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***Randomized Controlled Trial***

**Effect of anesthesia induction with butorphanol on postoperative nausea and vomiting: A randomized controlled trial**

Xie F *et al*. Butorphanol on PONV

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**Abstract**

BACKGROUND

Postoperative nausea and vomiting (PONV) are common complications that affect the recovery and well-being of elderly patients undergoing gastrointestinal laparoscopic surgery.

AIM

To investigate the effect of butorphanol on PONV in this patient population.

METHODS

A total of 110 elderly patients (≥ 65 years old) who underwent gastrointestinal laparoscopic surgery were randomly assigned to receive butorphanol (40 μg/kg) or sufentanil (0.3 μg/kg) during anesthesia induction in a 1:1 ratio.The measured outcomes included the incidence of PONV at 48 h after surgery, intraoperative dose of propofol and remifentanil, Bruggrmann Comfort Scale score in the postanesthesia care unit (PACU), number of compressions for postoperative patient-controlled intravenous analgesia (PCIA), and time to first flatulence after surgery.

RESULTS

The results revealed a noteworthy reduction in the occurrence of PONV at 24 h after surgery in the butorphanol group, when compared to the sufentanil group (T1: 23.64% *vs* 5.45%, T2: 43.64% *vs* 20.00%, *P* < 0.05). However, no significant variations were observed between the two groups, in terms of the clinical characteristics, such as the PONV or motion sickness history, intraoperative and postoperative 48-h total infusion volume and hemodynamic parameters, intraoperative dose of propofol and remifentanil, number of postoperative PCIA compressions, time until the first occurrence of postoperative flatulence, and incidence of PONV at 48 h post-surgery (all, *P* > 0.05). Furthermore, patients in the butorphanol group were more comfortable, when compared to patients in the sufentanil group in the PACU.

CONCLUSION

The present study revealed that butorphanol can be an efficacious substitute for sufentanil during anesthesia induction to diminish PONV within 24 h following gastrointestinal laparoscopic surgery in the elderly, simultaneously improving patient comfort in the PACU.

**Key Words:** Butorphanol; Sufentanil; Enhanced recovery after surgery; Anesthesiology; Gastrointestinal surgery; Postoperative nausea and vomiting

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**Core Tip:** In this study, butorphanol was used for anesthesia induction, and it was found that the incidence of postoperative nausea and vomiting (PONV) was significantly lower at 24 h after surgery in the butorphanol group, when compared to the sufentanil group. In addition, the Bruggrmann Comfort Scale scores in the postanesthesia care unit were significantly better in the butorphanol group, when compared to the sufentanil group.

**INTRODUCTION**

Postoperative nausea and vomiting (PONV) is the second most common postoperative adverse reaction after pain, which has an estimated incidence of 30% in the general surgical population, and an incidence that can reach as high as 80% in high-risk patients[1]. Aspiration pneumonia caused by PONV is a severe risk, particularly in elderly patients with poor pharyngeal reflex recovery after general anesthesia. In addition, PONV may cause electrolyte imbalance, poor incision healing, insufficient blood volume, and delayed discharge from the hospital.

The concept of enhanced rehabilitation after surgery emphasizes the role of minimizing adverse reactions after surgery, in order to improve the quality and pace of recovery[2]. The high-risk types of surgery with PONV include laparoscopic, bariatric, and gynecological surgery. The mechanism of PONV induced by the laparoscopic surgery remains unclear. Recent clinical studies have suggested that this may be correlated to the decrease in pain threshold of patients undergoing laparoscopic surgery, the stimulation of residual postoperative carbon dioxide in the abdominal cavity, and the pulling state of the peritoneum, which can result in increased demand for postoperative analgesia, such as opioids, leading to an increased likelihood of PONV[3]. For patients undergoing gastrointestinal laparoscopic surgery, nausea and vomiting are more likely to occur after surgery. Therefore, the balance between analgesia and PONV remains as a major challenge for anesthesiologists.

