the amount of extra propofol and the total amount of propofol used in Group CP were less than those in Group C. Compared with Group C, the patients in group CP had less postoperative pain and discomfort, shorter time of recovery and observation, and had no influence on endoscopist's operation. The reduction in the dosage of propofol in this study did not show obvious advantages in terms of circulation and breathing, this may have been due to multiple factors. On the one hand, the research subjects in this study were relatively healthy, so they may have been less sensitive to dosage reductions. On the other hand, the small sample size and short overall examination time may have limited the ability to detect subtle circulation and respiration differences between dosage groups. However, the reduction in the dosage of propofol may have positive clinical significance in elderly patients and patients with high ASA grades.

This study has several limitations. First, although some studies introduced BIS monitoring for endoscopic sedation, considering the cost and the lag in BIS monitoring, BIS was not used in this study. However, BIS monitoring holds the potential to enhance the consistency of anesthesia depth. Second, although a sample size calculation was conducted, the sample size is relatively small.

While chloroprocaine has exhibited a favorable safety profile in this study, it is imperative to acknowledge the contraindications associated with its use. Patients with a documented hypersensitivity to ester local anesthetics, as well as those with severe hepatic or renal impairment, are contraindicated for chloroprocaine administration. Moreover, in patients presenting with severe cardiac arrhythmias or seizure disorders, the use of chloroprocaine should be approached with caution, given that these conditions may potentially heighten the risk of adverse effects. Rigorous patient selection and strict adherence to contraindications are fundamental to ensuring the safe and effective utilization of chloroprocaine in clinical practice.

Conclusion

Intravenous chloroprocaine reduces the requirement for propofol, alleviates propofol injection pain, maintains respiratory and circulatory stability during examination, and improves post-gastroscopy pain and discomfort in patients undergoing gastrointestinal endoscopy, without adversely affecting the working conditions of endoscopists.

Abbreviations

The following abbreviations are used in this manuscript:

ASA, American Society of Anesthesiologists classification; BIS, Bispectral index; MOAA/S, the Modified Observer's Assessment of Alertness/Sedation Scale;

BP, Blood Pressure; ECG, Electrocardiography; SpO_2, Peripheral Capillary Oxygen Saturation; VAS, Visual Analogue Scale; PACU, Postanesthesia Care Unit.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Statement

The study was approved by the hospital's research ethics committee (the Second People's Hospital of Wuhu, 2024-KY -012) and was registered in the Chinese Clinical Trial Registry (ChiCTR2400085739, Date of registration: 2024-6-17). Written informed consent was obtained from each patient.

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Disclosure

The authors report that there is no conflicts of interest in this work.

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