Original Article
Premedication of butorphanol benefits gastrointestinal endoscopy screening under sedation: a randomized, controlled, double-blinded clinical trial

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Abstract: Background: Propofol is often used as a sedative agent in gastrointestinal endoscopy screening, but it has adverse effects like hypotension, bradycardia, and respiratory depression. This study aims to evaluate if premedication with butorphanol could decrease the total consumption of propofol to stable hemodynamics in patients and compare the benefits between premedication with butorphanol and sufentanil on patients undergoing gastrointestinal endoscopy screening under sedation with propofol. Methods: A total of 200 patients undergoing elective gastrointestinal endoscopy screening (esophagogastroduodenoscopy followed by colonoscopy) with American Society of Anesthesiologists physical status I and II were randomly grouped into group 1 (the placebo group), group 2 (5 μg/kg butorphanol group), group 3 (10 μg/kg butorphanol group), and group 4 (0.05 μg/kg sufentanil group). A similar total volume of medication was administrated to all patients respectively, and then they were all subsequently administrated propofol through target-controlled infusion (TCI) with an effect-site concentration of 3.5 μg/ml, before and during the procedure. We compared the total consumption of propofol, the cardiovascular parameters, duration of endoscopy procedure, satisfaction scores of the endoscopist and patients, adverse reactions in patients, RASS scores, injection pain scores, and recovery time among the four groups. Results: Patients in the four groups had similarly stable hemodynamics. The consumption of propofol was higher in the placebo group than in group 3 (236.2 ± 40.9 mg vs 213.6 ± 41.6 mg, P = 0.007). In addition, the recovery time of group 2 was shorter than those in the other groups (8.3 ± 3.0 vs 11.26 ± 3.3, 10.5 ± 2.3, 11.5 ± 3.0, P = 0.000), the injection pain score of placebo group was higher than the other groups (P = 0.000) and the scores in group 2, group 3 were lower than group 4 (0.2 ± 0.4 vs 0.45 ± 0.73, 0.16 ± 0.42 vs 0.45 ± 0.73, P < 0.05). The incidence of bucking/hiccupping was lowest in group 3 (6% vs 28%, 18%, 16%, P = 0.000). The incidence of body movement was also lowest in group 3 (8% vs 50%, 28%, 30%, P = 0.000), compared with the other three groups. The satisfaction scores by endoscopists were higher in group 3 than in the other three groups (P < 0.01), and the satisfaction scores by patients were higher in the experimental groups than in the placebo group (P < 0.001), and it was higher in group 3 than in group 4 (4.9 ± 0.3 vs 4.7 ± 0.5, P < 0.05). Conclusions: Premedication with butorphanol has many benefits, especially premedication with 10 μg/kg butorphanol. It can decrease the total consumption of propofol, relieve the propofol injection pain, increase patient and endoscopist satisfaction, and it has less effect on respiration compared with 0.05 μg/kg sufentanil. Thus, we recommended premedication of 10 μg/kg butorphanol for patients undergoing gastrointestinal endoscopy screening under sedation with propofol.

Keywords: Butorphanol, sufentanil, gastrointestinal endoscopy, target-controlled infusion, propofol, sedation

Introduction

Gastrointestinal endoscopy is a commonly performed diagnostic and therapeutic procedure [1]. Both patients and endoscopists prefer this invasive procedure performed under sedation because [2, 3] (i) it minimizes procedural pain and discomfort for patients; (ii) it improves patients' acceptance of having the procedure performed, which can lead to earlier diagnosis and treatment of gastrointestinal diseases; and (iii) it provides better satisfaction for endosco-

pists, due to the improved quality of the examination. Because of its [4] quick onset of action, reliable sedation, short half-life, and rapid recovery and discharge from the endoscopy unit, intravenous propofol is frequently used for sedation during gastrointestinal endoscopy. Moreover, multiple clinical reports have demonstrated its safety in a variety of patients, including the elderly [1], children [5], and even frail and critically ill patients [6]. However, adverse effects, including hypotension, bradycardia, respiratory depression, and injection pain have also been reported [7, 8], and they often occur during endoscopy. As a result, we aim to find a better endoscopy anesthesia technique through the premedication of some sedative and analgesic medication.