Traditional opioids produce an analgesic effect by exciting the μ (μ1 and μ2) receptors. However, the excitation of μ2 receptors can enhance the sensitivity to vestibule stimulation, affect the chemoreceptor triggering area, and delay gastric emptying, thereby triggering PONV[4]. In contrast, butorphanol, which is a synthetic opioid receptor agonist-antagonist with 5-8 times the analgesic potency of morphine, exhibits low activity to δ receptors, while stimulating the κ and μ1 receptors, and antagonizing μ2 receptors[5]. Through its antagonistic effect on μ2 receptors, butorphanol significantly reduces the incidence of PONV caused by traditional opioids. Furthermore, clinical studies have revealed that butorphanol has a good analgesic effect on patients with chronic visceral pain through the activation of κ receptors[6,7]. At present, few studies have compared butorphanol and sufentanil in the incidence of PONV during general anesthesia. Therefore, the present study aimed to investigate the effect of butorphanol on PONV in elderly patients who underwent gastrointestinal laparoscopic surgery.

**MATERIALS AND METHODS**

***General information***

The present study was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University (PJ-KS-KY-2020-161 [X]), and registered in the China Clinical Trial Center (ChiCTR2100045860). Patients ≥ 65 years old, who underwent gastrointestinal laparoscopic surgery from February 2020 to February 2021, were enrolled for the present study. Using the computer statistics software, these patients were randomly allocated into two groups in a 1:1 ratio: Sufentanil and butorphanol groups.

Based on preliminary experiments and previous studies[8], the sample size was calculated according to the incidence of PONV. The preliminary experiment results indicated that the incidence of PONV was approximately 35% in the sufentanil group, and 13% in the butorphanol group. In order to ensure adequate statistical power with 85% power at 5% level of significance, at least 49 patients were required for each group. Accounting for the potential 10% dropout rate, a total of 110 patients were included for the present study.

***Inclusion and exclusion criteria***

Inclusion criteria: Patients ≥ 65 years old, who underwent gastrointestinal laparoscopic surgery, and provided a written informed consent. Exclusion criteria: Hypersensitivity to butorphanol and sufentanil, serious respiratory complications, severe obstructive sleep apnea-hypopnea syndrome or obesity [body mass index (BMI) ≥ 28 kg/m2], opioid dependence, significant abnormalities in liver or kidney function, and severe visual or auditory impairment.

***Anesthesia monitoring***

The following basic clinical information were recorded at one day prior to surgery: Age, gender, height, weight, BMI, American Society of Anesthesiologists (ASA) classification, smoking status, and history of PONV and motion sickness. These patients were required to fast for six hours, and have water deprivation for two hours before the surgery, with no preoperative drugs administered. Upon entering the operation room, the electrocardiogram, heart rate, oxygen saturation (SpO2), non-invasive blood pressure, bispectral index, and oral and sublingual temperature were monitored. In addition, invasive arterial blood pressure was monitored *via* radial artery catheterization and internal jugular vein catheterization, in order to detect any hemodynamic changes, and facilitate the administration of fluids and medications, when necessary.

***Anesthetic method***

Anesthesia induction was administered to patients in the sufentanil group at a dose of 0.3 μg/kg of sufentanil, while patients in the butorphanol group were given 40 μg/kg of butorphanol, based on the analgesic titer ratio. During the anesthesia induction, the intravenous administration of 1-2 mg/kg of propofol and 0.3 mg/kg of benzensulfonate atracurium was performed, while remifentanil was pumped at a rate of 5-10 μg/kg/h. Then, tracheal intubation was performed under visual laryngoscopy after the muscle relaxant took effect. The anesthesia maintenance during the operation consisted of the intravenous infusion of 4-6 mg/kg/h of propofol, 5-10 μg/kg/h of remifentanil, and 0.10-0.15 mg/kg/h of benzenesulfonate atracurium. When the surgery was completed, the infusion of benzenesulfonate atracurium, propofol and remifentanil were stopped, while 0.1 mg/kg of butorphanol was given for patient-controlled intravenous analgesia (PCIA). Then, these patients were transferred to the postanesthesia care unit (PACU), and vital signs monitoring was continued for 48 h. The study assistants were responsible for the preparation and administration of the studied medications. The other assistants were responsible for the monitoring and recording of the results during data collection. All assistants were blinded to the study.

