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ORIGINAL RESEARCH

Effect of Different Doses of Butorphanol on Postoperative Shivering in Elderly Patients: A Randomized, Double-Blind, Placebo-Controlled Trial

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Purpose: This study was designed to investigate the effects of different doses of butorphanol on postoperative shivering and quality of recovery in elderly patients.

Patients and Methods: A total of 147 elderly patients (aged 60 or older) scheduled for elective transurethral resection of the prostate were enrolled in the current study. Patients were randomly and evenly assigned into four groups: Group C (0.9% normal saline), Group B1 (butorphanol 0.01 mg/kg), Group B2 (butorphanol 0.02 mg/kg) and Group B3 (butorphanol 0.03 mg/kg). All drugs were diluted to 5mL and injected intravenously slowly 5 min before induction of anesthesia. The primary outcome measure was the incidence of postoperative shivering in the post-anesthesia care unit. Quality of Recovery-40 (QoR-40) scores were assessed on postoperative day (POD) 1, 2 and 3. Perioperative core and skin temperature, extubation time and adverse events were also recorded.

Results: Patients among the four groups had comparable baseline characteristics. Compared with Group C, the incidence of shivering was significantly lower in Group B2 and B3 ($P = 0.006$ and $P = 0.005$, respectively). The QoR-40 scores on POD1 were significantly higher in all butorphanol groups than that in Group C ($P < 0.0083$). In Group B2 and B3, patients experienced lower pain intensity ($P < 0.001$). In addition, the incidence of catheter-related bladder discomfort (CRBD) was lower in all butorphanol groups than in Group C ($P < 0.0083$).

Conclusion: Butorphanol 0.02 or 0.03 mg/kg could effectively prevent the occurrence of postoperative shivering in elderly patients scheduled for transurethral resection of the prostate, provided effective postoperative recovery and postoperative analgesia.

Keywords: butorphanol, elderly patients, postoperative shivering, recovery quality, postoperative pain

Introduction

Postoperative shivering is a common complication during recovery from general anesthesia, with a reported incidence ranging from 20% to 80%.[1,2] Shivering is a thermoregulatory mechanism to core hypothermia, but it can cause a lot of harm to patients during the perioperative period. It can increase metabolic rate and oxygen consumption, induce lactic acidosis, increase the release of catecholamines and the incidence of cardiovascular complications. Shivering can also increase intracranial and intraocular pressures.[2,3] In addition, it may cause discomfort and increase the risk of post-operative complications such as infection, pain and bleeding, resulting in a prolonged hospital stay.[4] These are especially

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dangerous for elderly patients with multiple comorbidities and low cardiopulmonary reserves. Furthermore, with the increasing clinical application of perioperative mild hypothermia, the prevention and treatment of shivering have become increasingly important, which are also beneficial to improve the safety and comfort of elderly patients during the recovery period and accelerate postoperative rehabilitation.

The causes of postoperative shivering are not clearly understood. Existing studies suggested the following possible reasons: anesthetics inhibit the thermoregulation system and reduce the threshold of shivering; redistribution of body heat; intraoperative heat loss; release of thermogenic medium; pain.[5,6] Postoperative shivering can also occur in patients with normal body temperature, and they may not feel cold.[7,8] The above causes provide various ideas of resistance to shivering, and also show that physical measures alone are not enough to prevent postoperative shivering.

Previous studies have confirmed the effectiveness of various drugs in preventing and treating postoperative shivering, but the ideal drug is still not conclusive. The most used drug is meperidine, but it has different degrees of inhibition of respiratory and circulatory functions, resulting in nausea, vomiting, obvious drowsiness, dizziness and other adverse reactions. In addition, its metabolites can cause central nervous system symptoms of excitement.[4,9,10] Butorphanol is a mixed agonist and antagonist of the opioid receptor. It produces analgesic and shivering resistance effects for moderate affinity to the κ opioid receptor (KOR), with partial antagonism to the μ opioid receptor (MOR), so it has little effect on respiration and circulation with minor adverse reactions. Furthermore, it is mainly metabolized to inactive hydroxybutorphanol in the liver.[11–13] Butorphanol has been widely used for perioperative analgesia, however, its ideal dose to prevent postoperative shivering has not been studied.

The purposes of this study were to investigate the effect of butorphanol on the incidence of postoperative shivering during the recovery period from general anesthesia in elderly patients undergoing transurethral resection of the prostate and explore the dosage that can prevent shivering effectively with fewer side effects and improved quality of recovery.

Patients and Methods

This is a single-center, randomized, double-blind, placebo-controlled clinical trial and has been approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2022-KL035-01). The study was registered in the Chinese Clinical Trial Center (ChiCTR2200057411) and conducted at Affiliated Hospital of Xuzhou Medical University between March 2022 and October 2022. All patients were recruited after passing the ethical review, and they voluntarily chose general anesthesia due to fear of spinal anesthesia or surgical reasons. This research complied with the Declaration of Helsinki and CONSORT guidelines. Before enrollment, we obtained written informed consents from all patients or family authorized.

Patients

Patients scheduled for elective transurethral resection of the prostate under general anesthesia for benign prostatic hyperplasia were recruited for this study, with age 60 or older, BMI < 30 kg/m^2 and American Society of Anesthesiologists (ASA) physical status II–III. The exclusion criteria were as follows: severe cardiovascular, respiratory, liver or renal dysfunction; an initial body temperature above 38.0°C or below 36.0°C; severe hypothyroidism or hyperthyroidism, metabolic disease and neuromuscular disease; long-term use of analgesics, sedatives and antidepressants; language comprehension disorder or mental disorder; allergies to butorphanol tartrate; and refusing to sign written informed consent. Patients with intraoperative temperature below 36°C, operation duration more than 3 hours or those admitted to the intensive care unit (ICU) after operation were also excluded.