Butorphanol, is μ receptor agonist-antagonist and κ receptor agonist. It is extensively used in clinical practice with more potent analgesic, sedation effect and a better pharmaceutical formulation. Compared with a typical μ receptor agonist (eg. sufentanil), it isn't a state-controlled drug in China, so it is a clinical agent convenient to use, especially for outpatients. Besides, it has been used as an antitussive in humans [9]. However, there has been no published data regarding the effectiveness of butorphanol in painless gastrointestinal endoscopy screening. Hence, we designed this study to assess the effect of butorphanol hemodynamic stability, the incidence of propofol injection pain, bucking/hiccupping, recovery time, and so on.

Material and methods

Study design

This prospective, randomized, double-blinded, and placebo-controlled clinical trial was approved by the Institutional Medical Ethics Committee of the Second Affiliated Hospital and Yu Ying Children's Hospital of Wenzhou Medical University, chaired by Xueqiong Zhu (No. L-2018-06). The clinical trial was performed at the Department of Anesthesiology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (Wenzhou, Zhejiang, China) between January 2018 and May 2018 (Registration number: ChiCTR1800015252). Written informed consents were obtained prior to participation.

Participants

The inclusion criteria were: (1) American Society of Anesthesiologists (ASA) classification of I-II; (2) Scheduled for elective gastrointestinal endoscopy (esophagogastroduodenoscopy followed by colonoscopy); (3) Aged 18 to 65 years; (4) Body Mass Index (BMI) between 18 and 26 kg/m^2. The exclusion criteria were: (1) Patients with allergies to propofol, eggs, beans, or latex; (2) Patients with sinus tachycardia or other arrhythmia; (3) Patients with heart, liver or kidney dysfunction; (4) Patients who were scheduled for gastrointestinal endoscopic treatment; (5) Patients with a history of glaucoma or prostatic hypertrophy; (6) Patients with a history of abdominal surgery; (7) Patients with a history of hyperthyroidism, diabetes, or other endocrine disease.

Intervention and processes

The patients were randomly divided into four parallel groups with a random number generated by SPSS 21 (Group 1 = normal saline group, Group 2 = 5 μg/kg butorphanol group, Group 3 = 10 μg/kg butorphanol group, Group 4 = 0.05 μg/kg sufentanil group). An independent supervising nurse who was blinded to this study prepared the study medications (equivalent volume of normal saline, 5 μg/kg butorphanol, 10 μg/kg butorphanol or 0.05 μg/kg sufentanil) according to the random number sequence.

Oxygen at a rate of 5 L/min was delivered via a Venturi mask when patients entered the endoscopy unit. Monitors included blood pressure (NIBP), electrocardiogram (ECG), peripheral oxygen saturation (SpO2) and respiratory rate (the IntelliVue MP50; Philips, Shanghai, China). The vital signs were recorded every three minutes. The vital signs 10-minutes after the patients lay down on the mobile operating table were defined as the baselines and administrated with the clinical trial medicine.

Normal saline, butorphanol, and sufentanil were administered respectively, through peripheral vein access which was established preoperatively with a 20-gauge intravenous cannula by the same supervising nurse. Two minutes later, sedation scores were recorded according to the RASS scale and then propofol (Propofol Medium and Long Chain Fat Emulsion Injection;

Table 1. Pain scale for evaluation of propofol-induced injection pain

Response to propofol injection Pain score	Verbalization scale
0	No vocalization
1	Purposeless moaning
2	Explicit protest
3	Screams, cries

Fresenius Kabi, Graz, Austria) infusion was initiated via a TCI system (CONCERT-CL, Guangxi Veryark Technology Co. Ltd, Nanning, Guangxi, China) with the Marsh model and the effect-site concentration was set as 3.5 ug/ml. This concentration was chosen because it was proven to be effective in our pilot study. During the procedure, various standard interventions were employed depending on the clinical situation including (i) administration of a 0.5 mg/kg bolus of propofol if the patient moved; (ii) use of a jaw-thrust to open the airway and/or mask ventilation if the patients develop respiratory depression as determined by the anesthesiologist; and (iii) administration of 6mg ephedrine if the NIBP was reduced to lower than 20% of baseline.