***Outcome measures***

The primary outcome of the study was the incidence of PONV, which was evaluated using the PONV grading scale in the PACU (T1), and at 24 h (T2) and 48 h (T3) after surgery (Table 1). The other observed parameters were, as follows: Intraoperative dose of propofol and remifentanil, total infusion volume (at intraoperative and postoperative 24 and 48 h), operation time, the agitation[9] and Bruggrmann Comfort Scale (BCS)[10] scores in the PACU, the number of compressions for PCIA within 48 h after surgery, and the time to first postoperative flatulence. The cumulative dose of propofol and remifentanil administered through a micropump infusion device, both during the induction and maintenance phases of anesthesia, was calculated using the following formula: Dose = infusion rate (mg/kg/min) × patient weight (kg) × duration of surgery (min). The BCS scores were utilized to assess the level of patient comfort in the two groups: 0, indicates continuous pain; 1, represents no pain at rest, but with severe pain during deep breathing or coughing; 2, indicates no pain while lying at rest, and slight pain during deep breathing or coughing; 3, represents no pain during deep breathing; 4, represents no pain during coughing[11].

***Statistical methods***

For normally distributed measurement data, mean ± SD was used for the statistical description, and independent sample *t*-test was performed to determine the statistical difference. For non-normally distributed measurement data, median (M) and interquartile range were used for the statistical description, and the Mann-Whitney *U*-test was performed to determine the statistical difference. *χ2* test was used to analyze the difference between groups for the enumeration data. Frequency (rate) was used to describe the ordinal data, and this was analyzed using the Wilcoxon rank sum test. SPSS 26.0 was used for the statistical analysis. A *P*-value of < 0.05 was considered statistically significant.

**RESULTS**

A total of 168 elderly patients, who underwent gastrointestinal laparoscopic surgery from February 2020 to February 2021, were screened in the present study. Among these patients, 35 patients did not agree to participate, and 18 patients were excluded based on the exclusion criteria. During the trial, five patients were excluded due to the following reasons: Rejection and loss to follow-up. Finally, a total of 110 patients (66 male and 44 female patients) were included for the present study (Figure 1).

***Comparison of baseline characteristics***

No significant differences were observed between the two groups, in terms of age, BMI, gender, ASA grade, smoking history, PONV or motion sickness history, intraoperative and postoperative 48-h total infusion volume (Table 2), and hemodynamic parameters (Table 3) (*P >* 0.05).

***Comparison of PONVs at postoperative 48 h***

As shown in Table 4, there was a significant difference in the occurrence of PONV at T1 (*P* = 0.005) and T2 (*P* = 0.001), while there was no statistical difference at T3 (*P* = 0.169), between the sufentanil and butorphanol groups (Table 4).

***Comparison of intraoperative propofol and remifentanil***

There was no significant difference in the total dose of intraoperative propofol (*P* = 0.893) and remifentanil (*P* = 0.438) between the sufentanil and butorphanol groups (Table 5).

***Comparison of agitation and BCS scores***

The BCS scores were significantly better in the butorphanol group, when compared to the sufentanil group (*P* = 0.028), although there was no significant difference in agitation scores in the PACU between the two groups (*P* = 0.439) (Table 5).

***Comparison of PCIA effective compressions and time to first postoperative flatulence***

There were no statistically significant differences observed between the two groups, in terms of the number of PCIA effective compressions at postoperative 48 h (*P* = 0.881), and at the time to first postoperative flatulence (*P* = 0.822) (Table 5).