Randomization and Blinding

156 patients were randomly assigned to one of four groups in a 1:1:1:1 ratio according to a computer-generated random sequence (n=39): Group C (0.9% normal saline), Group B1 (butorphanol 0.01 mg/kg), Group B2 (butorphanol 0.02 mg/kg), Group B3 (butorphanol 0.03 mg/kg). Group numbers were randomly placed in sealed opaque envelopes. After the patient entered the operating room, a nurse not involved in the study opened the envelope and prepared the appropriate medications, all of which were diluted to 5mL. And all the drugs are clear and colorless, with no difference in appearance. Both butorphanol and saline are colorless and transparent, with no difference in appearance. All observations

in the PACU and postoperative follow-up were performed by the same observer. All patients, anesthesia managers, outcome assessors and statisticians were blinded to the group allocation.

Anesthetic Management and Intervention

All patients fasted for 8 h and forwent water for 2 h before surgery. After participants entered the operation room, vital signs were routinely monitored, including electrocardiogram (ECG), pulse oxygen saturation (SpO_2) and upper limb mean blood pressure (MBP). End-expiratory CO_2 ($P_{ET}CO_2$) and bispectral index (BIS) were monitored after induction of anesthesia. Upper extremity venous access was opened (liquid infusion speed was 10 mL/kg/h for the first 30 min and 5–7 mL/kg/h thereafter), and radial artery puncture and catheterization were performed local infiltration anesthesia with 2% lidocaine for measuring the arterial pressure and sampling the arterial blood gas.

Patients in Group B1, B2 and B3 received corresponding doses of butorphanol intravenously (0.01 mg/kg, 0.02 mg/kg or 0.03 mg/kg) 5 min before induction of anesthesia, whereas patients in Group C received the same volume of normal saline. Anesthesia induction was performed after pure oxygen inhalation for 5 min: midazolam (0.05 mg/kg), etomidate (0.3 mg/kg), sufentanil (0.5 μg/kg), and cisatracurium (0.15–0.2 mg/kg), tropisetron (2mg). When BIS < 50, the appropriate type of laryngeal mask was performed with muscle relaxation. Mechanical ventilation parameters settings were: respiratory rate (RR) 12–16 breath/min, tidal volume (V_T) 6–8 mL/kg, the ratio of inspiratory and exhalation time (I: E) 1:1.5, fraction of inspired oxygen (FiO_2) 60–80%, $P_{ET}CO_2$ 35–45 mmHg. Anesthesia was maintained with 2–5 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ propofol, 0.1–0.3 $\mu g{\cdot}kg^{-1}{\cdot}h^{-1}$ remifentanil and 1% sevoflurane. Cisatracurium was supplemented according to the TOF value and surgical progress. The infusion rate of intravenous anesthetics was adjusted during surgery to maintain the BIS value at 40–60, MAP and heart rate fluctuated within 20% of the basal value. Vasoactive agents would be used as appropriate. All intravenous and inhaled drugs were stopped after the prostate was removed and before a catheter was placed. The patient underwent bladder lavage with normal saline during the operation.

All patients were transferred to the post-anesthesia care unit (PACU) for resuscitation and further observation. When spontaneous respiration was restored and the ideal tidal volume was reached, the eyes could be opened upon call and the muscle tone is restored, the laryngeal mask would be removed. Neostigmine (30 μg/kg) and atropine (15 μg/kg) were used routinely to antagonize the residual muscle paralysis if there were no contraindications. After 30 minutes of observation after extubation and the modified Aldrete score reached 9 points, patients were returned to the ward.

The temperature in the operating room and PACU was kept at 22–23°C, and the humidity was kept at 50%-60%. All fluids used by the patients were at room temperature. Patients' upper bodies were covered with quilts and their legs were covered with surgical drapes, and a forced-air warming system set at 38°C was used from the beginning to the end of surgery. In the PACU, all patients were monitored and covered with a cotton blanket to keep warm. If NRS ≥ 4, fentanyl 1 μg/kg would be given intravenously, and additional drugs were given if necessary. The information about the drugs used in this study is shown in the Supplementary.

Primary and Secondary Study Outcomes

In this study, the primary outcome was the incidence of postoperative shivering in the PACU. Postoperative shivering was evaluated every 10 minutes over 30 minutes after extubation using Wrench's shivering grade: "0", no shivering; "1", one or more of: piloerection, peripheral vasoconstriction, peripheral cyanosis without other cause, but without visible muscular activity; "2", visible muscular activity confined to one muscle group; "3", visible muscular activity in more than one muscle group; and "4", gross muscular activity involving entire body.[14] When the patient experienced severe postoperative shivering (shivering grade ≥ 3), dexmedetomidine was continuously infused at 0.5 ug/kg for 10 min, and a forced-air warming system set at 43°C was used for active heating.

The secondary outcomes included (1) the incidence of severe postoperative shivering; (2) the Quality of Recovery-40 (QoR-40)[15] scores on postoperative day (POD) 1, 2 and 3; (3) extubation time; (4) consumption of propofol, remifentanil and vasoactive drugs; (5) the Richmond Agitation Sedation Scale (RASS) score and the numerical rating scale for pain (NRS); (6) adverse events including somnolence, nausea, vomiting, respiratory depression and catheter-related bladder discomfort (CRBD, defined as the urge to void or a burning sensation in the suprapubic area).[16] The QoR-40 scale provides a comprehensive assessment of the quality of recovery. It is rated on a 40–200 scale, with higher scores

representing better recovery quality. RASS is a 10-level scale that assesses agitation and calmness (+4 "combative" to −5 "unarousable").[17] The NRS scale uses numbers to indicate pain levels (0 = no pain, 10 = worst imaginable pain).

In addition, forehead body temperature (BT_F) was recorded as body surface temperature before anesthesia induction (time 0 [T0]), at the beginning of surgery (time 1 [T1]), at 30 minutes after T1 (time 2 [T2]), at 1 hour after T1 (time 3 [T3]), at the end of surgery (time 4 [T4]), immediately after extubation (time 5 [T5]), at 30 minutes after extubation (time 6 [T6]). Nasopharyngeal body temperature (BT_N) was recorded as core body temperature at T1-T4.

