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# Effect of butorphanol on visceral pain in patients undergoing gastrointestinal endoscopy: a randomized controlled trial

Jing Wang<sup>1,2†</sup>, Xinyan Wang<sup>1†</sup>, Haiyang Liu<sup>1</sup> and Ruquan Han<sup>1\*</sup>

## Abstract

**Background** Butorphanol slightly influences the respiratory and circulatory systems, has a better effect on relieving the discomfort caused by mechanical traction, and has a low incidence of postoperative nausea and vomiting (PONV). Combined butorphanol and propofol may suppress postoperative visceral pain, which is avoidable in gastrointestinal endoscopy. Thus, we hypothesized that butorphanol could decrease the incidence of postoperative visceral pain in patients undergoing gastroscopy and colonoscopy.

**Methods** This was a randomized, placebo-controlled, and double-blinded trial. Patients undergoing gastrointestinal endoscopy were randomized to intravenously receive either butorphanol (Group I) or normal saline (Group II). The primary outcome was visceral pain after the procedure 10 min after recovery. The secondary outcomes included the rate of safety outcomes and adverse events. Postoperative visceral pain was defined as a visual analog scale (VAS) score  $\geq 1$ .

**Results** A total of 206 patients were enrolled in the trial. Ultimately, 203 patients were randomly assigned to Group I ( $n = 102$ ) or Group II ( $n = 101$ ). In total, 194 patients were included in the analysis: 95 in Group I and 99 in Group II. The incidence of visceral pain at 10 min after recovery was found to be statistically lower with butorphanol than with the placebo (31.5% vs. 68.5%, respectively; RR: 2.738, 95% CI [1.409–5.319],  $P = 0.002$ ), and the notable difference was in pain level or distribution of visceral pain ( $P = 0.006$ ).

**Conclusions** The trial indicated that adding butorphanol to propofol results in a lower incidence of visceral pain after surgery without noticeable fluctuations in circulatory and respiratory functions for gastrointestinal endoscopy patients.

**Trial registration** Clinicaltrials.gov NCT04477733 (PI: Ruquan Han; date of registration: 20/07/2020).

**Keywords** Butorphanol, Visceral pain, Propofol, Gastroscopy, Colonoscopy

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## Background

More than two million people die of gastrointestinal cancer, accounting for approximately 60% of new cases, based on Global Cancer Statistics 2018 [1]. Gastrointestinal endoscopy is the most popular measure to screen and diagnose gastrointestinal cancer [2]. A recent study showed that the incidence of moderate or severe abdominal pain after colonoscopy was 16.7% (601 of 3611) in participants examined with standard air insufflation [3]. More people prefer painless endoscopy for more comfortable medical experiences and patient safety.

Propofol is widely used in endoscopy due to its fast onset of action, short action time, and quick and complete postoperative recovery [4–6]. However, the use of propofol alone varies, and increasing the dose causes circulatory and respiratory depression related to the infusion dose and rate [6, 7]. Therefore, the combination of propofol and low-dose opioids has been promoted to reduce propofol consumption and adverse effects [8, 9].

Butorphanol is a mixed opioid receptor agonist and antagonist that acts on  $\kappa$  receptors [10]. It has a faster onset through intravenous injection, a lower risk of addiction with a single dose, and a more prolonged analgesic effect [11]. Butorphanol also slightly influences the respiratory and circulatory systems, has a better impact on relieving the discomfort caused by mechanical traction, and has a low incidence of postoperative nausea and vomiting (PONV) [11–14]. These advantages make it more suitable for painless gastrointestinal endoscopy. However, sedation can also cause dizziness, drowsiness, and other adverse reactions during recovery [15].

In this randomized controlled study, we intended to confirm that butorphanol can significantly improve postoperative visceral pain, reduce the dosage of propofol needed and improve quality in patients undergoing gastroscopy and colonoscopy.

## Methods

### Study design and participants

This dual-center, randomized, placebo-controlled study was conducted at Beijing Tiantan Hospital, Capital Medical University, and Beijing Daxing People's Hospital between August 14th, 2020, and September 30th, 2021. This study was approved by the China Ethics Committee of Registering Clinical Trials (Registration number: ChiECRCT20200200) and registered at Clinicaltrials.gov (NCT04477733, 20/07/2020) in July 2020. All patients or their legal representatives provided written informed consent. The study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

We recruited adult patients aged 18 to 65 with an American Society of Anesthesiologists physical status from I to III who underwent colonoscopy or gastroscopy.

