Heart Surgery Forum 2024; 27(3): E289–E294
doi: 10.59958/hsf.7221
https://journal.hsforum.com/

Article

Safety and Efficacy of Butorphanol as an Analgesic for Patients on Mechanical Ventilation after Cardiac Surgery: An Exploratory Prospective Observational Study

Kaiqin Huang[1], Yuping Xiang[1], Tianhui Luo[1], Min Lin[1], Ling Zeng[1,*]

[1]Department of Critical Care Medicine, West China Hospital, Sichuan University/West China School of Nursing, Sichuan University, 610041 Chengdu, Sichuan, China

*Correspondence: zengling510@163.com (Ling Zeng)

Submitted: 7 January 2024 Revised: 5 March 2024 Accepted: 14 March 2024 Published: 20 March 2024

Abstract

Purpose: This study assessed the safety and analgesic efficacy of butorphanol in patients receiving mechanical ventilation after cardiac surgery. **Methods**: This was a prospective study. A consecutive cohort of patients from our medical center who underwent cardiac surgery followed by mechanical ventilation between January 2021 and April 2022 were divided into two groups and received either butorphanol or morphine for analgesia, and all patients also received propofol for sedation. Statistical analysis was performed using the *t*-test or chi-square test, and the pain levels of the two groups were compared based on the Critical-Care Pain Observation Tool (CPOT), as well as sedation based on the Richmond Agitation-Sedation Scale (RASS), and incidences of adverse events. **Results**: The two groups, each of which contained 70 patients, reported similar analgesic efficacy; the CPOT score was almost 0 and the RASS score was between 0 and –3. The butorphanol group experienced significantly lower rates of nausea, respiratory depression, and drowsiness. However, the two groups experienced similar rates of vomiting, pruritus, drowsiness, constipation, and delirium, durations of mechanical ventilation, use of sedative drugs, and lengths of stay in the intensive care unit. **Conclusions**: For patients on mechanical ventilation after cardiac surgery, butorphanol can provide analgesic effects similar to those of morphine with a potentially lower risk of certain adverse events.

Keywords

cardiac surgery; butorphanol; analgesia; prospective study

Introduction

Critically ill patients who require cardiac surgery often experience substantial postoperative pain [1,2], defined as acute pain occurring immediately after surgery and typically lasting no more than one week [3]. Postoperative analgesia can alleviate anxiety and stress, reduce oxygen consumption, maintain hemodynamic stability, and improve sleep [4]. Therefore, patients are typically treated with benzodiazepines, opioids such as morphine, and/or nonsteroidal anti-inflammatory drugs after cardiac surgery [5]. While some guidelines prefer opioids for their analgesic efficacy [6], these drugs increase the risk of various adverse effects, such as drowsiness, respiratory depression, urine retention, nausea, and vomiting [7].

Butorphanol tartrate may be a safer opioid to use as it induces analgesia by stimulating κ-opioid receptors [8] and, therefore, may have a lower risk of adverse events, such as respiratory depression, gastrointestinal inhibition, immune suppression, itching, and addiction, than opioids that stimulate μ-opioid receptors [9]. Currently, butorphanol tartrate is not widely administered to patients undergoing cardiac surgery. Instead, it is primarily administered to women who have given birth or to patients undergoing orthopedic or vascular surgery [10]. One study showed that, in patients receiving mechanical ventilation after cardiac surgery, butorphanol tartrate led to analgesic effects similar to those of a higher dose of fentanyl [11].

Therefore, we aimed to investigate whether butorphanol tartrate provides analgesic effects similar to those of morphine but with a lower risk of adverse events during mechanical ventilation after cardiac surgery. Our findings may guide the selection of sedative and analgesic drugs for the treatment of these patients [12].

Methods

Patients

This study was approved by the Ethics Committee of West China Hospital of Sichuan University (approval 2020-796). We prospectively recruited a consecutive cohort of patients who underwent cardiac surgery followed by mechanical ventilation between January 2021 and April 2022 in the cardiothoracic intensive care unit of the West China Hospital. Patients were enrolled if they were at least 18 years old and had undergone general anesthesia, fol-

Table 1. Clinical demographic characteristics of the two groups of patients.