Statistical Analysis

According to the result of the preliminary experiment, the incidence of postoperative shivering in elderly patients undergoing transurethral resection of the prostate was 40%, supposed the incidences in Group B1, B2 and B3 were 20%, 15% and 10%, respectively. We calculated that 35 patients would be enrolled in each group with a power of 80% and an α risk of 0.05 by using PASS version 15.0. Considering a 10% dropout rate, 156 patients were eventually enrolled in this trial.

SPSS (Version 25.0, IBM SPSS, Chicago, IL, USA) and GraphPad Prism (Version 9, GraphPad Software, La Jolla, CA, USA) were used for statistical data analysis. For continuous data, data normality was tested by Shapiro–Wilk test and the homogeneity of variance was performed by Levene's test. Normally distributed variables were presented as mean ± standard deviation (Mean ± SD), one-way analysis of variance (ANOVA) and SNK-q test were used to compare the differences among the groups. Non-normally distributed data were presented as median (M) and inter-quartile range (IQR) and were analyzed by Kruskal–Wallis test and Bonferroni's test. Enumeration data were expressed as frequency (%) and were analyzed with the chi-squared test or Fisher's exact test. Multiple interpolations were made to the missing value. All P values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

A total of 171 patients were screened for eligibility, and 156 patients ultimately met the inclusion criteria and underwent randomization. 9 participants were excluded during the test, including 4 cases with intraoperative body temperature < 36°C and 5 cases with surgical duration > 3 hours. Ultimately, 147 patients were included in the analysis. There were no statistically significant differences in baseline characteristics among the four groups (Figure 1, Table 1).

The number of patients who experienced postoperative shivering in Group C, Group B1, Group B2 and Group B3 was 13 (35.1%), 6 (16.2%), 3 (8.3%) and 3 (8.1%), respectively. Compared with Group C, the incidences of postoperative shivering in Group B2 and B3 were lower, and the differences were statistically significant ($P = 0.006$; $P = 0.005$, respectively, Figure 2). In addition, fewer patients in Group B3 experienced severe shivering requiring treatment compared to Group C ($P = 0.003$).

QoR-40 scores on preoperative (Pre) were comparable in the four groups. Compared with Group C, the global QoR-40 scores of Group B1, B2 and B3 increased significantly on POD 1, and the differences were statistically significant ($P = 0.001$; $P < 0.001$; $P < 0.001$; respectively). The same results were seen on POD 2, but the latter differences among the groups did not reach the minimal clinically important difference (MCID) of 6.3 points.[18] The QoR-40 scores of Group B3 on POD 3 were higher than that in Group C ($P = 0.034$, after Bonferroni adjustment, Table 2), but the differences did not reach the MCID.

The consumption of remifentanil in Group B3 was lower than that in Group C ($P = 0.003$). The use of vasopressors was different among the four groups, but there was no significant difference in any pairwise comparison between groups ($P > 0.0083$). Consumption of propofol had no significant difference among the four groups ($P = 0.216$). The NRS scores during recovery from general anesthesia were significantly lower in Group B2 and B3 than in Group C ($P < 0.001$; $P < 0.001$, respectively). More patients developed CRBD in Group C than in the butorphanol three groups ($P = 0.006$; $P < 0.001$; $P < 0.001$, respectively). There was no significant difference in extubation time, RASS score and adverse events in PACU (including hyoxemia, somnolence, nausea or vomiting) among the four groups ($P > 0.05$, Table 3).

There was no significant difference in BT_N at the four time points during surgery among the four groups ($P > 0.05$, Figure 3A). What's more, no significant difference was identified about the BT_F at all recorded time points among the four groups ($P > 0.05$, Figure 3B).