**DISCUSSION**

The present study compared the effects of sufentanil and butorphanol on the incidence of PONV in elderly patients who underwent gastrointestinal laparoscopic surgery. The results revealed that the incidence of PONV was lower in the PACU, and at 24 h after surgery in the butorphanol group, when compared to the sufentanil group, although there was no statistical difference observed at 48 h after surgery between the two groups.

The complex mechanism of PONV involves the following risk factors: Female gender, smoking, history of PONV or motion sickness, and opioids[12,13]. Several studies have revealed that traditional opioids that are commonly used for pain management, such as μ agonists, have been associated with nausea and vomiting, while providing analgesic efficacy[14,15]. Traditional opioids produce an analgesic effect by exciting the μ (μ1 and μ2) receptors. However, the excitation of μ2 receptors can enhance the sensitivity to vestibule stimulation, affect the chemoreceptor triggering area, and delay gastric emptying, thereby triggering PONV[4].

Butorphanol, which is a synthetic opioid receptor agonist-antagonist with 5-8 times the analgesic potency of morphine, exhibits low activity to δ receptors, while stimulating the κ and μ1 receptors, and antagonizing μ2 receptors[5]. Sufentanil has a long clearance half-life in elderly patients, and its effect on opioid receptors can persist for several hours after surgery, increasing the incidence and duration of PONV. Since sufentanil undergoes metabolism and clearance over time, its effect on opioid receptors decreases, which may explain the different effects of sufentanil and butorphanol on PONV at different time points.

Recent studies have revealed that butorphanol can effectively inhibit the hemodynamic fluctuations caused by tracheal intubation during anesthesia induction, which is consistent with the results of the hemodynamic parameter analysis in a previous study[16]. In the present study, there was no significant difference in hemodynamic fluctuations before and after endotracheal intubation between the sufentanil and butorphanol groups, and both drugs effectively inhibited the circulation fluctuations caused by the endotracheal intubation. Furthermore, there was no significant difference in intraoperative remifentanil dose, PACU agitation score, or the number of effective compressions for postoperative PCIA between the sufentanil and butorphanol groups. Thus, it was considered that the induction of anesthesia with butorphanol can produce similar and relatively complete analgesic effects as sufentanil. More importantly, butorphanol can activate the κ receptors, and exert sedative effects. Although there was no statistical difference in intraoperative propofol dose between the two groups in the present study, the BCS scores were higher in the butorphanol group, indicating that the postoperative comfort level of patients induced by butorphanol was higher.

Previous studies have reported that intravenous butrophanol can promote the recovery of postoperative gastrointestinal function, and shorten the time to first postoperative flatulence in elderly patients undergoing radical laparoscopic nephrectomy[17]. However, there was no statistical difference in the time to first postoperative flatulence between the sufentanil and butorphanol groups, which was possibly due to the following factors: Postoperative ambulation time, postoperative dietary recovery, and the use of glycerine enema. Therefore, further comprehensive analyses are required to verify this conclusion.

The limitations of the present study should be acknowledged. Merely the occurrence of nausea and vomiting within 48 h after surgery were observed, and the PDNV was not followed up. Furthermore, the present study merely included elderly patients ≥ 65 years old, who underwent gastrointestinal laparoscopic surgery. Thus, patients in other age groups, especially young women, needs to be investigated. Moreover, the specific operation methods of gastrointestinal surgery were not statistically analyzed in the present study. In addition, other high-risk surgeries, such as pelvic surgery, thyroid surgery, strabismus repair, and middle ear surgery, were not included in the present study[18,19]. Therefore, the conclusions need to be supported by further evidence and more information.

**CONCLUSION**

In summary, the administration of butorphanol has shown potential in significantly reducing the occurrence of PONV within 24 h after gastrointestinal surgery in elderly patients, and improving the comfort of patients in the PACU. Therefore, the present study contributes valuable evidence that support strategies targeted at mitigating PONV during the perioperative period.