Characteristic	Category	Butorphanol group (n = 70)	Morphine group (n = 70)	Test statistic	*p*
Sex	All	51.41 ± 13.54	53.87 ± 10.21	–1.212	0.228
	Male	39 (55.71)	40 (57.14)	0.029	0.865
	Female	31 (44.29)	30 (42.86)		
Educational level	Elementary and below	22 (31.43)	21 (30.00)	0.288	0.592
	Junior high to college	37 (52.86)	43 (61.43)		
	Bachelor and above	11 (15.71)	6 (8.57)		
Body mass index, kg/m^2		24.04 ± 3.22	24.23 ± 3.88	–0.313	0.755
Heart function grade	I	1 (1.43)	3 (4.29)	4.902	0.179
	II	35 (50.00)	25 (35.71)		
	III	32 (45.71)	36 (51.42)		
	IV	2 (2.86)	6 (8.58)		
Surgery type	Valve replacement	64 (9.43)	58 (82.86)	2.295	0.317
	CABG	2 (2.86)	4 (5.71)		
	Other	4 (5.71)	8 (11.43)		
Duration of anesthesia, h		5.50 ± 1.23	5.49 ± 0.93	0.047	0.963
Duration of extracorporeal circulation, min		124.11 ± 42.71	116.29 ± 37.30	1.155	0.250

Values represent the mean ± SD or n (%), unless otherwise noted. CABG, coronary artery bypass grafting.

lowed by surgery involving cardiopulmonary bypass (e.g., valve replacement or coronary artery bypass graft) and subsequent postoperative mechanical ventilation using the synchronized intermittent mandatory ventilation (SIMV) mode, followed by postoperative sedation and analgesics that lasted for at least 6 h.

Patients were excluded if they had a history of nausea, vomiting, pruritus, or drug allergies; they showed poor heart function (defined as ejection fraction <30%) or severe dysfunction of the liver or kidneys prior to surgery; they required epinephrine or norepinephrine at doses above 0.1 µg/kg/min or an intra-aortic balloon pump in order to restore or maintain hemodynamic stability after surgery; they required reoperation for bleeding or a second intubation after surgery; or they received hypothermic therapy after surgery.

The sample size was calculated based on previous studies involving butorphanol on patients received mechanical ventilation after cardiac surgery in intensive care unit [13], the outcomes considered in the calculation were Critical-Care Pain Observation Tool (CPOT), for this outcome, we considered a power of 80% with 0.05 significance, a difference to be detected of 0.04 liters and a standard deviation of 0.31, generating a sample of 14 patients per group. However, since Hu *et al*. [13] sample size was 249 cases, we decided to recruit 120 patients. Overall, a total of 144 patients were included d to compensate for possible dropouts. Of these, four were unable to fulfill the study and the final sample comprised 140 patients.

Interventions

Patients were assigned to one of two groups at the discretion of the attending physician. For sedation and analgesia, one group of patients received butorphanol tartrate (National Medical Products Administration of China with Approval Number H20020454, Jiangsu Hengrui Pharmaceutical Co., LTD., Lianyungang City, Jiangsu Province, China) at an initial dose of 6–10 µg/kg/h, while the other received morphine (National Medical Products Administration of China with Approval Number H20020454, Northeast Pharmaceutical Group Shenyang First Pharmaceutical Co., LTD., Shenyang, Liaoning, China) at an initial dose of 2 mg/h. All the patients received propofol (China Import Drug Registration Certificate Number H20171275, Corden Pharma S.P.A, Viale dell'Industria 3,20867 Caponago, ltaly) at an initial dose of 50 mg/h. The initial doses were adjusted according to the patient's level of sedation, analgesia, heart rate, and blood pressure. The analgesia Critical-Care Pain Observation Tool (CPOT) scores were between 0–2 and the Richmond Agitation-Sedation Scale (RASS) scores were between 0–3.