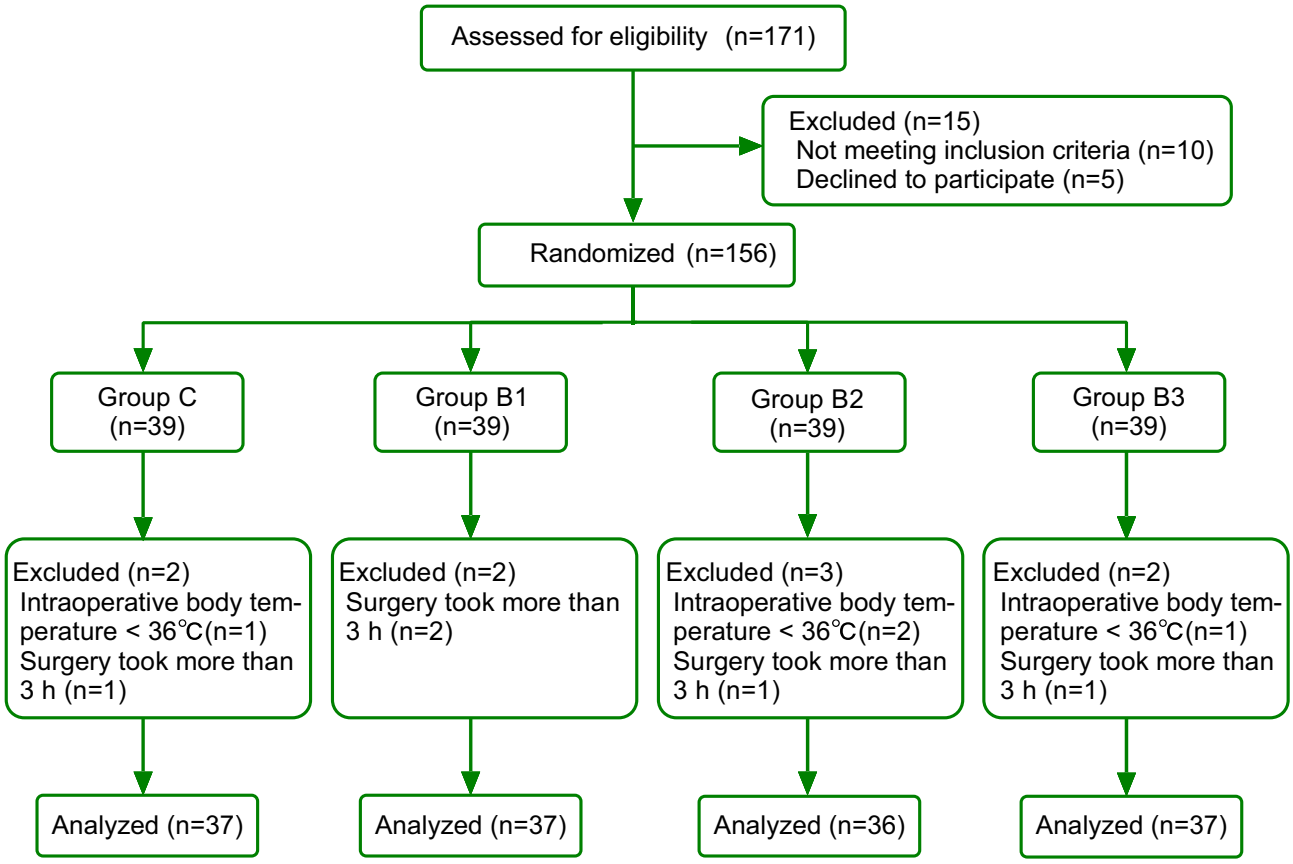

Figure 1 Flow diagram of the study.
Abbreviations: Group C, control group; Group B1, butorphanol 0.01 mg/kg group; Group B2, butorphanol 0.02 mg/kg group; Group B3, butorphanol 0.03 mg/kg group.

Discussion

In this prospective, double-blind, randomized controlled study, we found that butorphanol 0.02 or 0.03 mg/kg effectively prevented the occurrence of postoperative shivering in elderly patients with transurethral resection of the prostate

Table 1 Patient's Characteristics and Surgical Data

Variables	Group C (n=37)	Group B1 (n=37)	Group B2 (n=36)	Group B3 (n=37)	*P*
Age (y)	72.4±7.5	72.1±7.8	72.3±6.5	72.5±5.7	0.993
Height (cm)	170 (165–172.5)	165 (160–173)	169.5 (165–171.8)	168 (165–171.5)	0.396
Body weight (kg)	66.4±8.9	66±10.8	64.9±8.6	65.4±7.8	0.912
BMI (kg/m^2)	23.3±2.5	23.7±2.9	22.9±2.3	23.0±2.1	0.519
ASA (II/III)	26/11	26/11	24/12	27/10	0.951
Hypertension (%)	11 (29.7)	13 (35.1)	8 (22.2)	14 (37.8)	0.492
Diabetes mellitus (%)	5 (13.5)	7 (18.9)	5 (13.8)	5 (13.5)	0.894
Duration of surgery (min)	82 (71.5–134.5)	90 (66.5–112.5)	90 (61.3–115)	85 (61.5–135)	0.957
Duration of anesthesia (min)	101 (91–146)	109 (82.5–125)	105 (75–130)	98 (77.5–147.5)	0.638

(*Continued*)

Table 1 (Continued).

Variables	Group C (n=37)	Group B1 (n=37)	Group B2 (n=36)	Group B3 (n=37)	*P*
Surgery types, n (%)					
TURP	4 (11.1)	2 (5.4)	3 (8.3)	3 (8.1)	0.346
PVP	10 (27)	15 (40.5)	8 (22.2)	17 (45.9)	–
TUPKRP	23 (63.9)	20 (54.1)	25 (69.4)	17 (45.9)	–
Intravenous fluid (mL)	900 (700–1100)	900 (750–1225)	900 (750–1100)	850 (600–1200)	0.745
Bladder flushing solution (L)	27 (18–45)	30 (21–42)	27 (18–33)	24 (21–39)	0.421
Bladder puncture fistula (%)	6 (16.2)	6 (16.2)	4 (11.1)	3 (8.1)	0.683

Notes: Data are presented as Mean ± SD, median (IQR) or number (%).
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; Group C, control group; Group B1, butorphanol 0.01 mg/kg group; Group B2, butorphanol 0.02 mg/kg group; Group B3, butorphanol 0.03 mg/kg group; TURP, transurethral resection of prostate; PVP, photoselective vaporization of prostate; TUPKRP, transurethral plasmakinetic resection of prostate.

compared with saline. Butorphanol 0.01 mg/kg decreased the incidence of shivering as well, but the difference was not statistically significant.

The elderly are less likely to shiver than the young because of their reduced ability to adjust to changes in body temperature.[19–21] A regression analysis of 1340 patients found that age was the most important risk predictor of shivering after general anesthesia.[7] The population selected for this study was elderly patients undergoing transurethral resection of the prostate, who received large amounts of lavage fluid to flush the bladder during surgery. This type of surgery caused a lot of body heat loss, although we used passive warmth and active heating measures for patients, it could not prevent the loss of body heat, which may have increased the incidence of postoperative shivering.