The exclusion criteria included patients with a body mass index  $> 30 \text{ kg/m}^2$ , a history of depression, opioid dependence, poorly controlled hypertension (systolic blood pressure  $> 180 \text{ mmHg}$ ), myocardial infarction, severe liver disease, and significant abdominal pain before surgery; patients with sensory system or language dysfunctions who could not cooperate to complete the scale; and pregnant women.

### Blinding and randomization

Patients were randomly assigned to receive butorphanol (Group I) or normal saline (Group II) in a 1:1 ratio based on computer-generated stratified randomization numbers. The random numbers were sealed in separate opaque envelopes until the analysis was complete. Patients in Group I received  $10 \mu\text{g/kg}$  butorphanol intravenously 3 min before the intravenous injection of propofol. The patients assigned to Group II received an identical volume of normal saline at the same infusion rate.

The investigators did not participate in other processes while preparing the research solution. A designated staff prepared the solution, enclosed in a dark syringe (volume: 5 ml) labeled "study solution." The two solutions seemed identical. Randomization was blinded to the participants, chief anesthesiologists, and outcome assessors.

### Perioperative management

The regimens were standardized in both groups. Patients were deprived of water for 2 h and fasted for 8 h before surgery. Based on the requirements of anesthesia and surgery, venous access (central vein of the upper limb) was established. As perioperative fasting and bowel preparation are believed to cause intravascular hypovolemia, preemptive intravenous fluid was infused with  $10\text{--}15 \text{ ml/kg}$  normal saline. Standard intraoperative monitoring, which included electrocardiogram (ECG), heart rate (HR), blood pressure (BP), respiratory rate (RR), and pulse oxygen saturation ( $\text{SpO}_2$ ), was applied. Preinduction medication was not administered. The patient received preoxygenation with a mask filled with 100% oxygen ( $4\text{--}6 \text{ L/min}$ ) for at least  $3\text{--}5 \text{ min}$  before induction. The induction of anesthesia was performed with  $1.5\text{--}2 \text{ mg/kg}$  propofol as a bolus infused slowly ( $60 \text{ to } 120 \text{ s}$ ) until the eyelash reflex disappeared. When the vital signs were stable, an endoscopic examination was started. If there was a body movement reaction during the examination, a dose of  $0.5\text{--}1 \text{ mg/kg}$  propofol was added. Moreover, the mean arterial pressure (MAP) and HR were maintained within  $\pm 20\%$  of the values before anesthesia induction during the procedure with vasoactive drugs

such as dopamine and atropine. After the procedure, the patients were transferred to the postanesthetic care unit (PACU) and followed up regularly for any adverse events for at least 30 min. If the pain persisted after 30 min, regardless of the patient’s assigned group (Group I or Group II), a single dose (0.01 µg/kg) of sufentanil was given, and the patients could leave the PACU after the pain was relieved.

**Data collection and outcomes**

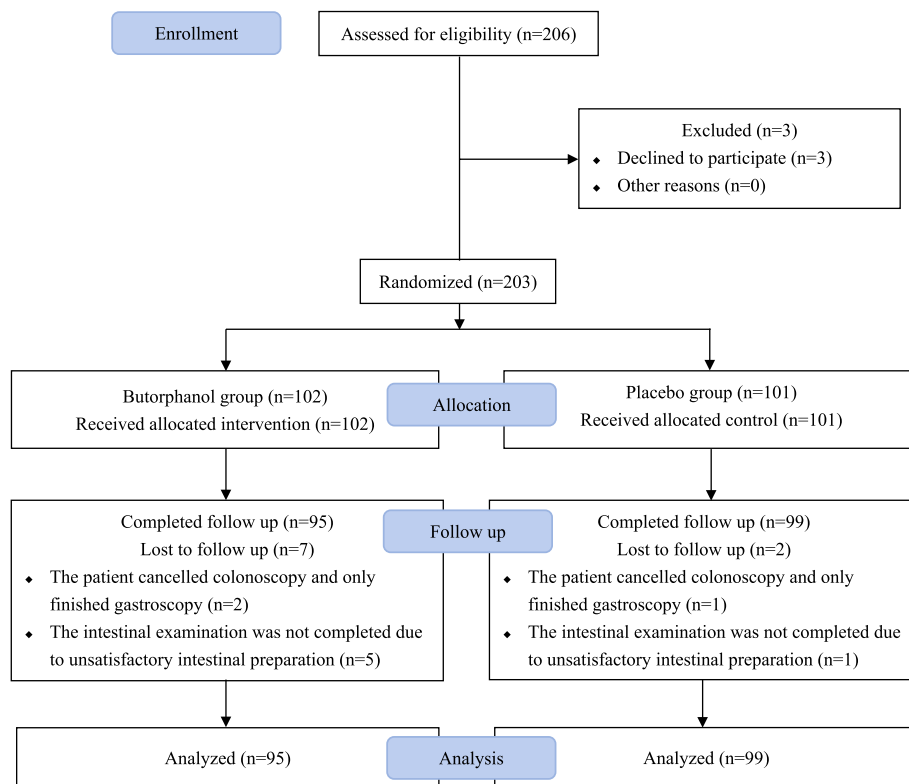
Baseline data were recorded, such as age, sex, height, weight, body mass index, ASA physical status, and type of operation. The MAP, HR, RR, and SpO<sub>2</sub> of the patients were recorded at seven time points: T0, at admission; T1, before anesthesia; T2, 5 min after propofol administration; T3, at the end of the operation; T4, after 5 min in the PACU; T5, after 10 min in the PACU; and T6, after 30 min in the PACU.