Assessments and Outcomes

Bedside nurses, all of whom were trained in assessing sedation and analgesia, collected data on the clinicodemographic patient characteristics, type of surgery, duration of anesthesia, cardiopulmonary bypass, and invasive mechanical ventilation. They also collected pain data using CPOT and sedation data using the RASS [14]. Pain and analgesia were assessed at the following time points: when patients awoke after surgery, 15 min after sedation and receiving

Table 2. Comparison of scores for pain and sedation as well as heart rate between the two groups at different time points.

Outcome	Time point	Butorphanol group (n = 70)	Morphine group (n = 70)	Test statistic	*p*
Critical Care Pain Observation Tool score	T1	0.13 ± 0.70	0.14 ± 0.60	–0.13	0.90
	T2	0.11 ± 0.69	0.04 ± 0.27	0.81	0.42
	T3	0.06 ± 0.29	0.04 ± 0.27	0.30	0.76
	T4	0.07 ± 0.35	0.06 ± 0.29	0.26	0.79
	T5	0.06 ± 0.34	0	1.43	0.16
	T6	0.04 ± 0.29	0	0.90	0.37
	T11	0.03 ± 0.24	0	1	0.32
	T12	0.01 ± 0.12	0	1	0.32
	T13	0.26 ± 0.77	0.04 ± 0.20	2.24	0.27
Richmond Agitation-Sedation Scale score	T1	–0.34 ± 0.78	–0.56 ± 0.75	1.65	0.10
	T2	–1.37 ± 1.24	–1.47 ± 0.88	0.55	0.58
	T3	–1.97 ± 1.13	–2.17 ± 0.82	1.20	0.23
	T4	–2.39 ± 0.82	–2.56 ± 0.79	1.26	0.21
	T5	–2.59 ± 0.81	–2.81 ± 0.60	1.90	0.06
	T6	–2.58 ± 0.97	–2.77 ± 0.58	1.08	0.28
	T11	–1.64 ± 1.22	–1.86 ± 1.20	1.05	0.30
	T12	–0.24 ± 0.67	–0.30 ± 0.60	0.53	0.60
	T13	0.01 ± 0.12	0	1	0.32
Heart rate	T1	86.54 ± 11.55	85.81 ± 12.89	0.35	0.73
	T2	87.10 ± 10.69	85.81 ± 13.31	0.63	0.53
	T3	86.57 ± 11.05	86.41 ± 14.94	0.08	0.94
	T4	86.41 ± 11.77	86.39 ± 14.48	0.01	0.99
	T5	85.94 ± 12.01	84.03 ± 13.60	0.88	0.38
	T6	82.67 ± 11.24	83.03 ± 11.94	–0.15	0.89
	T11	86.21 ± 12.02	84.76 ± 11.41	0.74	0.46
	T12	86.04 ± 12.07	86.07 ± 13.92	–0.01	0.99
	T13	87.03 ± 12.17	86.80 ± 10.96	0.11	0.91
Mean arterial pressure (MAP)	T1	81.67 ± 10.71	81.31 ± 9.98	0.20	0.84
	T2	78.94 ± 9.56	78.14 ± 8.88	0.51	0.61
	T3	78.14 ± 8.28	76.64 ± 8.75	1.04	0.30
	T4	77.49 ± 8.30	76.46 ± 7.91	0.75	0.45
	T5	80.21 ± 8.54	77.94 ± 8.20	1.61	0.11
	T6	80.85 ± 8.11	80.00 ± 9.11	0.47	0.64
	T11	84.09 ± 7.88	80.07 ± 8.70	2.86	0.005*
	T12	86.13 ± 8.03	83.01 ± 7.99	2.30	0.023*
	T13	85.87 ± 8.64	83.99 ± 8.88	1.27	0.21

Note: T1 (patient awake), T2 (sedation 15 min), T3 (sedation 30 min), T4 (sedation 1 h), T5 (sedation 5 h), T6 (sedation 9 h), T11 (sedation stopped), T12 (1 h after withdrawal of analgesics), T13 (1 h after extubation). *, $p <$ 0. 05).

analgesics, 1 h after the end of sedation and analgesia, and 1 h after extubation. At the same time points, heart rate and mean arterial pressure were measured.

