Comparison of ED95 of Butorphanol with Sufentanil for Gastrointestinal Endoscopy Sedation: a randomized controlled trial

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Abstract

Background: Butorphanol, a synthetic opioid partial agonist analgesic, has been widely used for the control of perioperative pain. However, the ideal dose and availability of butorphanol for gastrointestinal (GI) endoscopy are not well known. The aim of this study was to evaluate the 95% effective dose (ED95) of butorphanol and sufentanil in GI endoscopy and compared their clinical efficacy, especially the recovery time.

Methods: The study was divided into two parts. For the first part, voluntary patients who needed GI endoscopy anesthesia were recruited to measure the ED95 of butorphanol and sufentanil when they reached successful sedation during GI endoscopy using the sequential method (the Dixon up-and-down method). In the second part, this was a double-blind, randomized study. Two hundred cases of painless GI endoscopy patients were randomly divided into two groups (n=100), including group B (butorphanol at the ED95 dose) and group S (sufentanil at the ED95 dose). Propofol was infused intravenously to both groups as the sedative. The recovery time, VAS (visual analogue scale) score, hand grip strength, fatigue severity scores, incidence of nausea and vomiting, and incidence of dizziness were recorded.

Results: The ED95 of butorphanol in painless GI endoscopy was 9.07 μ g/kg (95% confidence interval: 7.81-19.66 μ g/kg). The ED95 of sufentanil was 0.1 μ g/kg (95% CI, 0.079-0.422 μ g/kg). Both butorphanol and sufentanil provided a good analgesic effect in GI endoscopy. However, the recovery time for butorphanol was significantly shorter than sufentanil ($P<0.05$, group B versus group S: 21.26 $\pm$ 7.70 vs. 24.03 $\pm$ 7.80, min).

Conclusions: Butorphanol at 9.07 μ g/kg showed a better effect compared with sufentanil in GI endoscopy sedation, notably reduced the recovery time.

Background

The morbidity of gastric and intestinal cancer is ranked in second and fifth of cancer in China, respectively [1]. The GI (gastrointestinal) examination has been used as a standard method for the diagnosis of esophagus, gastroduodenal, and colorectal disease. However, unbearable abdominal pain can be caused by the distension and traction of viscera during GI endoscopy, which finally results in poor observation conditions and severe arrhythmia [2]. At the present stage, sedative drugs combined with analgesics are usually used to alleviate the pain and nervousness in GI endoscopy.

Nowadays, Opioid μ receptor agonists are the leading analgesics, such as sufentanil and fentanyl. The stomach and intestine are mainly innervated by the sympathetic and parasympathetic nervous systems [3]. The kappa receptor agonist showed higher concentration in the spinal cord, thus relieving visceral pain [4]. Butorphanol is a kappa receptor agonist, which had advantages of light respiratory depression, stable hemodynamics, rapid onset, and moderate effective duration [5], which may be more suitable for intraoperative and postoperative analgesia in painless GI endoscopy.

The analgesic effect of butorphanol is more effective than morphine, while its respiratory depression is only 1/5 of morphine [6]. Nowadays, butorphanol can be safely applied to maternal analgesia, especially for pregnant women with pre-eclampsia and chronic hypertension, which did not cause severe blood pressure fluctuations [7]. Butorphanol was also used in outpatient undergoing laparoscopic tubal sterilization at the early stage [8], while the analgesic dose has not been standardized [9, 10]. It was essential to find an optimal dose for producing effect analgesia and reducing the side effects of butorphanol in outpatient sedation.

The objective of this study was to detect ED₅₀, ED₉₅, and 95% confidence interval of butorphanol by using the sequential method, and compared to the ED₉₅ dose of sufentanil to determine the feasibility and superiority of butorphanol in GI endoscopy.

Methods

This clinical study was approved by the Hospital Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University and was registered in the clinical trial registration center of China (ChiCTR1900022780). Informed consent was obtained from all individual participants included in the study. This study adhered to CONSORT guidelines.