The primary outcome was the incidence of visceral pain after the procedure. Because there is no universal scale for quantifying visceral pain, we defined a visual analog scale (VAS) score of ≥ 10 min after recovery as visceral pain. The secondary outcomes were visceral pain at 20 and 30 min after recovery, propofol consumption, the incidence of injection pain caused by propofol, episodes of hypotension (defined as an MAP less than 60 mmHg

or 30% of the values before the induction of anesthesia) or bradycardia (defined as an HR less than 60 bpm), the operation time, the recovery time, and the adverse events at 24 h after recovery, such as fatigue, nausea or vomiting, abdominal bloating, dizziness or headache, hypoxemia (blood oxygen saturation below 90% for more than a minute or requiring any airway intervention), and involuntary body movement.

**Sample size calculation**

We used PASS software to calculate the necessary sample size for this study. A cohort study reported that 45% of participants (124 of 277) undergoing colonoscopy and gastroscopy complained of pain during follow-up [16]. The incidence of pain after colonoscopy was higher in two other randomized controlled studies, at 47.8% and 51%, respectively [17, 18]. In our pretrial test, the incidence of visceral pain after colonoscopy or gastroscopy was 54%. Combining all the above data, we estimated that the incidence of pain in Group II was 50%, with a 20% reduction in Group I. Thus, 186 people were included in this trial (power = 80%, and α = 0.05). The ratio of the two sets of samples was 1:1. Considering an overall withdrawal rate of 10%, the sample size was estimated to be 206 patients (103 patients per group).



**Fig. 1** CONSORT flow diagram. CONSORT: Consolidated Standards of Reporting Trials

**Table 1** Demographic and clinical features (median and interquartile range, mean and standard deviation, or number and percentage)

| Characteristics         | Group I: Butorphanol (n = 95) | Group II: Normal Saline (n = 99) | Sig   |
|-------------------------|-------------------------------|----------------------------------|-------|
| Age(years)              | 49(23–67)                     | 49(26–65)                        | 0.727 |
| Gender(male/female)     | 43/53                         | 50/49                            | 0.465 |
| Height(cm)              | 167(9)                        | 166(8)                           | 0.898 |
| Weight(kg)              | 68(12)                        | 66(12)                           | 0.248 |
| BMI(kg/m <sup>2</sup> ) | 24.5(3.3)                     | 24.8(3.0)                        | 0.109 |
| Smoking history(%)      | 26(27.4)                      | 34(34.3)                         | 0.293 |
| Drinking history(%)     | 38(40.0)                      | 43(43.4)                         | 0.628 |
| Hypertension(%)         | 31(32.6)                      | 20(20.2)                         | 0.049 |
| Diabetes mellitus(%)    | 9(9.5)                        | 7(7.1)                           | 0.543 |
| Hyperlipemia(%)         | 20(21.1)                      | 17(17.2)                         | 0.492 |
| Heart disorders(%)      | 3(3.2)                        | 5(5.1)                           | 0.508 |
| Coronary heart disease  | 1(1.1)                        | 2(2.0)                           |       |
| Heart valve disease     | 1(1.0)                        | 0(0)                             |       |
| Arrhythmia              | 0(0)                          | 2(2.0)                           |       |
| ASA physical status     |                               |                                  |       |
| I                       | 67                            | 66                               | 0.563 |
| II                      | 28                            | 33                               |       |
| Type of operations      |                               |                                  |       |
| Total                   | 95                            | 99                               | 0.886 |
| Colonoscopy             | 47                            | 48                               |       |
| Gastro-colonoscopy      | 50                            | 49                               |       |