Nurses collected data on adverse events that occurred during sedation and within 24 h after extubation, such as nausea, defined as self-reported upper abdominal discomfort and urgency to vomit; vomiting, defined as expulsion of stomach contents with or without intestinal contents through the mouth; respiratory depression, defined as obvious difficulty in breathing and CO_2 partial pressure >50 mmHg [15]; apnea; pruritus; drowsiness, defined as a score of –1 or below on the RASS; constipation, defined as the first bowel movement occurring >3 days after surgery; and delirium. Delirium was evaluated using the confusion assessment method for the diagnosis of delirium in the ICU (CAM-ICU) and every 4 h post-operation. Levels of C-reactive protein and interleukin-6 were recorded as markers of inflammation.

Statistical Analysis

All data were entered into Excel and analyzed using SPSS software (version 21.0; IBM, Chicago, IL, USA). Continuous variables were reported as mean ± standard de-

Table 3. Mechanical ventilation time, intensive care unit (ICU) stay, and inflammatory indicator levels of the two groups.

Object	Type	Butorphanol group (n = 70)	Morphine group (n = 70)	Statistical value	*p*-value
Mechanical ventilation time		21.48 ± 10.82	21.21 ± 18.20	0.107	0.915
ICU stay time		72.70 ± 33.28	72.13 ± 37.15	0.095	0.124
Inflammatory indicators	C-reactive protein	55.34 ± 53.80	59.94 ± 51.59	–0.520	0.610
	Interleukin-6	372.65 ± 432.16	394.70 ± 393.13	–0.310	0.750

viation and comparisons between groups were made using Student's *t* test if normally distributed; otherwise, the median (interquartile range) was calculated and compared using the Mann-Whitney U test. Categorical variables were presented as n (%) and compared using the chi-square test or Fisher's exact test. Differences were considered statistically significant at $p < 0.05$.

Results

Of the 144 patients screened for enrollment, we excluded two from the butorphanol group because they required reoperation due to postoperative bleeding and two from the morphine group because one experienced hemodynamic instability and the other underwent hypothermia treatment. The characteristics of the two groups, each containing 70 patients, did not differ significantly in terms of age, sex distribution, education level, body mass index, preoperative cardiac function, type of surgery, duration of anesthesia, or extracorporeal circulation (Table 1).

The CPOT and RASS scores did not differ significantly between the groups at any time point (Table 2). Heart rate did not differ significantly between the groups at any time point, and mean arterial pressure only differed between the two groups at the end of sedation and analgesia and 1 h after. Both groups received similar doses of butorphanol and morphine. The rates of nausea, respiratory depression, and drowsiness were significantly lower in the butorphanol group compared to those in the morphine group, whereas the rates of all other adverse events were similar between the two groups. The groups did not differ significantly in terms of the duration of mechanical ventilation, duration of stay in the intensive care unit, C-reactive protein levels, or interleukin-6 levels (Table 3).

Discussion

Our results indicate that butorphanol is a safe and effective analgesic for patients receiving mechanical ventilation after cardiac surgery. It provided our patients with a comparative analgesic effect to that at a similar dose of morphine but with a lower incidence of certain adverse events. Our study justifies the need for larger trials to verify and extend our findings, which may establish butorphanol as a safe analgesic option for patients undergoing cardiac surgery. Our study showed no statistically significant differences between the two groups in terms of inflammatory indicator levels.

Here, an initial dose of butorphanol 6–10 µg/kg/h was used, which is lower than the recommended dose of 10–20 µg/kg/h in previous studies [16]. Our results demonstrated that a lower dose of butorphanol can provide a similar analgesic effect to that of morphine [17], while reducing the risk of nausea, respiratory depression, and drowsiness. In this way, our results support the idea that butorphanol and other so-called "partial opioid receptor agonists" can reduce the risk of respiratory depression and gastrointestinal adverse reactions [18,19]. Butorphanol may also protect the myocardium [20] and help stabilize hemodynamic parameters [21], especially when administered with propofol [22]. Comparison of the effects of butorphanol with those of the opioid tramadol in women after receiving a cesarean section showed that butorphanol had significantly better analgesic activity as well as significantly lower risk of nausea, vomiting, dizziness, and 24-hour sedation after analgesia [23], leading to significantly higher patient satisfaction [24].