Butorphanol is a hybrid opioid that exerts its clinical effects through strong KOR agonism and weak MOR agonism-antagonism. Its effect on KOR activation is dose-dependent and has a ceiling effect.[22] Previous studies have proved that

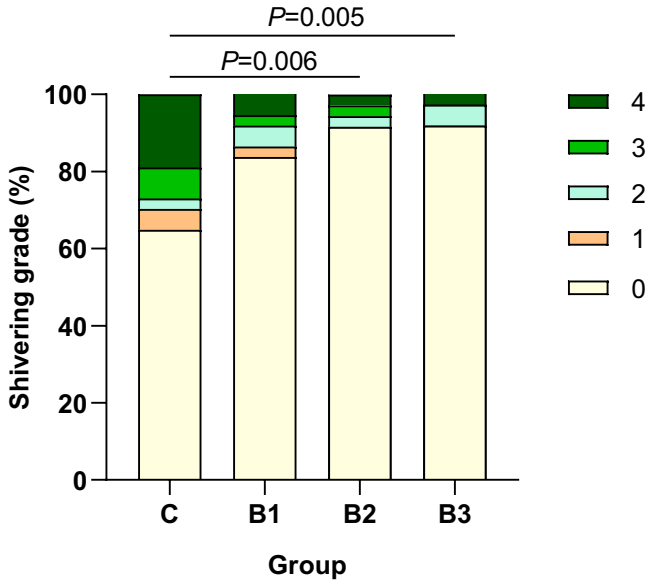

Figure 2 The Incidence of Postoperative Shivering Among the Four Groups.
Notes: Data are presented as percentage (%). "0", no shivering; "1", one or more of: piloerection, peripheral vasoconstriction, peripheral cyanosis without other cause, but without visible muscular activity; "2", visible muscular activity confined to one muscle group; "3", visible muscular activity in more than one muscle group; and "4", gross muscular activity involving entire body.
Abbreviations: C, control group; B1, butorphanol 0.01 mg/kg group; B2, butorphanol 0.02 mg/kg group; B3, butorphanol 0.03 mg/kg group.

Table 2 QoR-40 Score

Variables	Group C (n=37)	Group B1 (n=37)	Group B2 (n=36)	Group B3 (n=37)	*P*
Pre	187 (186–187.5)	187 (186–188)	187 (185.3–188)	187 (186–188)	0.961
POD 1	174 (170–177)	179 (177–181)*	181.5 (179.3–182)*	181 (179–182)*	<0.001
POD 2	183 (180–184)	184 (183–186)*	185 (184–186)*	184 (184–185)*	<0.001
POD 3	187 (186–188)	188 (187–189)	188 (187–189)	188 (186.5–189.5)*	0.022

Notes: Data are presented as median (IQR). *Compared with Group C, $P < 0.0083$.
Abbreviations: Group C, control group; Group B1, butorphanol 0.01 mg/kg group; Group B2, butorphanol 0.02 mg/kg group; Group B3, butorphanol 0.03 mg/kg group; Pre, preoperative day; POD 1, postoperative day 1; POD 2, postoperative day 2; POD 3, postoperative day 3; QoR-40, quality of recovery 40.

Table 3 Intraoperative Medication and Recovery Data After Extubation

Variables	Group C (n=37)	Group B1 (n=37)	Group B2 (n=36)	Group B3 (n=37)	*P*
Intraoperative Medication					
Consumption of propofol (mg)	210 (185–285)	205 (154–295)	195 (157.5–255)	190 (160–275)	0.216
Consumption of remifentanil (mg)	0.9 (0.7–1)	0.7 (0.5–0.9)	0.7 (0.5–0.8)	0.6 (0.5–0.9)*	0.002
Receiving vasopressors, n (%)	27 (73)	28 (75.7)	19 (52.8)	30 (81.1)	0.045
Recovery Data after Extubation					
Extubation time (min)	21.3±8.2	20.9±7.4	21.4±5.4	21.2±6.4	0.99
NRS score	1 (0–2)	0 (0–1.5)	0 (0–0.75)*	0 (0–0.5)*	<0.001
RASS score	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.122
Hyoxemia, n (%)	5 (13.5)	4 (10.8)	3 (8.3)	6 (16.2)	0.834
Somnolence, n (%)	4 (10.8)	3 (8.1)	4 (11.1)	7 (18.9)	0.614
Nausea or vomiting, n (%)	2 (5.4)	1 (2.7)	1 (2.8)	0 (0)	0.756
CRBD, n (%)	35 (94.6)	26 (70.3)*	16 (44.4)*	15 (40.5)*	<0.001

Notes: Data are presented as Mean ± SD, median (IQR) or number (%). *Compared with Group C, $P < 0.0083$.
Abbreviations: Group C, control group; Group B1, butorphanol 0.01 mg/kg group; Group B2, butorphanol 0.02 mg/kg group; Group B3, butorphanol 0.03 mg/kg group; RASS, Richmond Agitation Sedation Scale; NRS, Numerical Rating Scale for Pain; CRBD, catheter-related bladder discomfort.

butorphanol can effectively treat shivering after spinal anesthesia, but there are few studies on general anesthesia and shivering prevention.[23–25] In this study, we found that butorphanol can effectively reduce the occurrence and intensity of postoperative shivering, which is similar to the results of previous studies. Sujeet[6] concluded that 2 mg of butorphanol administered intravenously before induction of anesthesia or performing the regional block reduced shivering after general anesthesia or intraspinal anesthesia. Vikramjeet[26] observed that induction of anesthesia with 0.04 mg/kg butorphanol significantly decreased the incidence of shivering after laparoscopic cholecystectomy. In our study, the body temperature of the patients began to decrease after induction. The rate of decrease was faster in the first hour after induction and then became more gradual. In addition, there was no difference in BT_N and BT_F among the four groups at each time point, so we can speculate that the mechanism by which butorphanol resists shivering may be the reduction of postoperative shivering threshold rather than the promotion of thermogenesis.