Once anesthesia induction was achieved, which was confirmed by the loss of eyelid reflex, the same senior endoscopist (20 years of experience, more than 1000 gastrointestinal endoscopies performed annually in the last 10 years) executed the gastrointestinal endoscopy, starting with esophagogastroduodenoscopy, then colonoscopy. When the colonoscope is at the ileocecal valve and being prepared to be removed, the infusion of propofol by the TCI system was terminated. Both the endoscopist and the anesthesiologist were blinded to the grouping information.

Measurement

The primary outcomes of this research were the total consumption of propofol, the hemodynamic stability characterized by fluctuations of mean arterial pressure (MAP) compared to baseline (presented as the D-value of MAP, different values of measurement MAP with baseline) at 7 different time-points. The seven different time-points were, T1, the baseline of vital sign; T2, the time-point after induction; T3, the time-point of insertion of the gastroscope into the oropharynx. T4, the time-point of the gastroscope removal from the mouth; T5, the time-point of colonoscope entry into the anus; and T6, the time point of the colonoscope reaching the ileocecal valve; T7, the recovery time-point. The following time consumptions during the endoscopy were respectively recorded and compared, (i) the duration of esophagogastroduodenoscopy: the time from gastroscope insertion into the mouth until its removal from the mouth; and (ii) the duration of the colonoscopy insertion time: the time from colonoscope insertion into the anus to reaching the ileocecal valve.

The duration of withdrawal of the colonoscope was not included because the withdrawal time was fairly different for individual patients and was not comparable. The secondary outcomes were of satisfaction scores of the endoscopists and patients, and adverse events such as bucking/hiccupping, body movement, injection pain scores and recovery time. The satisfaction scores of the endoscopist and patients were acquired by a survey (0-5 points, representing Not Satisfied at All to Highly Satisfied) when the endoscopy was completed. The injection pain scores were scored according to the injection pain score scale presented in **Table 1**. Patients were fully oriented as determined by whether patient could tell his/her correct birth date.

Power of the study and statistical analysis

The sample size was calculated based on the result of our pilot study, with a commercial software, Pass11, in which we found that the total consumption of propofol was (255 ± 42) mg, (210 ± 36) mg, (193 ± 28) mg, (213 ± 35) mg, respectively in a placebo group, 5 μg/kg butorphanol group, 10 μg/kg butorphanol group and 0.05 μg/kg sufentanil group (n = 10). Thus, we determined that 40 patients for each group would meet the minimum requirement of α = 0.05 and power = 0.9. Considering that some subjects would drop-out, we decided to enroll 50 patients per group for a total of 200 patients.

The data are presented as the mean ± SD or numbers, as appropriate. The normal distribution of the data was examined with the Kolmogorov-Smirnov test. The measurement data in the groups were analyzed with the analysis of variance and post hoc tests Least Significant Difference, LSD. A Chi-square test was used for gender comparison. The quantitative data sets were expressed as frequency or rate and were compared using a Chi-Square test or Fisher's exact test. The recorded *P* value was 2-sided,
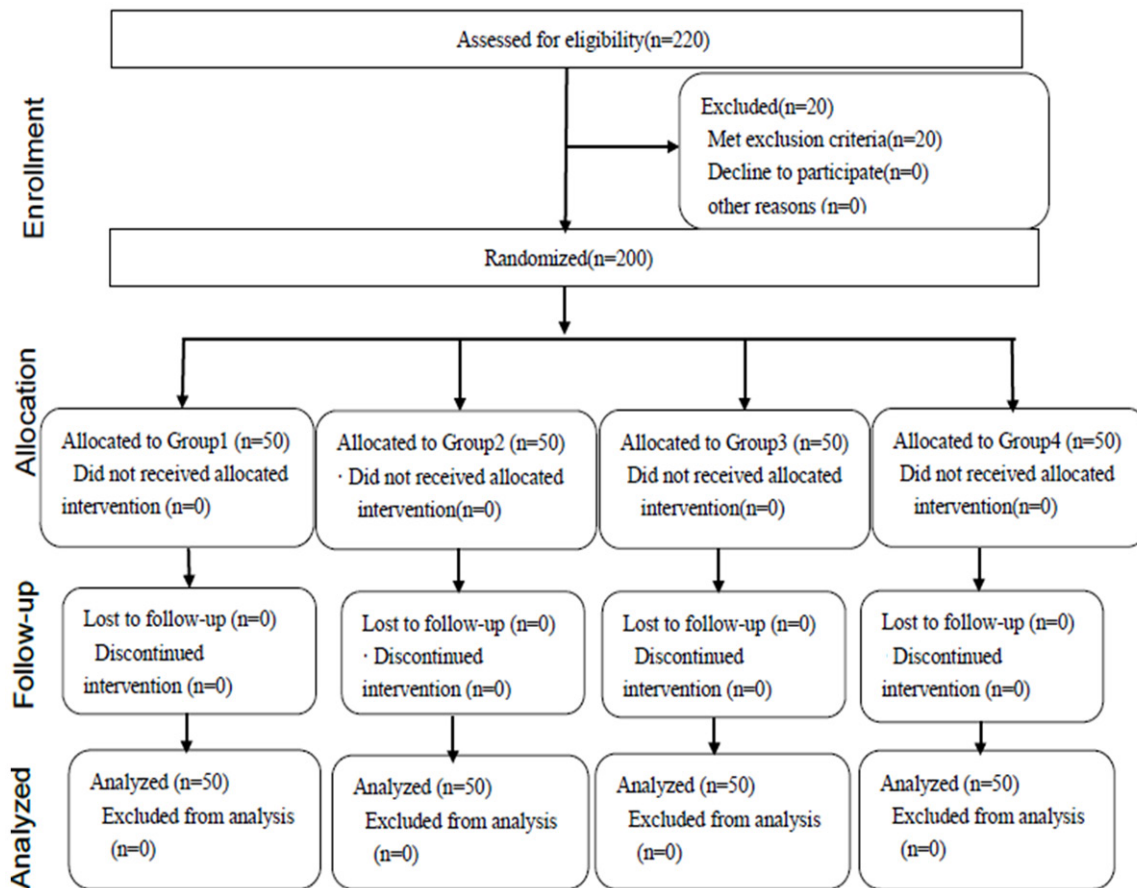
Figure 1. Flow chart of the patients' enrollment.