This study was based on medical records of ASA I-II patients aged 18 to 65 who underwent an outpatient GI endoscopy (diagnostic esophagogastroduodenoscopy and colonoscopy, without therapeutic procedures) and requiring anesthesia in endoscopy center from May to July of 2019, and an operation time within 30 min. Patients were excluded from the study based on the following criterion: not willing or unable to finish the whole study, acute upper respiratory tract infections, hepatitis, and renal failure, habitual sedative or analgesic use, analgesic use for acute pain, chronic fatigue syndrome, low potassium, myasthenia gravis, psychiatric disease and allergy to butorphanol, sufentanil or propofol.

This study was divided into two parts: 1. determination of the ED₉₅ of butorphanol and sufentanil; 2. comparison of clinical efficacy of butorphanol with equivalent sufentanil.

ED₉₅ of butorphanol and sufentanil

All the patients were completed routine gastrointestinal preparation before endoscopy, fasting from solids for 8 hr and liquids for 2 hr before the operation. Anesthesia machine was inspected, and intravenous access was established. Standard monitoring was applied before the induction of anesthesia in the outpatient operating room, including non-invasive blood pressure (BP), electrocardiogram (ECG), and oxygen saturation (SpO₂), and the patients were placed in the left lateral position. All the patients received supplemental oxygen inhalation through nasal 3 L per minute and hold the facial mask by themselves.

Butorphanol (Batch number: 190411BP Jiangsu Hengrui Pharmaceutical Co, Ltd .) or sufentanil (Batch number: 3018511505 Yichang Humanwell Pharmaceutical Co, Ltd .) was slowly injected intravenously.

Given the 3 min onset time, propofol (Batch number: 1811236 Beijing Fresenius Kabi Pharmaceutical Co., Ltd.) was administered intravenously at a constant speed until the patient lost consciousness and dropped the hand-held mask, followed by a continuous intravenous infusion at a rate of $50\text{--}150\ \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Monitoring bispectral index (BIS Complete Monitoring System, Covidien.co), controlled BIS value between 50–60 by adjusting propofol speed; then, the endoscopy began (operated by the same gastroenterologist). If the patient showed “failure sedation” (definition of failure sedation: occurrence of gag reflex [11], coughing, or body movement during esophagogastroduodenoscopy, or body movement during colonoscopy) during the GI, additional propofol of 0.5-1 mg/kg was administered. Once the SpO_2 fell to 90%, assisted ventilation by a facial mask with oxygen was applied. If the heart rate was less than 45 beats per minute, atropine (0.5 mg) was applied. If the mean arterial pressure was less than 50 mmHg, ephedrine 5–10 mg was used. After surgery, the patients were transported to the PACU (postanesthesia care unit) to have a rest and recovery.

Dixon up-and-down method

The dose of butorphanol to each patient was determined by the Dixon up-and-down method [12]. According to geometric progression, the dose gradient was divided into 6 steps: 12.00 $\mu\text{g}/\text{kg}$, 10.00 $\mu\text{g}/\text{kg}$, 8.33 $\mu\text{g}/\text{kg}$, 6.94 $\mu\text{g}/\text{kg}$, 5.79 $\mu\text{g}/\text{kg}$, 4.82 $\mu\text{g}/\text{kg}$. In a preliminary experiment, the ED_{95} of butorphanol of “successful sedation” (definition of successful sedation: without gag reflex, coughing, or body movement in esophagogastroduodenoscopy and body movement in colonoscopy) with propofol in outpatient GI endoscopy was 9.8 $\mu\text{g}/\text{kg}$. So, the primal patient received a prescription dose of 10.00 $\mu\text{g}/\text{kg}$. The dose grade was increased or decreased by using the up-down method based on the failure or successful sedation in the previous patient. This process was repeated until there were nine cross-over pairs [13] (i.e., one successful sedation, followed by one failure sedation).

The dose of sufentanil to each patient was also determined by the Dixon up-and-down method. According to geometric progression, the dose gradient was divided into 6 steps: 0.12 $\mu\text{g}/\text{kg}$, 0.1 $\mu\text{g}/\text{kg}$, 0.083 $\mu\text{g}/\text{kg}$, 0.069 $\mu\text{g}/\text{kg}$, 0.058 $\mu\text{g}/\text{kg}$, 0.048 $\mu\text{g}/\text{kg}$. In a preliminary experiment, the ED_{95} of sufentanil of “successful sedation” with propofol in outpatient GI endoscopy was 0.085 $\mu\text{g}/\text{kg}$. So, the primal patient received a prescription dose of 0.083 $\mu\text{g}/\text{kg}$. The following process was also pretreated similarly to testing the ED_{95} of butorphanol.