Limitations

Our results should be interpreted with caution because of the small, single-center sample size and because we only tested one dose of the drug. The fact that we used a dose lower than the recommended dose may mean that our work underestimates the efficacy of the drug and the risk of its adverse effects. Future studies should include a large, randomized trial and different drug doses to further verify and extend our findings. This study also used different definitions of respiratory depression to those of previous studies [15]. In the future, we will conduct further relevant studies to explore the analgesic effect of different doses of butorphanol in patients receiving mechanical ventilation during cardiac surgery.

Conclusions

For patients on mechanical ventilation after cardiac surgery, butorphanol can provide analgesic effects similar to those of morphine with a potentially lower risk of nausea, respiratory depression, and drowsiness.

Availability of Data and Materials

Data available on request from the authors.

Author Contributions

KH: Write the first draft of the manuscript, collected and organized data, contributed to editorial changes in the manuscript, read and approved the final manuscript. YX: Research Design, contributed to editorial changes in the manuscript, read and approved the final manuscript. TL: Data collection, contributed to editorial changes in the manuscript, participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. ML: Data collection, contributed to editorial changes in the manuscript, read and approved the final manuscript. LZ: Guide manuscript revision and submission, read and approved the final manuscript, agreed to be accountable for all aspects of the work in ensuring.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of West China Hospital of Sichuan University (approval 2020-796). All patients signed informed consent forms.

Acknowledgment

Not applicable.

Funding

This research was supported by Jiangsu Hengrui Pharmaceutical Co., LTD. (HX-H2010205).

Conflict of Interest

Our research team once again stated that although the research was funded, the implementation of clinical research was completed by our team, without conflict of interest.

References

[1] Vilīte B, Strīķe E, Rutka K, Leibuss R. Pain management in intensive care unit patients after cardiac surgery with sternotomy approach. Acta Medica Lituanica. 2019; 26: 51–63.

[2] Kurtaiş Aytür Y, Köseoğlu BF, Özyemişçi Taşkıran Ö, Ordu-Gökkaya NK, Ünsal Delialioğlu S, Sonel Tur B, *et al*. Pulmonary rehabilitation principles in SARS-COV-2 infection (COVID-19): A guideline for the acute and subacute rehabilitation. Turkish Journal of Physical Medicine and Rehabilitation. 2020; 66: 104–120.

[3] Brennan TJ. Pathophysiology of postoperative pain. Pain. 2011; 152: S33–S40.

[4] Zheng L, Zhao J, Zheng L, Jing S, Wang X. Effect of Dexmedetomidine on Perioperative Stress Response and Immune Function in Patients With Tumors. Technology in Cancer Research & Treatment. 2020; 19: 1533033820977542.

[5] Edinoff AN, Houk GM, Patil S, Bangalore Siddaiah H, Kaye AJ, Iyengar PS, *et al*. Adjuvant Drugs for Peripheral Nerve Blocks: The Role of Alpha-2 Agonists, Dexamethasone, Midazolam, and Non-steroidal Anti-inflammatory Drugs. Anesthesiology and Pain Medicine. 2021; 11: e117197.

[6] Wheeler KE, Grilli R, Centofanti JE, Martin J, Gelinas C, Szumita PM, *et al*. Adjuvant Analgesic Use in the Critically Ill: A Systematic Review and Meta-Analysis. Critical Care Explorations. 2020; 2: e0157.

[7] van der Schier R, Roozekrans M, van Velzen M, Dahan A, Niesters M. Opioid-induced respiratory depression: reversal by non-opioid drugs. F1000prime Reports. 2014; 6: 79.

[8] Ji J, Lin W, Vrudhula A, Xi J, Yeliseev A, Grothusen JR, *et al*. Molecular Interaction Between Butorphanol and κ-Opioid Receptor. Anesthesia and Analgesia. 2020; 131: 935–942.