Table 2. The characteristics of the patients

Variables	Group 1	Group 2	Group 3	Group 4	P value
Age (yr)	47.1 ± 10.7	46.1 ± 8.6	45.6 ± 8.2	48.0 ± 10.8	0.457
Weight (kg)	62.1 ± 9.5	63.5 ± 10.4	62.8 ± 9.1	61.3 ± 9.4	0.724
Height (cm)	165.6 ± 7.5	166.1 ± 7.6	164.6 ± 10.8	164 ± 7.2	0.698
BMI (kg/m^2)	22.5 ± 2.0	22.9 ± 2.5	23.4 ± 5.2	22.6 ± 2.4	0.474
Gender (boy/girl)	25/25	27/23	26/24	21/29	0.646

Group 1 = normal saline group, Group 2 = 5 μg/kg butorphanol group, Group 3 = 10 μg/kg butorphanol group, Group 4 = 0.05 μg/kg sufentanil group (all P > 0.05, compared with each other in the four groups).

with $P < 0.05$ considered statistically significant. All of the data were analyzed with SPSS 21.

Results

A total of 200 patients were enrolled. Without dropouts, 50 patients remained in the four groups respectively. The patient flowchart is presented in **Figure 1**. All patients underwent diagnostic endoscopy. None of the patients had severe complications. The characteristics of the patients are presented in **Table 2**. There were no differences in these parameters including the proportion of genders, the mean age, BMI, weight, and height in the four groups (all P > 0.05).

The consumption of propofol was less in group 3 than in the placebo group (213.6 ± 41.6 mg in the group 3 vs 236.2 ± 40.9 mg in the placebo group, $P = 0.007$), but there was no statistically significant difference for the consumption of propofol among the other groups.