**ARTICLE HIGHLIGHTS**

***Research background***

Postoperative nausea and vomiting (PONV) are common complications after surgery, seriously affects the prognosis of elderly patients for laparoscopic gastrointestinal surgery.

***Research motivation***

This prospective, double-blind randomized controlled trial aimed to investigate the effect of butorphanol on PONV in this patient population.

***Research objectives***

Elderly patients (≥ 65 years old) who underwent gastrointestinal laparoscopic surgery.

***Research methods***

Patients were randomly assigned to receive butorphanol (40 μg/kg) or sufentanil (0.3 μg/kg) during anesthesia induction in a 1:1 ratio. The measured outcomes included the incidence of PONV at 48 h after surgery, intraoperative dose of propofol and remifentanil, Bruggrmann Comfort Scale (BCS) score in the postanesthesia care unit (PACU), number of compressions for postoperative patient-controlled intravenous analgesia (PCIA), and time to first flatulence after surgery.

***Research results***

The results revealed a noteworthy reduction in the occurrence of PONV at 24 h after surgery in the butorphanol group, when compared to the sufentanil group. However, no significant variations were observed between the two groups, in terms of the clinical characteristics, such as the PONV or motion sickness history, intraoperative and postoperative 48-h total infusion volume and hemodynamic parameters, intraoperative dose of propofol and remifentanil, number of postoperative PCIA compressions, time until the first occurrence of postoperative flatulence, and incidence of PONV at 48 h post-surgery. Furthermore, patients in the butorphanol group were more comfortable, when compared to patients in the sufentanil group in the PACU.

***Research conclusions***

The administration of butorphanol has shown potential in significantly reducing the occurrence of PONV within 24 h after gastrointestinal surgery in elderly patients, and improving the comfort of patients in the PACU.

***Research perspectives***

Anesthesia induction with butorphanol may reduce the incidence of PONV, especially for some patients with a high risk of PONV (young women, no-smoking, PONV or motion sickness history, high-risk surgeries, such as pelvic surgery, thyroid surgery, strabismus repair, and middle ear surgery).

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**Footnotes**

**Institutional review board statement:** The study was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University (PJ-KS-KY-2020-161 [X]).

**Clinical trial registration statement:** The study is registered in the China Clinical Trial Center (ChiCTR2100045860, 25/04/2021).

**Informed consent statement:** All participants provided a signed informed consent.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** The datasets generated and/or analyzed in the study are not publicly available due to the limitations of ethical approval, which involve the patient data and anonymity. However, these are available from the corresponding author on reasonable request.

**CONSORT 2010 statement:** The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

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**Figure Legends**



**Figure 1 The patient inclusion, randomization, and follow-up flowchart.**

**Table 1 Postoperative nausea and vomiting grading scale**

|  |  |
| --- | --- |
| **PONV grade** | **Patient response** |
| 0 | Without PONV |
| I | Nausea without vomiting |
| II | Nausea with vomiting (< 3 times/d) |
| III | Vomiting ≥ 3 times/d |

PONV: Postoperative nausea and vomiting.

**Table 2 Comparison of baseline characteristics between the sufentanil and butorphanol groups**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Sufentanil group (*n* = 55)** | **Butorphanol group (*n* = 55)** | ***P* value** |
| Age | 71.0 ± 5.7 | 69.6 ± 5.7 | 0.199 |
| Gender (male/female) | 32/23 | 34/21 | 0.698 |
| ASA (I/II/III) | 0/33/22 | 0/30/25 | 0.847 |
| Weight (kg) | 63.6 ± 10.3 | 68.6 ± 11.3 | 0.058 |
| BMI (kg/m2) | 21.1 ± 1.8 | 20.81 ± 1.7 | 0.403 |
| Smoking (yes/no) | 25/30 | 26/29 | 0.703 |
| PONV or motion sickness history (yes/no) | 14/41 | 20/35 | 0.218 |
| Operation time (h) | 3.41 ± 1.30 | 3.25 ± 1.07 | 0.484 |
| Intraoperative infusion volume (mL) | 1290.9 ± 404.7 | 1243.6 ± 316.8 | 0.497 |
| Postoperative 24-h infusion volume (mL) | 2380.9 ± 137.6 | 2342.7 ± 133.8 | 0.143 |
| Postoperative 48-h infusion volume (mL) | 2152.7 ± 128.9 | 2125.5 ± 117.4 | 0.249 |

ASA: American Society of Anesthesiologists; BMI: Body mass index; PONV: Postoperative nausea and vomiting.