[9] Boom M, Niesters M, Sarton E, Aarts L, Smith TW, Dahan A. Non-analgesic effects of opioids: opioid-induced respiratory depression. Current Pharmaceutical Design. 2012; 18: 5994–6004.

[10] Fortuna A, Alves G, Serralheiro A, Sousa J, Falcão A. Intranasal delivery of systemic-acting drugs: small-molecules and biomacromolecules. European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik E.V. 2014; 88: 8–27.

[11] Zhu Z, Zhang W. Efficacy and Safety of Butorphanol Use in Patient-Controlled Analgesia: A Meta-Analysis. Evidence-based Complementary and Alternative Medicine: ECAM. 2021; 2021: 5530441.

[12] Baker TR, Baker BB, Johnson SM, Sladky KK. Comparative analgesic efficacy of morphine sulfate and butorphanol tartrate in koi (Cyprinus carpio) undergoing unilateral gonadectomy. Journal of the American Veterinary Medical Association. 2013; 243: 882–890.

[13] Hu S, Wu XL. Clinical study of butorphanol on patients received mechanical ventilation after cardiac surgery in intensive care unit. The Journal of Practical Medicine. 2018; 34: 3458–3461.

[14] Chinese Society of Critical Care Medicine. Guidelines for analgesia and sedation in Chinese adult ICU.Chinese Journal of Critical Care Medicine. 2018; 30: 497–514. (In Chinese)

[15] Chen Y, Wang S, Huang J, Fu Y, Wen J, Zhou C, *et al*. Application of extracorporeal carbon dioxide removal combined with continuous blood purification therapy in ARDS with hypercapnia in patients with critical COVID-19. Clinical Hemorheology and Microcirculation. 2021; 78: 199–207.

[16] Zhang X, Qi S, Lin Z, Zhang Y, Dai W, Tian W, *et al*. Preoperative administration of butorphanol mitigates emergence agitation in patients undergoing functional endoscopic sinus surgery: A randomized controlled clinical trial. Frontiers in Psychiatry. 2023; 13: 1090149.

[17] Caulkett N, Read M, Fowler D, Waldner C. A comparison of the analgesic effects of butorphanol with those of meloxicam after elective ovariohysterectomy in dogs. The Canadian Veterinary Journal = La Revue Veterinaire Canadienne. 2003; 44: 565–570.

[18] Pathan H, Williams J. Basic opioid pharmacology: an update. British Journal of Pain. 2012; 6: 11–16.

[19] French AR, van Rijn RM. An updated assessment of the trans-

lational promise of G-protein-biased kappa opioid receptor agonists to treat pain and other indications without debilitating adverse effects. Pharmacological Research. 2022; 177: 106091.

[20] Folden DV, Gupta A, Sharma AC, Li SY, Saari JT, Ren J. Malondialdehyde inhibits cardiac contractile function in ventricular myocytes via a p38 mitogen-activated protein kinase-dependent mechanism. British Journal of Pharmacology. 2003; 139: 1310–1316.

[21] Wang X, Meng J. Butorphanol versus Propofol in Patients Undergoing Noninvasive Ventilation: A Prospective Observational Study. International Journal of General Medicine. 2021; 14: 983–992.

[22] Hosseinzadeh H, Eidy M, Golzari SE, Vasebi M. Hemodynamic Stability during Induction of Anesthesia in ElderlyPatients: Propofol + Ketamine versus Propofol + Etomidate. Journal of Cardiovascular and Thoracic Research. 2013; 5: 51–54.

[23] Du J, Li JW, Jin J, Shi CX, Ma JH. Intraoperative and postoperative infusion of dexmedetomidine combined with intravenous butorphanol patient-controlled analgesia following total hysterectomy under laparoscopy. Experimental and Therapeutic Medicine. 2018; 16: 4063–4069.

[24] Xu G, Zhao J, Liu Z, Liu G, Liu L, Ren C, *et al*. Dexmedetomidine Combined With Butorphanol or Sufentanil for the Prevention of Post-operative Nausea and Vomiting in Patients Undergoing Microvascular Decompression: A Randomized Controlled Trial. Frontiers in Medicine. 2020; 7: 583031.