There was no statistically significant difference for the baseline of MAP in four groups between any two groups (P = 0.828). The fluctuations of MAP (presented as the D-value of MAP) and HR were similar in the 7 recorded time-points, as presented in **Figures 2 and 3**, but compared
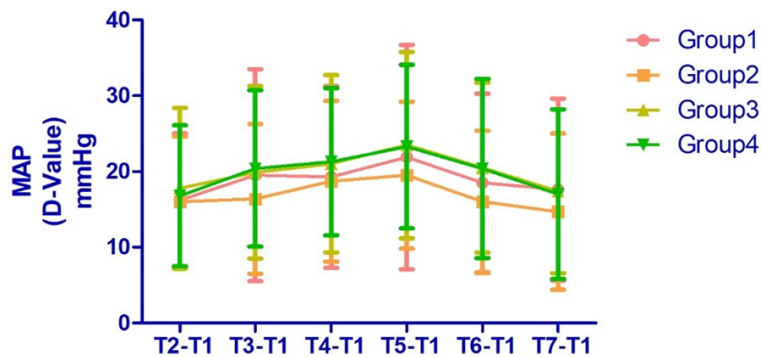
Figure 2. Results of D-values of MAP. T2-T1, T3-T1, T4-T1, T5-T1, T6-T1, T7-T1 represent the different value between six time-points and the time-point of vital sign baseline. There were no significant differences among the groups.
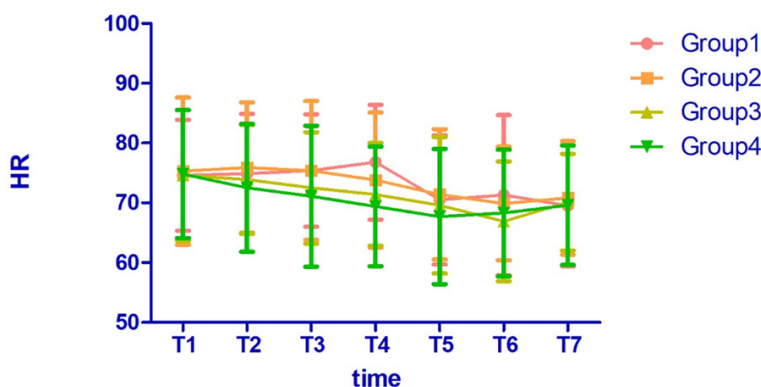

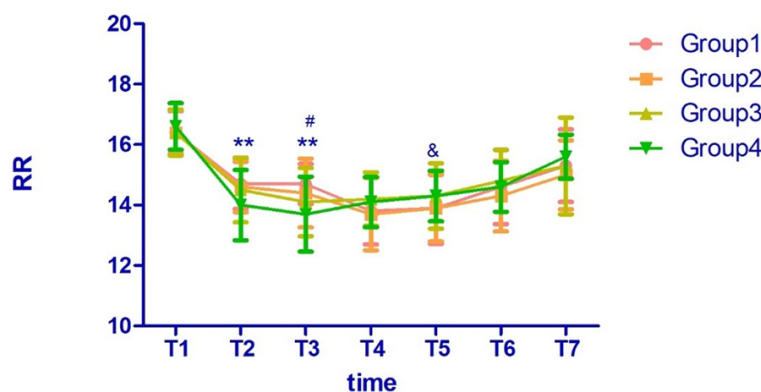**Figure 3.** HR in the four groups at seven time points. There were no significant differences among the groups.

Figure 4. RR in the four groups at seven time points. Compared Group 1, 2 with Group 4, **$P < 0.01$; Compared Group 3 with Group 4, #$P < 0.05$; Compared Group 2 with Group 4, &$P < 0.05$.

noscopy were also nearly the same in the four groups ($P > 0.05$), but the recovery time of group 2 was shorter than the other groups (8.3 ± 3.0 vs 11.26 ± 3.3, 8.3 ± 3.0 vs 10.5 ± 2.3, 8.3 ± 3.0 vs 11.5 ± 3.0, $P = 0.000$), as presented in **Figure 5**. In addition, the incidence of bucking/hiccupping was lowest in group 3 (6% vs 28%, 18%, 16%, $P = 0.000$) and the incidence of body movement was also lowest in group 3 (8% vs 50%, 28%, 30%, $P = 0.000$), compared with the other three groups, as presented in **Table 3**.

The endoscopist satisfaction scores in group 3 were higher than the other groups, otherwise the patients' satisfaction of the other three groups was higher than it was in the placebo group ($P = 0.000$) and it was higher in group 3 than group 4 (4.9 ± 0.3 vs 4.7 ± 0.5, $P = 0.031$). In addition, the injection pain score of the placebo group was higher than the other groups ($P = 0.000$) and the scores in groups 2 and 3 were lower than those in group 4 (0.2 ± 0.4 vs 0.45 ± 0.73, 0.16 ± 0.42 vs 0.45 ± 0.73, $P < 0.05$), as shown in **Figure 6**. The difference of the RASS scores scored according to **Table 4** at the seven time points among the four groups is of no statistical significance, as shown in **Figure 7**.