BMI body mass index, ASA American Society of Anesthesiologists

### Statistical analysis

The data were analyzed using SPSS 26.0, and the figures were created by GraphPad Prism 9.0. All analyses were based on the intention-to-treat (ITT) principle. The Kolmogorov–Smirnov test was used to analyze continuous outcomes to judge the normality of their distributions. Normally distributed continuous variables were summarized as the mean value  $\pm$  standard deviation and were compared using independent t tests. Skewed continuous variables were summarized as the median value and interquartile range and were compared using the Mann–Whitney U test. As appropriate, categorical variables were summarized as the number and percentage and compared using the chi-square or Fisher's exact test. The primary endpoint was the incidence of visceral pain in the recovery room, and the chi-square test was used to compare the differences between the two groups. The risk ratios and 95% confidence intervals were reported for the primary and secondary outcomes. MAP, HR, RR, and SpO<sub>2</sub> were compared four times between the groups at T0, T1, T2, and T3 using a two-sample Student's t test. Bonferroni correction was used to justify the P values for these three variables, and an  $\alpha$  level of 0.0125 was considered statistically significant. Moreover, an  $\alpha$  level of 0.05 was considered statistically significant for the remaining variables.

### Results

#### Patient demographics and perioperative characteristics

In the ITT population, 206 patients were consecutively enrolled at two hospitals between August 14th, 2020,

**Table 2** Comparison of efficacy and safety outcomes (median and interquartile range or frequency and percentage)

|  | Group I: Propofol and Butorphanol (n = 95) | Group II: Propofol and Saline (n = 99) | RR (95%CI)          | P     |
|--|--|--|---------------------|-------|
| Primary outcome(%)                     |  |  |                     |       |
| Visceral pain at 10 min after recovery | 17 (31.5)                                  | 37(68.5)                               | 2.738(1.409–5.319)  | 0.002 |
| Pain level at 10 min after recovery(%) |  |  | NA                  | 0.006 |
| No pain (0)                            | 78(82.1)                                   | 62(62.6)                               |                     |       |
| mild pain (1–3)                        | 13(13.7)                                   | 32(32.3)                               |                     |       |
| moderate pain (4–6)                    | 4(4.2)                                     | 5(5.1)                                 |                     |       |
| severe pain (7–10)                     | 0(0)                                       | 0(0)                                   |                     |       |
| Secondary outcome                      |  |  |                     |       |
| Visceral pain at 20 min after recovery | 25(38.5)                                   | 40(61.5)                               | 1.898(1.033–3.487)  | 0.038 |
| Visceral pain at 30 min after recovery | 22(37.9)                                   | 36 (62.1)                              | 1.896(1.011–3.555)  | 0.045 |
| Propofol consumption (mg)              | 200(170–280)                               | 250(200–320)                           | NA                  | 0.007 |
| Hypotension (%)                        | 48(50.5)                                   | 44(44.4)                               | 0.783(0.445– 1.378) | 0.396 |
| Bradycardia (%)                        | 1(1.1)                                     | 0(0)                                   | 0.487(0.421– 0.563) | 0.984 |
| Incidence of injection pain (%)        | 7(7.4)                                     | 12(12.1)                               | 1.734(0.652– 4.611) | 0.266 |
| Operation time(min)                    | 15(12–21)                                  | 16(10–25)                              | NA                  | 0.331 |
| Recovery time (min)                    | 25(18–30)                                  | 30(19–30)                              | NA                  | 0.417 |

and September 30th, 2021. Eventually, 203 patients were randomly assigned to Group I ( $n=102$ ) or Group II ( $n=101$ ). At the primary time point, nine patients were lost to follow-up. A total of 194 patients in the two groups completed the study (Fig. 1). The data from all 194 patients were included in the analysis. The demographics, baseline assessment, and intraoperative details were similar between the two groups and are presented in Table 1.