Comparison with sufentanil

Groups. Two hundred cases of painless GI patients were recruited. The patients were randomly divided into two groups, including the butorphanol group (group B, $n = 100$) and the sufentanil group (group S, $n = 100$).

Anesthesia methods. In this part, this was a double-blind, randomized study. The patients were grouped according to the envelope method. The dispensing nurse dispensed the medicine to the anesthetist. The preoperative preparation and anesthesia methods were the same as in the first part performed by the

anesthetist. The ED₉₅ dose of butorphanol (9.07 µg/kg) was administered in group B. The ED₉₅ dose of sufentanil (0.1 µg/kg) was administered in group S. ED₉₅ dose of butorphanol and sufentanil were achieved in the first part. Postoperative indications in the PACU were evaluated and recorded by another postoperative observer who was blinded to the group division.

Efficacy measurements and variables. Our primary outcome in this study was the recovery time that represented the time between completion of the examination and departure from the PACU). The standard of leaving the hospital is our outpatient operation standard [14] (including vital signs, pain, orientation, dizziness, and walking). Secondary outcomes included the demographic and medical data, including the incidence of respiratory depression (respiratory rate < 10 beats/min or SpO₂ < 90% in nasal catheter oxygenation with 3 L/min), the incidence of circulatory inhibition (MAP < 50 mmHg or HR < 45 beats /min), dosage of propofol, the incidence of failed sedation, fatigue severity scores (assessed an 11-point (0–10) scale [15] 15 min after awakening time), VAS score of abdominal pain (15 min after awakening time), value of hand grip strength before and 15 min after operation (by an electronic hand dynamometer (EH101, Camry Co. Zhongshan, China)), the incidence of nausea and vomiting, and dizziness after awakening.

Statistical analysis.

SPSS statistical software (IBM Corporation, version 19) was used for statistical analysis. The median effective dose (ED₅₀) and ED₉₅ and the 95% confidence intervals (CI) of butorphanol and sufentanil were determined by binary regression (probit) [16].

The sample size of part two was evaluated by PASS 11.0. The primary indicator was recovery time. The pre-experimental measurement showed that the recovery time in the butorphanol group was 22.12 ± 7.9 min, and in the sufentanil group was 25.57 ± 8.1 min. A sample size of 93 in each group was determined to be required for a β value of 0.10 and an α value of 0.05. Considering the loss of data and the patients who could not be interviewed after endoscopy, 100 patients were selected in each group to ensure that the experiment had a large enough sample size.

Normally distributed data were analyzed with the Mean ± standard deviation, and a two independence sample t-test was used to evaluate the differences between the two groups in this condition. The non-parametric data were analysed using the median (Q1, Q3) or ratio, and a non-parametric test was used to evaluate the differences between the two groups in this condition. The rate comparison of complications was using a four-square table chi-square test. P-value < 0.05 was considered to indicate statistical significance.

Results

The data of 30 patients were screened for the first part of the study. One patient was excluded due to poor gastrointestinal preparation, thus the remaining 29 cases. The individual responses to butorphanol using Dixon's up-and-down method are shown in Fig. 1. The ED₅₀ of butorphanol in inhibiting body movement

during painless GI endoscopic was 6.58 µg/kg (95% CI, 5.57–7.49 µg / kg) and the ED₉₅ was 9.07 µg/kg (95% CI, 7.81–19.66 µg / kg). The data of 37 patients were screened for the second part of the study. The individual responses to sufentanil using Dixon's up-and-down method are shown in Fig. 2. The ED₅₀ of sufentanil in inhibiting body movement during painless GI endoscopic was 0.060 µg/kg (95% CI, 0.048–0.073 µg / kg) and the ED₉₅ was 0.100 µg/kg (95% CI, 0.079–0.422 µg / kg). No significant circulatory depression, respiratory depression occurred during the operation.

A total of 200 patients were recruited and completed in the second part of the study, and their data were analyzed to produce the final results (n = 100 per group). The characteristics of the enrolled subjects are shown in Table 1. There were no significant differences between the two groups regarding patient age-gender composition, SBP, heart rate, weight, height, BMI, GI endoscopy operation time, preoperative hand grip strength, and ASA grade composition (P > 0.05).