Discussion

This study aimed to evaluate the potential benefits of butorphanol for patients undergoing an endoscopy screening with TCI of propofol and the superiority of butorphanol to sufentanil. The results revealed that compared with the placebo, premedication with butorphanol and sufentanil have no obvious effect on hemo-

with the other three groups, RR is the lowest in the sufentanil group at the time of the end of induction and the time of gastroscope insertion as presented in **Figure 4**. Durations of esophagogastroduodenoscopy and the colo-
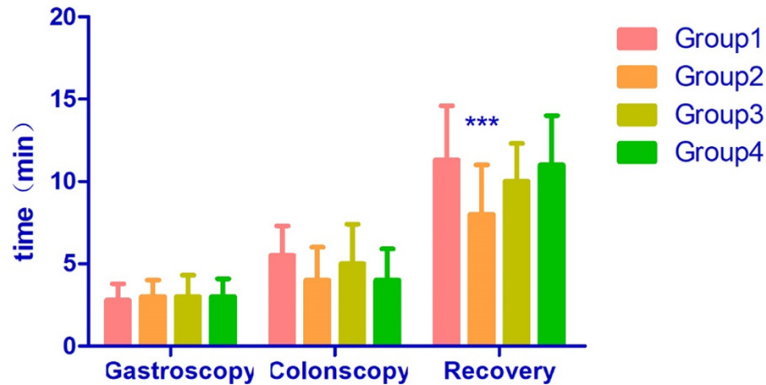
Figure 5. The operating time and recovery time of the four groups. Compared Group 2 with other three groups, ***P < 0.001.

Table 3. The incidence of bucking/hiccupping and body movement

Groups	Bucking/hiccupping	Body movement
Group 1	28%	50%
Group 2	18%	28%
Group 3	6%***	8%***
Group 4	16%	30%

Group 3 vs one of other three groups ***P < 0.001.

dynamic stability. However, premedication with 10 μg/kg butorphanol can reduce propofol requirements compared to the other groups. In addition, premedication with 5 μg/kg butorphanol can shorten recovery time, compared with other three groups. Premedication with either butorphanol or sufentanil improves the satisfaction scores of endoscopists and patients, and the satisfaction scores of patients were significantly higher in the 10 ug/kg butorphanol group than they were in the sufentanil group. In addition, the incidence of bucking/hiccupping which is a risk factor of aspiration was lowest in 10 μg/kg butorphanol group. The injection pain scores were lower in the butorphanol group and the sufentanil group, compared with the placebo group, which is consistent with the conclusion drawn by Singh [10], and the analgesic effect of butorphanol on propofol injection pain was better than sufentanil.

In this study, the selection of the TCI of propofol as the anesthetic method related to which target-controlled infusion (TCI) system is used in anesthetic practice as an automatically adjusted system to achieve and maintain a target anesthetic blood concentration based on a pharmacokinetics model [11]. And the TCI system can effectively avoid the adverse effects

caused by fluctuations of anesthetic blood concentration. The TCI of propofol has been demonstrated to be safe and effective for sedation during endoscopy [11-13].

Given the results of our previous research [14] and our pilot trial, we set the effect-site concentration of TCI of propofol as 3.5 ug/ml and compared the difference between premedication with an intravenous 0.05 μg/kg sufentanil and butorphanol .

Butorphanol is a μ receptor agonist-antagonist and κ receptor agonist [15]. It can be used as an anesthesia premedication for sedation [16]. The incidence of respiratory depression and pruritus is lower than typical μ receptor opioid agents like morphine or fentanyl. Even the effect of butorphanol decreasing the pruritus incidence of morphine is demonstrated [17]. However, the pruritus incidence difference between the four groups in our study was of no statistical significance. This could be because of the low dose of butorphanol and sufentanil used and the small sample size. In this study, the respiratory rate was lowest in the sufentanil group among the four groups, which is similar to previous studies. But there was no obvious respiratory depression because the dosage of sufentanil used in the study was low. The analgesic effect and recovery time of intravenous 20 ug/kg butorphanol was similar with 2 ug/kg intravenous fentanyl [18]. In our study, compared with intravenous 0.05 μg/kg sufentanil, the recovery time in the intravenous 5 μg/kg butorphanol group was shorter, but the time in the intravenous 10 μg/kg butorphanol group was similar. The result may be explained by different doses. 5 μg/kg butorphanol can take a sedative effect but it doesn't influence recovery time, otherwise the sedative effect of 10 μg/kg butorphanol could be much more beneficial. The incidence of bucking/hiccupping was lowest in the 10 μg/kg butorphanol group, and this may be explained by the antitussive properties [9] and the sufficient sedation effect.