**Visceral pain**

The incidence of visceral pain at 10 min after recovery was significantly lower with butorphanol (31.5% vs. 68.5%, respectively; RR: 2.738, 95% CI [1.409–5.319],  $\chi^2=9.157$ ,  $P=0.002$ ; see Table 2). The significant difference in Fig. 2 and Table 2 shows the pain level and distribution of visceral pain ( $P=0.006$ ).

The incidence of visceral pain at 20 and 30 min after recovery showed a similar change (Fig. 2, Table 2). Butorphanol infusion allowed for an apparent reduction in propofol consumption (200 vs. 250, respectively;  $Z=-2.720$ ,  $P=0.007$ ), which was more pronounced in patients undergoing colonoscopy than in those undergoing gastro-colonoscopy ( $Z=-6.999$ ,  $P<0.001$ ; Online Resource 1). This may be because of the prolonged

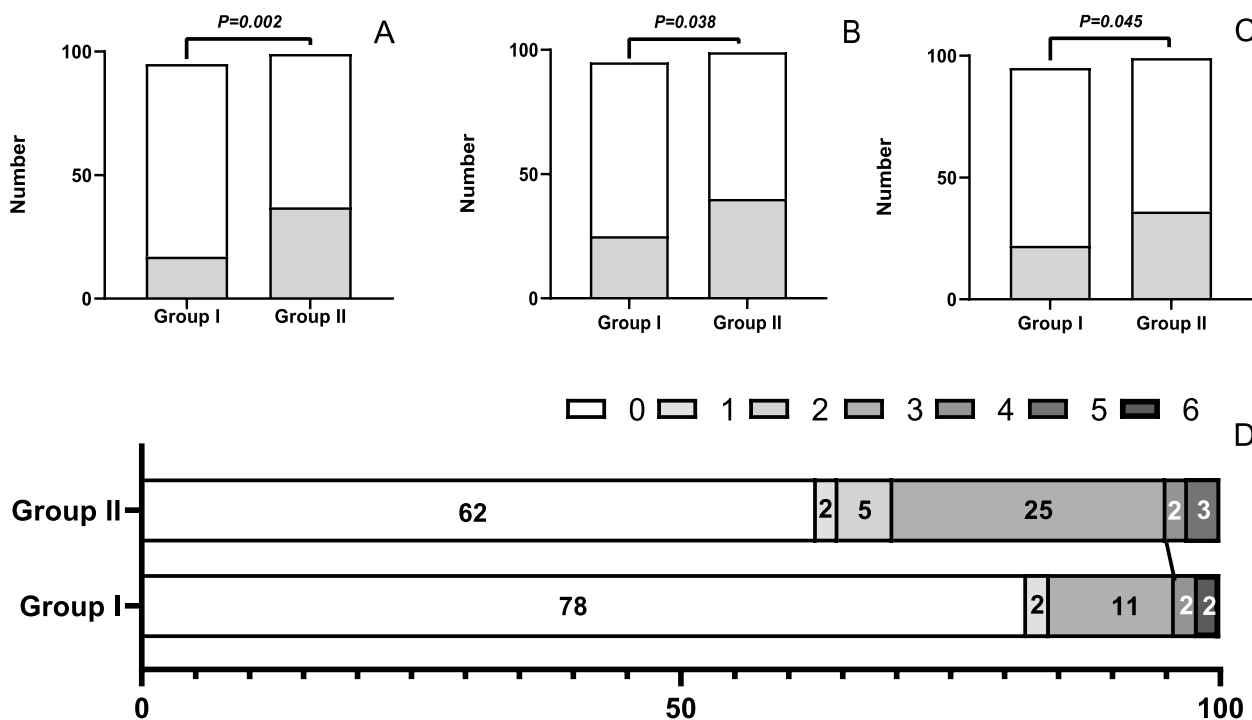
operation time in gastro-colonoscopy ( $Z=-3.095$ ,  $P=0.002$ ; Online Resource 2). However, there were no significant differences in episodes of bradycardia or hypotension, operation time, recovery time, or incidence of injection pain between the two groups ( $P>0.05$ , Table 2).

Perioperative monitoring parameters (MAP, SpO<sub>2</sub> and RR).