Many studies have shown that remifentanil was associated with an increased incidence of postoperative shivering, which they believed was related to acute opioid tolerance and stimulation of N-methyl-D-aspartate (NMDA) receptors as in hyperalgesia.[5,27,28] Butorphanol three groups used less remifentanil during surgery, and butorphanol has been

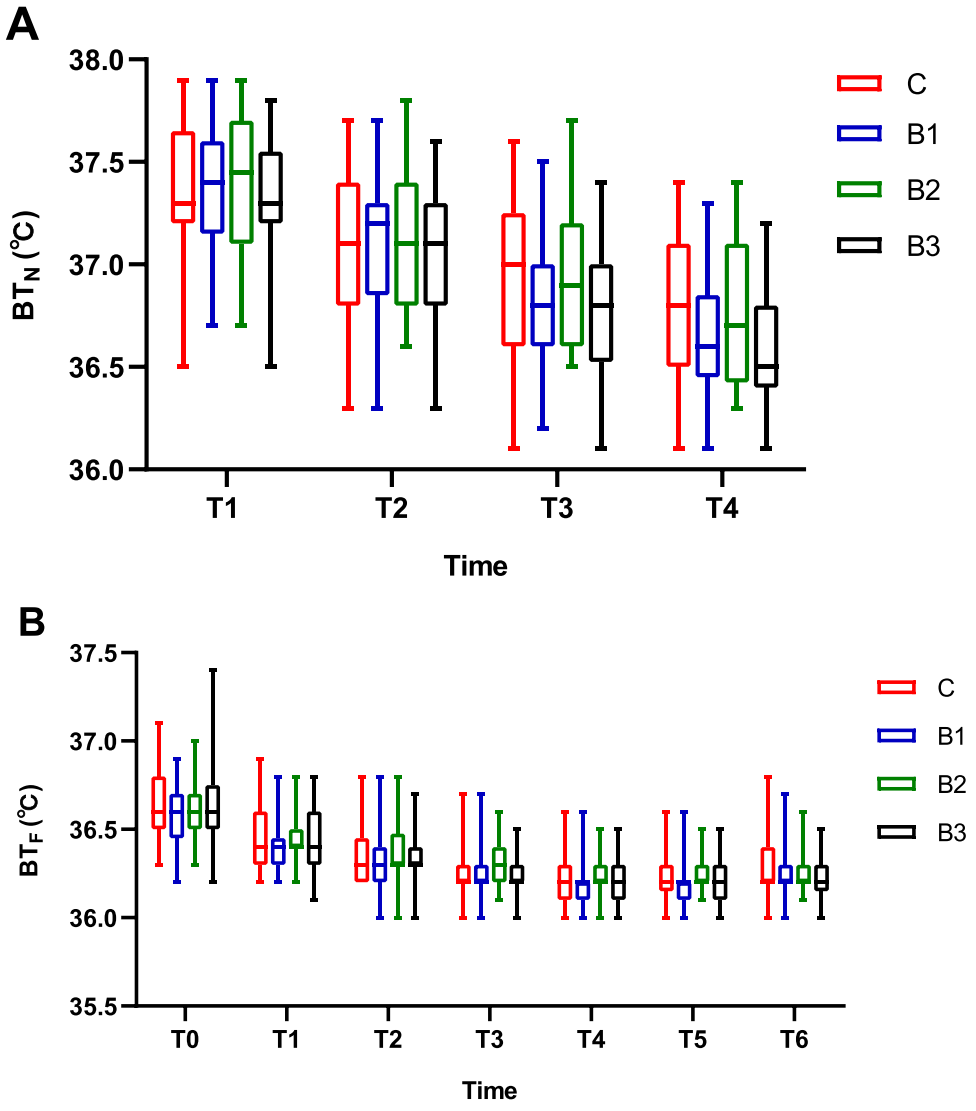

Figure 3 Perioperative Body Temperature (°C).

Notes: Median values shown as solid line within box of 25th and 75th percentile values. Whiskers represent maximum and minimum values. (**A**) BT_N (°C); (**B**) BT_F (°C). T0, before anesthesia induction; T1, at the beginning of surgery; T2, at 30 minutes after T1; T3, at 1 hour after T1; T4, at the end of surgery; T5, immediately after extubation; T6, at 30 minutes after extubation.

Abbreviations: C, control group; B1, butorphanol 0.01 mg/kg group; B2, butorphanol 0.02 mg/kg group; B3, butorphanol 0.03 mg/kg group; BT_N, nasopharyngeal body temperature; BT_F, forehead body temperature.

confirmed to significantly alleviate postoperative hyperalgesia induced by remifentanil,[29] both of which may account for the reduction of postoperative shivering in butorphanol groups. Many studies have found that postoperative pain was also a contributing factor to the occurrence of shivering. This is because pain and temperature signals are transmitted along similar fiber systems that synapse in dorsal horn regions.[30,31] Butorphanol has been a widely used analgesic in the clinic, as a KOR agonist, it is more effective for the treatment of visceral pain.[32] In the PACU, patients in Group B2 and B3 also had lower postoperative NRS scores than Group C. This suggested that butorphanol might reduce pain and postoperative hyperalgesia induced by remifentanil, thereby contributing to the reduction of postoperative shivering.

Recently, numerous studies have demonstrated the protective effects of KOR on the heart, lung, kidney and other key organs.[32–35] In addition, butorphanol can make anesthesia induction and recovery more smoothly and reduce the occurrence of postoperative cognitive dysfunction (POCD).[13,22,26] But they did not comprehensively assess the effect of butorphanol on the quality of postoperative recovery. The QoR-40 scale comprehensively assesses the quality of recovery from five clinical dimensions: physical comfort, emotional state, psychological support, physical independence

and pain perception. The higher the postoperative QoR-40 score is, the better the quality of postoperative recovery.[36] In the present study, we found that butorphanol could improve postoperative recovery quality scores. However, there was no significant difference among the three doses.

Evidence is increasing to demonstrate that activation of the KOR opposes a variety of μ-receptor-mediated actions throughout the brain and in the spinal cord.[37] As a mixed agonist and antagonist, butorphanol can not only exert a good analgesic effect, but also reduce the incidence of adverse effects associated with MOR.[29,32,38] In our results, butorphanol 0.02 or 0.03 mg/kg significantly reduced the postoperative NRS scores, and all three butorphanol doses reduced the incidence of postoperative CRBD, showing a significant analgesic effect. However, there was no significant difference in adverse effects such as nausea or vomiting among the four groups, which could be resulted from the routine use of antiemetics or insufficient sample size. Butorphanol can produce a certain degree of sedation and may cause somnolence, respiratory depression or hypoxemia.[22,26,38] But in our study, butorphanol did not prolong extubation time or result in excessive postoperative sedation. This may be related to the use of BIS to adjust the depth of sedation during operation.