Table 1
General comparison between group S and group B

	S group(n = 100)	B group(n = 100)
Weight, kg	63 ± 11	64 ± 10
Sex(male, female)	(60,40)	(63,37)
SBP, mmHg	128 ± 15	130 ± 21
Heart rate, beats/min	69 ± 17	77 ± 13
Height, cm	165 ± 8	166 ± 8
BMI, kg/m ²	23.3 ± 3.0	23.4 ± 2.8
Operation time, min	14.4 ± 4.9	14.6 ± 4.9
Preoperative hand grip strength, kg	42.9 ± 9.5	44.4 ± 8.9
ASA classification,I/II	60/40	66/34
ASA, American Society of Anesthesiologists ASA physical status classification. Normally distributed statistics dates were mean ± SD, and a two independent sample t-test was used to evaluate the differences between the two groups. Sex and ASA classification were ratio and were compared by χ ² test. There were no significant differences between the two groups (P > 0.05).		

There was no statistically significant difference in the incidence of respiratory depression (P = 0.469), the incidence of circulatory inhibition (P = 0.489), the incidence of failure sedation (P = 0.352), propofol dosage (P = 0.171), and the incidence of dizziness (P = 0.205). Compared to group S, group B showed lower fatigue severity scores (P = 0.001) and better postoperative hand grip strength (P < 0.001). Furthermore, the recovery time for group B was significantly shorter than for group S (P = 0.012). The incidence of nausea and vomiting for group B was significantly lower than for group S (P = 0.014), as shown in Table 2.

Table 2
Comparison of the indicators between group S and group B.

	S group(n = 100)	B group(n = 100)	P value
Incidence of respiratory depression	11%	8%	0.469
Incidence of circulatory inhibition	12%	9%	0.489
Dosage of propofol,mg	222.6 ± 38.4	215.0 ± 39.7	0.171
Incidence of failed sedation	7%	4%	0.352
VAS score	2(1,3)	2(1,2)	0.001*
Fatigue severity scores	2.18 ± 1.30	1.66 ± 0.87	0.001*
Postoperative grip strength, kg	31.8 ± 6.8	35.5 ± 7.7	0.000*
Incidence of nausea and vomiting	7%	0	0.014*
Incidence of dizziness	6%	11%	0.205
Recovery time, min	24.03 ± 7.80	21.26 ± 7.70	0.012*
The VAS scores are the median (Q1, Q3). The Mann-Whitney U-test was used to evaluate the differences. Normally distributed statistics dates were mean ± SD, and a two independent sample t-test was used to evaluate the differences. Ratios were compared by χ^2 test.* P < 0.05			

Discussion

In our study, the ED₅₀ for inhibiting body movement of butorphanol in painless GI endoscopy was 6.58 µg/kg, (95%CI: 5.57–7.49 µg/kg) and the ED₉₅ was 9.07 µg/kg (95%CI: 7.81–19.66 µg/kg). The ED₅₀ for inhibiting body movement of sufentanil in painless GI endoscopy was 0.060 µg/kg (95% CI, 0.048–0.073 µg / kg) and the ED₉₅ was 0.100 µg/kg (95% CI, 0.079–0.422 µg / kg). In the second part of our study, the primary indicator (recovery time) in group B was significantly shorter than that in group S. Compared to group S, VAS score and fatigue severity score were lower in group B, the incidence of postoperative nausea and vomiting were also lower in group B.

In order to select the accurate optimal dose of butorphanol and sufentanil for GI endoscopy, a sequential method was used. The advantage of this method could evaluate the efficacy of drugs with fewer cases in a short time. The ED₉₅ of butorphanol was 9.07 µg/kg, which was close to the dose of the first case we designed (10 µg/kg). The ED₉₅ of sufentanil was 0.1 µg/kg, which was close to the dose of the first case we designed (0.83 µg/kg). In our study, we testified that the incidence of successful sedation by using the ED₉₅ dose of butorphanol and sufentanil during GI endoscopy is without differences.