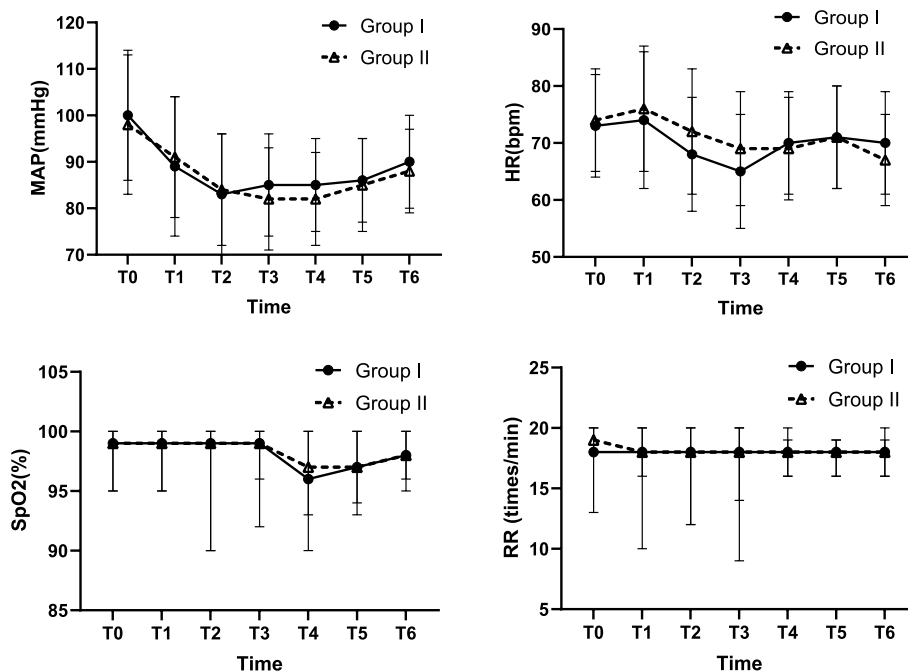
The MAP, SpO<sub>2</sub>, and RR were not significantly different between the two groups of patients at the seven time points. Only after 5 min of propofol administration (T2,  $t=-2.716$ ,  $P=0.007$ ) and at the end of the operation (T3,  $t=-2.261$ ,  $P=0.025$ ) was the HR of Group I slightly lower than that of Group II, and the other time points were significantly different (Fig. 3).

**Adverse events.**

Only one patient in the butorphanol group developed fatigue during the operation and recovery room. After 24 h of recovery in the butorphanol group, the number of people with nausea or vomiting, abdominal bloating, dizziness, or headache was 2, 7, and 5, respectively. In Group II, only seven people had abdominal pain and bloating. No cases of hypoxemia or body movements were reported. There were no significant differences between the two groups in adverse events ( $\chi^2=4.345$ ,  $P=0.182$ ).



**Fig. 2** Incidence of visceral pain recovery at 10 (A), 20 (B), and 30 min (C) and distribution of visceral pain scores at 10 min (D). Data are frequency. Group I: Propofol and Butorphanol; Group II: Propofol and Saline. Visceral pain was defined as  $\geq 1$  of the visual analog score (VAS). The incidence of visceral pain at 10 min in the recovery room was found to be significantly lower in Group I than in Group II (propofol and butorphanol vs. propofol and saline, respectively;  $\chi^2=9.157$ ,  $P=0.002$ , RR: 2.738, 95% CI [1.409- 5.319]). The white bar indicates patients with VAS 0, and the black bar indicates patients with more than VAS 1



**Fig. 3** Changes in MAP, HR, SpO<sub>2</sub>, and RR. MAP, HR: Normal distribution, mean, and SD. SpO<sub>2</sub>, RR: Nonnormal distribution, median, and upper/lower limit. T0, at admission; T1, before anesthesia; T2, 5 min after propofol administration; T3, at the end of the operation; T4, 5 min in the PACU; T5, 10 min after recovery; T6, 30 min after recovery. Only after the administration (T2,  $t = -2.716$ ,  $P = 0.007$ ) and the end of the operation (T3,  $t = -2.261$ ,  $P = 0.025$ ) was the HR of Group I slightly lower than that of Group II, and the other time points were not significantly different

## Discussion

This study demonstrates that butorphanol results in a statistically lower incidence of visceral pain after surgery and reduced propofol consumption for gastrointestinal endoscopy without noticeable fluctuations in circulatory and respiratory functions. Intravenous butorphanol neither prolongs recovery time nor increases adverse events.