**Table 3 Comparison of hemodynamics between the sufentanil and butorphanol groups**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **HR (BPM)** | **SBP (mmHg)** | **DBP (mmHg)** |
| **Sufentanil** | **Butorphanol** | ***P* value** | **Sufentanil** | **Butorphanol** | ***P* value** | **Sufentanil** | **Butorphanol** | ***P* value** |
| Pre-operation | 69.2 ± 9.0 | 67.9 ± 7.1 | 0.400 | 145.2 ± 15.2 | 146.1 ± 12.0 | 0.748 | 67.8 ± 6.2 | 67.51 ± 5 ± 5.1 | 0.828 |
| One minute before induction | 70.2 ± 9.5 | 68.8 ± 6.5 | 0.348 | 149.5 ± 17.9 | 149.3 ± 12.4 | 0.966 | 71.2 ± 8.8 | 68.4 ± 5.4 | 0.056 |
| One minute after tracheal intubation | 69.8 ± 9.2 | 68.8 ± 6.1 | 0.480 | 144.3 ± 18.4 | 147.8 ± 10.5 | 0.233 | 69.5 ± 8.7 | 67.6 ± 4.3 | 0.156 |
| Intraoperative maintenance | 67.3 ± 8.1 | 68.5 ± 6.3 | 0.388 | 145.2 ± 13.9 | 149.1 ± 9.8 | 0.098 | 68.3 ± 7.6 | 68.1 ± 4.5 | 0.867 |

HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

**Table 4 Comparison of postoperative nausea and vomiting within postoperative 48 h between the sufentanil and butorphanol groups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Sufentanil group (*n* = 55)** | **Butorphanol group (*n* = 55)** | ***Z*** | ***P* value** |
| T1 PONV (0/I/II/III) | 42/6/6/1 | 52/3/0/0 | -2.786 | 0.005a |
| T2 PONV (0/I/II/III) | 21/11/11/2 | 44/4/7/0 | -3.188 | 0.001a |
| T3 PONV (0/I/II/III) | 50/3/2/0 | 54/1/0/0 | -1.375 | 0.169 |

aThere is significant statistical difference between the two groups, with *P* < 0.05.

T1: During the postanesthesia care unit period; T2: Return to the ward for 24 h; T3: Return to the ward for 24-48 h. PONV: Postoperative nausea and vomiting.

**Table 5 Comparison of actual doses of propofol and remifentanil, agitation scores, Bruggrmann comfort scale scores, and effective compressions of patient-controlled intravenous analgesia pump**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Sufentanil group (*n* = 55)** | **Butorphanol group (*n* = 55)** | ***Z*** | ***P* value** |
| Propofol (mg) | 1027.2 ± 461.6 | 1016.4 ± 379.4 | - | 0.893 |
| Remifentanil (mg) | 1.3 ± 0.6 | 1.2 ± 0.5 | - | 0.438 |
| Agitation score (0/1/2/3) | 42/8/5/0 | 47/6/2/0 | -0.774 | 0.439 |
| BCS score (0/1/2/3/4) | 6/5/30/14/0 | 1/4/24/25/1 | -2.195 | 0.028\* |
| Effective compressions of PCIA | 1.00 (2.00-1.00) | 1.00 (2.00-1.00) | - | 0.881 |

BCS: Bruggrmann comfort scale; PCIA: Patient-controlled intravenous analgesia pump.