This study has some limitations. Firstly, the sample population consisted only of elderly male patients, further studies will be required to determine whether the present findings can be generalized to other age groups and the female sex. Secondly, in this study, we only observed the effect of butorphanol on early postoperative shivering and recovery quality in elderly patients. The long-term effect of butorphanol needs further study. Thirdly, the use of physical heating measures during operation also has a certain prevention effect on postoperative shivering.[4,39,40] Although we routinely used a forced-air warmer set at 38°C during surgery, further studies will be needed to explore the best combination of antishivering medications and nonpharmacological antishivering interventions.

Conclusion

Butorphanol 0.02 or 0.03 mg/kg significantly reduced the incidence and severity of postoperative shivering in elderly patients scheduled for transurethral resection of the prostate, improved postoperative early recovery quality and provided effective postoperative analgesia with no additional significant adverse effects.

Data Sharing Statement

Access to the individual participant's data on which the results reported in this article may be available 6 months after the publication of this study with the approval of the corresponding author. Study protocols, statistical analysis plans and clinical study reports will also be available.

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Disclosure

All authors have no conflicts of interest in this work.

References

1. Lopez MB. Postanaesthetic shivering - from pathophysiology to prevention. *Rom J Anaesth Intensive Care*. 2018;25(1):73–81. doi:10.21454/rjaic.7518.251.xum
2. Kinjo T, Tadokoro T, Tokushige A, et al. Effects of perioperative administration of acetaminophen on postoperative shivering. *Anesth Analg*. 2020;130(4):983–990. doi:10.1213/ANE.0000000000004306
3. Hoshijima H, Takeuchi R, Kuratani N, et al. Incidence of postoperative shivering comparing remifentanil with other opioids: a meta-analysis. *J Clin Anesth*. 2016;32:300–312. doi:10.1016/j.jclinane.2015.08.017
4. Choi K, Park B, Moheet AM, Rosen A, Lahiri S, Rosengart A. Systematic quality assessment of published antishivering protocols. *Anesth Analg*. 2017;124(5):1539–1546. doi:10.1213/ANE.0000000000001571
5. Nakasuji M, Nakamura M, Imanaka N, Tanaka M, Nomura M, Suh SH. Intraoperative high-dose remifentanil increases post-anaesthetic shivering. *Br J Anaesth*. 2010;105(2):162–167. doi:10.1093/bja/aeq121