There are some limitations in this study, (i) This is a single-center research. (ii) The sample size was not sufficient to show the statistically significant difference in the adverse effects such
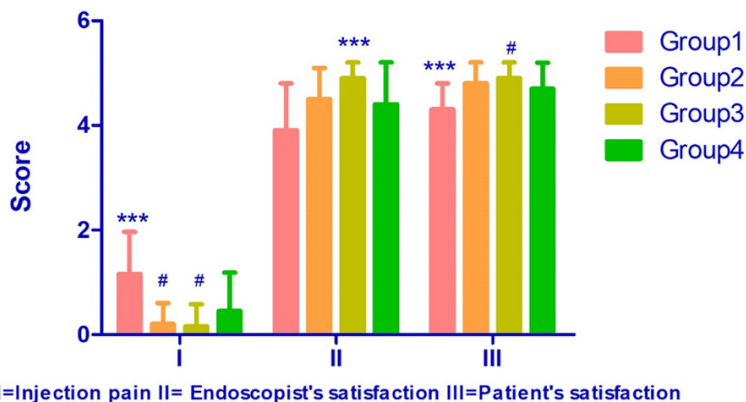
Figure 6. The injection pain score, and the endoscopists' and patients' satisfaction scores in the four groups. Compared with other three groups, in I, II, III, ***P < 0.001; Compared group 2, 3 with group 4, in I, #P < 0.05. Compared group 3 with group 4, in III, #P < 0.05.

Table 4. Ramsay scale for the assessment of the level of sedation
Levels Response

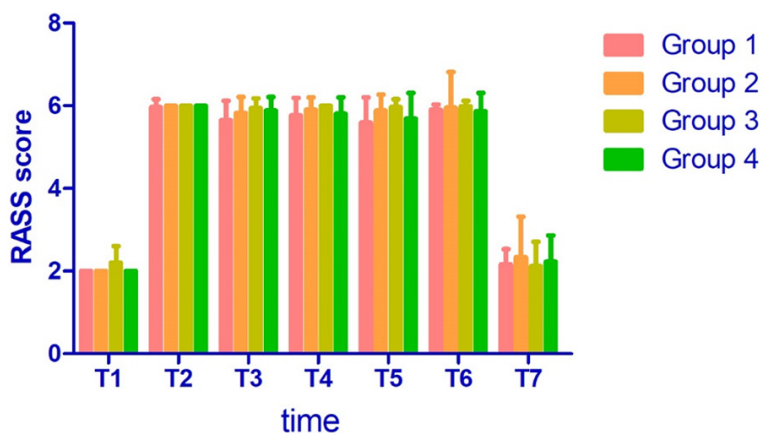| 1	Patient anxious, agitated, restless
2	Patient cooperative, oriented, tranquil
3	Patient responds to commands only
4	Brisk response to light glabellar tap or auditory stimulus
5	Sluggish response to light glabellar tap or auditory stimulus
6	No response to the stimulus mentioned in items 4 and 5

Figure 7. The RASS score at seven time points in the four groups. There was no significant different among the groups.

as respiratory depression and pruritus. (iii) The recovery time of patients was recorded, but the endoscopic center discharge time of patients was not recorded.

In conclusion, premedication with butorphanol may offer more benefits in gastrointestinal endoscopy screening with TCI propofol sedation, compared with sufentanil and premedication with 10 ug/kg butorphanol, maybe much better.

Disclosure of conflict of interest

None.

Abbreviations

ASA, American Society of Anesthesiologists; BP, Blood pressure; ECG, Electrocardiogram; HR, Heart rate; PACU, Post-anesthesia care unit; RR, Respiratory rate; SpO2, Pulse oximetry; MAP, Mean arterial pressure; D-Value, The difference of value; TCI, Target-controlled infusion; BMI, Body mass index.

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