First, we selected 10  $\mu\text{g}/\text{kg}$  butorphanol as the administration dosage in this study. One reason is that the patients had minimal discomfort at this dose in our pretest. The other is that 9.07  $\mu\text{g}/\text{kg}$  of butorphanol was more effective than sufentanil for gastrointestinal endoscopy sedation and notably reduced the recovery time [19]. However, Lv Sun and colleagues found that compared with other dosages of butorphanol (2.5, 5, or 10  $\mu\text{g}/\text{kg}$ ), intravenous preinjection of 7.5  $\mu\text{g}/\text{kg}$  of butorphanol with propofol had the lowest incidence of body movement, drowsiness, and dizziness [20]. A 7.5  $\mu\text{g}/\text{kg}$  dosage of butorphanol can be optimal for gastroscopy and colonoscopy patients. The difference may come from the sample size and clinicians.

The incidence of visceral pain was significantly lower in the butorphanol group at 10, 20, and 30 min after recovery. This is consistent with most previous studies [21, 22].

Butorphanol infusion allowed for a noticeable reduction in propofol consumption, which was more

pronounced in colonoscopy than in gastro-colonoscopy. This may be because of the prolonged operation time in gastro-colonoscopy. Forster and colleagues found similar outcomes for lidocaine: lidocaine resulted in a 50% reduction in propofol dose requirements during colonoscopy and significantly lower postcolonoscopy pain and fatigue [23]. Propofol-based combination therapy reduces propofol consumption, resulting in fewer cardiopulmonary complications and improving anesthesia safety [23]. However, the incidence of propofol-related injection pain was not significantly different, which is inconsistent with previous studies [20, 24]. We may have selected a higher drug dose, or the sample size needed to be increased.

The incidence of hypoxemia was between 8.2% and 15% [20, 25], but we did not observe any cases of hypoxemia. The incidence of other adverse events was extremely low. Only one patient had fatigue; two patients had nausea or vomiting; fourteen had abdominal pain or bloating; and five had dizziness or headache. This was mainly because of our strict monitoring and perfect operation perioperative management in the clinical process. At the same time, there was no difference in the operation time, recovery time, or incidence of injection pain between the groups in our study. There was no clear distinction between the MAP and SpO<sub>2</sub>. RR or HR was found during the procedure. All these reasons prove the safety of butorphanol.

Our study should be interpreted with several limitations. As mentioned earlier, the high dosage of butorphanol (10 µg/kg) makes it difficult to find significant differences in the incidence of complications. We should conduct more research on the dosage of butorphanol. Finally, we recorded the total propofol consumption, so it is unclear which stage (the induction of sedation or during the infusion of study medications) caused the increase in the propofol dosage.

In conclusion, butorphanol decreases the incidence of visceral pain and propofol consumption for gastrointestinal endoscopy with minimal fluctuations in circulatory and respiratory functions. However, the rate of adverse events and recovery time did not differ significantly after the use of butorphanol. The clinical application needs to be weighed according to the actual situation of the patients.

#### Abbreviations

|                  |                                   |
|------------------|-----------------------------------|
| PONV             | Postoperative nausea and vomiting |
| VAS              | Visual analog score               |
| ECG              | Electrocardiogram                 |
| HR               | Heart rate                        |
| BP               | Blood pressure                    |
| RR               | Respiratory rate                  |
| SpO <sub>2</sub> | Pulse oxygen saturation           |
| MAP              | Mean arterial pressure            |
| PACU             | Postanesthetic care unit          |
| ITT              | Intention to treat                |

#### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12871-023-02053-9>.

Additional file 1.

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Not Applicable.

#### Authors' contributions

Each author's individual contributions to the manuscript are as follows: HL, RH: Conceptualization and design. JW, HL: Investigation. XW: Writing - Original draft of the manuscript and statistical analysis. HL, RH: Writing - Review & Editing. XW, HL and RH had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JW and XW contributed equally to this work. All authors read and approved the final manuscript.

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#### Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to institutional restrictions but are available from the corresponding author on reasonable request.

#### Declarations

##### Ethics approval and consent to participate

This study was approved by the China Ethics Committee of Registering Clinical Trials (Registration number: ChiECRCT20200200) and registered at Clinicaltrials.

gov (NCT04477733). The study protocol followed the CONSORT guidelines. The study protocol was performed according to the relevant guidelines. Written informed consent was obtained from all patients.

##### Consent for publication

Not Applicable.

##### Competing interests

The authors declare no competing interests.

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