6. Rai S, Verma S, Pandey HP, Yadav P, Patel A. Role of butorphanol and ondansetron premedication in reducing postoperative shivering after general and spinal anesthesia: a randomized comparative study from North India. *Anesth Essays Res*. 2016;10(2):319–323. doi:10.4103/0259-1162.172724
7. Eberhart LHJ, Döderlein F, Eisenhardt G, et al. Independent risk factors for postoperative shivering. *Anesth Analg*. 2005;101(6):1849–1857. doi:10.1213/01.ANE.0000184128.41795.FE
8. Horn EP, Sessler DI, Standl T, et al. Non-thermoregulatory shivering in patients recovering from isoflurane or desflurane anesthesia. *Anesthesiology*. 1998;89(4):878–886. doi:10.1097/00000542-199810000-00012
9. Kang P, Park S, Yoo S, et al. Comparative effectiveness of pharmacologic interventions to prevent shivering after surgery: a network meta-analysis. *Minerva Anestesiol*. 2019;85(1):60. doi:10.23736/S0375-9393.18.12813-6
10. Cao C, Lv M, Wei C, Yan J, Wang Y, Gu C. Comparison of dexmedetomidine and meperidine for the prevention of shivering following coronary artery bypass graft: study protocol of a randomised controlled trial. *BMJ Open*. 2022;12(2):e053865. doi:10.1136/bmjopen-2021-053865
11. Lv S, Sun D, Li J, Yang L, Sun Z, Feng Y. Anesthetic effect of different doses of butorphanol in patients undergoing gastroscopy and colonoscopy. *BMC Surg*. 2021;21(1):266. doi:10.1186/s12893-021-01262-8
12. Juneja M, Ackerman WE. Butorphanol for the relief of shivering associated with extradural anesthesia in parturients. *J Clin Anesth*. 1992;4(5):390–393. doi:10.1016/0952-8180(92)90162-t
13. Yang L, Sun DF, Wu Y, Han J, Liu RC, Wang LJ. Intranasal administration of butorphanol benefits old patients undergoing H-uvulopalatopharyngoplasty: a randomized trial. *BMC Anesthesiol*. 2015;15:20. doi:10.1186/1471-2253-15-20
14. Wrench IJ, Singh P, Dennis AR, Mahajan RP, Crossley AW. The minimum effective doses of pethidine and doxapram in the treatment of post-anaesthetic shivering. *Anaesthesia*. 1997;52(1):32–36. doi:10.1111/j.1365-2044.1997.006-az006.x
15. Myles PS, Weitkamp B, Jones K, Melick J, Hensen S. Validity and reliability of a postoperative quality of recovery score: the QoR-40. *Br J Anaesth*. 2000;84(1):11–15. doi:10.1093/oxfordjournals.bja.a013366
16. Park J, Hong JH, Yu J, et al. Effect of Ketorolac on the Prevention of Postoperative Catheter-Related Bladder Discomfort in Patients Undergoing Robot-Assisted Laparoscopic Radical Prostatectomy: a Randomized, Double-Blinded, Placebo-Controlled Study. *J Clin Med*. 2019;8(6):759. doi:10.3390/jcm8060759
17. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;166(10):1338–1344. doi:10.1164/rccm.2107138
18. Myles PS, Myles DB, Galagher W, Chew C, MacDonald N, Dennis A. Minimal Clinically Important Difference for Three Quality of Recovery Scales. *Anesthesiology*. 2016;125(1):39–45. doi:10.1097/ALN.0000000000001158
19. O'Brien MW, Johns JA, Petterson JL, Mekary S, Kimmerly DS. The impact of age and sex on popliteal artery endothelial-dependent vasodilator and vasoconstrictor function. *Exp Gerontol*. 2021;145:111221. doi:10.1016/j.exger.2020.111221
20. Shirozu K, Umehara K, Ikeda M, Kammura Y, Yamaura K. Incidence of postoperative shivering decreased with the use of Acetaminophen: a propensity score matching analysis. *J Anesth*. 2020;34(3):383–389. doi:10.1007/s00540-020-02763-1
21. Jo YY, Kim YB, Lee D, Chang YJ, Kwak HJ. Implications of palonosetron in elderly patients undergoing laparoscopic cholecystectomy with respect to its anti-shivering effect. *Aging Clin Exp Res*. 2016;28(1):83–88. doi:10.1007/s40520-015-0373-9
22. Kaur J, Srilata M, Padmaja D, et al. Dose sparing of induction dose of propofol by fentanyl and butorphanol: a comparison based on entropy analysis. *Saudi J Anaesth*. 2013;7(2):128–133. doi:10.4103/1658-354X.114052
23. Bansal P, Jain G. Control of shivering with clonidine, butorphanol, and tramadol under spinal anesthesia: a comparative study. *Local Reg Anesth*. 2011;4:29–34. doi:10.2147/LRA.S15366
24. Juneja M, Ackerman WE. Butorphanol for the relief of shivering associated with extradural anesthesia in parturients. *J Clin Anesth*. 1992;4(5):390–393. doi:10.1016/0952-8180(92)90162-t
25. Manne VS, Gondi SR. Comparison of Butorphanol and Fentanyl for the Relief of Postoperative Shivering Associated with Spinal Anesthesia. *Anesth Essays Res*. 2017;11(1):84–87. doi:10.4103/0259-1162.186861
26. Arora V, Bajwa SJS, Kaur S. Comparative evaluation of recovery characteristics of fentanyl and butorphanol when used as supplement to propofol anaesthesia. *Int J Appl Basic Med Res*. 2012;2(2):97–101. doi:10.4103/2229-516X.106350
27. Hoshijima HD, Takeuchi RD, Kuratani NM, et al. Incidence of postoperative shivering comparing remifentanil with other opioids: a meta-analysis. *J Clin Anesth*. 2015;32:300–312. doi:10.1016/j.jclinane
28. Jung KT, So KY, Jee IG, Kim SH. Effect of intraoperative infusion of sufentanil versus remifentanil on postoperative shivering in Korea: a prospective, double-blinded, randomized control study. *Turk J Med Sci*. 2018;48(4):737–743. doi:10.3906/sag-1709-161
29. Kong M, Yang L, Li J, et al. Low-dose butorphanol alleviates remifetanil-induced hyperalgesia in patients undergoing laparoscopic cholecystectomy. *J Clin Anesth*. 2016;34:41–45. doi:10.1016/j.jclinane.2016.03.042
30. De Witte J, Sessler DI. Perioperative shivering: physiology and pharmacology. *Anesthesiology*. 2002;96(2):467–484. doi:10.1097/00000542-200202000-00036
31. Kranke P, Eberhart LH, Roewer N, Tramèr MR. Single-dose parenteral pharmacological interventions for the prevention of postoperative shivering: a quantitative systematic review of randomized controlled trials. *Anesth Analg*. 2004;99(3):718–727. doi:10.1213/01.ANE.0000130589.00098.CD
32. Wang X, Zeng S, Li X, et al. The Protective Effects of Butorphanol on Pulmonary Function of Patients with Obesity Undergoing Laparoscopic Bariatric Surgery: a Double-Blind Randomized Controlled Trial. *Obes Surg*. 2020;30(10):3919–3929. doi:10.1007/s11695-020-04755-2
33. Luan G, Pan F, Bu L, Wu K, Wang A, Xu X. Butorphanol Promotes Macrophage Phenotypic Transition to Inhibit Inflammatory Lung Injury via κ Receptors. *Front Immunol*. 2021;12:692286. doi:10.3389/fimmu.2021.692286
34. Zhou Y, Wang Y, Wang X, et al. The Protective Effects of Kappa-Opioid Receptor Stimulation in Hypoxic Pulmonary Hypertension Involve Inhibition of Autophagy Through the AMPK-MTOR Pathway. *Cell Physiol Biochem*. 2017;44(5):1965–1979. doi:10.1159/000485886
35. Franklin C, Fortepiani L, Nguyen T, Rangel Y, Strong R, Gottlieb HB. Renal responses produced by microinjection of the kappa opioid receptor agonist, U50-488H, into sites within the rat lamina terminalis. *Pharmacol Res Perspect*. 2015;3(2):e00117. doi:10.1002/prp2.117
36. Chen Y, Wang J, Liu S, et al. Development and Validation of the Chinese Version of the Quality of Recovery-40 Questionnaire. *Ther Clin Risk Manag*. 2020;16:1165–1173. doi:10.2147/TCRM.S281572
37. Pan ZZ. mu-Opposing actions of the kappa-opioid receptor. *Trends Pharmacol Sci*. 1998;19(3):94–98. doi:10.1016/s0165-6147(98)01169-9
38. Du BX, Song ZM, Wang K, et al. Butorphanol prevents morphine-induced pruritus without increasing pain and other side effects: a systematic review of randomized controlled trials. *Can J Anaesth*. 2013;60(9):907–917. doi:10.1007/s12630-013-9989-4

39. Hara K, Kuroda H, Matsuura E, et al. Underbody blankets have a higher heating effect than overbody blankets in lithotomy position endoscopic surgery under general anesthesia: a randomized trial. *Surg Endosc*. 2022;36(1):670–678. doi:10.1007/s00464-021-08335-y
40. Park B, Lee T, Berger K, et al. Efficacy of nonpharmacological antishivering interventions: a systematic analysis. *Crit Care Med*. 2015;43 (8):1757–1766. doi:10.1097/CCM.0000000000001014