With a published affinity for opioid receptors in vitro of 1:4:25 (mu: delta: kappa), butorphanol has been known to act on kappa-opioid receptors of the upper spinal cord to inhibiting nociceptive stimulus

conduction [5]. Ozaki N et al. demonstrated that kappa-, but not mu- or delta-opioid receptor agonists modulate visceral sensation conveyed by vagal afferent fibers innervating the stomach [17]. Soichiro et al. reported that the butorphanol-induced visceral chemical antinociception was entirely blocked by pretreatment with kappa-opioid receptor antagonist [18]. Kappa receptor shows absent related to respiratory depression, nausea and vomiting. Mu receptor shows high effects on respiratory depression and relates to nausea and vomiting [19]. As the doses of butorphanol and sufentanil used in our study were low, thus leading to a low incidence of respiratory depression and not reach a significant difference between them. Our experimental results also confirmed that butorphanol is less likely to cause nausea and vomiting, and showed lower postoperative VAS score than the pure mu-opioid receptor agonist sufentanil in their ED₉₅ dose. The duration of the analgesic effect of butorphanol is about 4 hours. Although the average examination time of painless GI endoscopy is not that long, the patient still needs excellent analgesia after waking up. PremyslFalt et al. reported that intravenous inject 2 mg of midazolam, after the end of routine air-inflated GI endoscopy, 1% of patients still have abdominal pain and 2% of patients still have flatulence during 30 minutes and 3 hours after procedure finished [20]. It is essential to have excellent analgesia during this period, and butorphanol is suitable.

Postoperative fatigue influences the emotional and mental state of the patient after surgery, which affects the recovery of the patient [21]. Sufentanil is the classic analgesic drug painless GI endoscopy. However, during the application of it in clinical, there are several patients who arise fatigue phenomenon which lasts beyond 1 hour in our study. In a C¹¹ labeled positron emission tomography, it was found that exercise can evoke and relate change the μ receptors in most of the limbic systems, and the deactivation of the μ receptor is the main reason for fatigue [22]. There was a strong correlation between grip strength and fatigue after adjustment for age, height, and was independent of physical activity level[23] [24]. Butorphanol showed less fatigue degree than sufentanil in both subjective and objective indicators. We speculate that butorphanol can reduce visceral pain in painless GI endoscopy, for it targets the kappa receptor and decreases the deactivation of the μ receptor, thereby reducing postoperative fatigue.

We believe that butorphanol, compared with sufentanil, reduces postoperative nausea and vomiting, improves postoperative analgesia, and reduces postoperative fatigue, thus reducing the time at PACU after GI endoscopy.

This study had several limitations: 1. The fatigue itself is a multi-factor subjective experience. We only evaluate its objective indicators in our experiment by grip strength and use a simplified scale. 2, Clinical examinations of outpatients are usually incomplete. The existence of hidden diseases and the different sensitivity to drugs in individuals may affect the results of the trial.

Conclusion

In summary, the ED₉₅ of butorphanol in inhibiting body movement during painless GI endoscopy was 9.07 μ g/kg, and butorphanol combined with propofol for GI endoscopy anesthesia reduced the recovery time, it was an excellent sedation strategy.

List Of Abbreviations

ED95, effective dose; CI, confidence intervals; GI, gastrointestinal; ASA, American Society of Anesthesiologists; BP, blood pressure; ECG, electrocardiogram; SpO2, oxygen saturation; BIS, bispectral index; PACU, postanesthesia care unit.

Declarations

Ethical approval and consent to participate

The Ethics Committee at the First Affiliated Hospital of Wenzhou Medical University approved this prospective trial, and the trial was registered at the Chinese Clinical Trial Registry (ChiCTR1900022780, 2019). Before study entry, all subjects reviewed and signed an informed consent document explaining the study procedures and potential risks.

Consent for publication

Not applicable.

Competing Interests:

Xiaona Zhu, Limei Chen, Shuang Zheng, and Linmin Pan declare no competing interests.

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Availability of data and materials

The datasets during and analyzed during the current study are available from the corresponding author on reasonable requests.

Authors' contributions:

XZ Contribution: Design and conduct the study, analyze the data, and write the manuscript. LC Contribution: Write the manuscript and critical manuscript review. SZ Contribution: Design and conduct the study. LP: Design the study, analyze the data, and write the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Responses (successful sedation) of 29 consecutive patients who received butorphanol as an analgesic during GI endoscopy.

Figure 2

Responses (successful sedation) of 37 consecutive patients who received sufentanil as an analgesic during GI endoscopy.

Supplementary Files

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