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Analgesic efficacy of butorphanol combined with sufentanil after heart valve surgery

A propensity score-matching analysis

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Abstract

Pain is common after heart valve surgery and can stimulate the sympathetic nervous system, causing hemodynamic instability and respiratory complications. Current treatments for postoperative pain are insufficient, and postoperative pain is difficult to control effectively with a single analgesic. Therefore, we investigated the analgesic efficacy of butorphanol with sufentanil after heart valve surgery and its hemodynamic effects. The records of 221 patients admitted to the intensive care unit after cardiac valve replacement between January 1, 2018, and May 31, 2021, were retrospectively analyzed. Patients were allocated to 2 groups based on the postoperative pain treatment they received: treatment group (administered butorphanol combined with sufentanil), and control group (administered conventional sufentanil analgesia). After propensity score matching for sex, age, Acute Physiology and Chronic Health Evaluation II score, type of valve surgery, and operation duration, 76 patients were included in the study, and analgesic efficacy, hemodynamic changes, and adverse drug reactions were compared between the 2 groups. After propensity score matching, the baseline characteristics were not significantly different between the groups. The histogram and jitter plot of the propensity score distribution indicated good matching. No significant differences were observed in the duration of mechanical ventilation, duration of stay in the intensive care unit, duration of total hospital stay, and hospitalization expenditure between the groups ($P > .05$). The treatment group had notably higher minimum systolic blood pressure ($P = .024$) and lower heart rate variability ($P = .049$) than those in the control group. Moreover, the treatment group exhibited better analgesic efficacy and had lower critical-care pain observation tool scores and consumption of sufentanil 24 hours after surgery than the control group ($P < .05$). The incidence of vomiting was notably lower in the treatment than in the control group ($P = .028$). Butorphanol combined with sufentanil can be used in patients after heart valve replacement. This combined treatment has good analgesic efficacy and is associated with reduced adverse drug reactions and, potentially, steady hemodynamics.

Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II, CPOT = critical-care pain observation tool, ICU = intensive care unit, IQR = interquartile range, PSM = propensity score matching.

Keywords: analgesics, butorphanol, cardiovascular surgical procedures, hemodynamics, propensity score, sufentanil

1. Introduction

Postoperative pain management following heart surgery is usually inadequate,[1] and patients often experience moderate-to-severe pain. Most patients experience moderate or worse pain in a non-resting state within 7 days of either thoracotomy or laparoscopy.[2] Postoperative pain can stimulate the sympathetic nervous system and lead to poor outcomes. It can cause changes in the heart rate, increase myocardial oxygen consumption, and lead to hemodynamic instability in severe cases. Postoperative pain can also increase pulmonary complications and prolong the duration of mechanical ventilation.[3] It can also delay the recovery of gastrointestinal motility and cause anxiety and fear in the patients. Poor pain control can result in long-term chronic pain, which can seriously affect the daily activities of patients.[4]

Butorphanol is a mixed-action opioid receptor agonist-antagonist that acts on the central nervous system. It has different effects on κ, μ, and δ receptors[5] and is increasingly being used for postoperative pain management.[6,7] Fentanyl and sufentanil are common analgesics used after cardiac surgery[8]; both are opioid receptor agonists with similar mechanisms of action. Sufentanil acts primarily on the μ opioid receptor,[9] and butorphanol acts primarily on the κ opioid receptor. Previous studies

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study only included secondary analysis based on existing clinical data, and no human tissue collection and storage process was included during the study. The need for written informed consent was waived by the Ethical Committee of Dongyang People's Hospital because of the retrospective nature of this study. This study was approved by the Ethical Committee of Dongyang People's Hospital (Dong Ren Yi 2021-YX-172). This study followed all related local guidelines and regulations, including human genetic-related regulations.

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have shown that the combination of butorphanol and fentanyl enhances the analgesic effects of both drugs[10] and reduces their adverse reactions. Therefore, butorphanol combined with sufentanil for pain management after surgery may produce a better effect. This study aimed to investigate the analgesic efficacy and hemodynamic effects of butorphanol combined with sufentanil in patients after heart valve surgery.

2. Methods

2.1. General data

The study followed the reporting guidelines of Strengthening the Reporting of Observational Studies in Epidemiology. The records of 221 patients admitted to the intensive care unit (ICU) at the Dongyang People's Hospital after cardiac valve replacement between January 1, 2018, and May 31, 2021, were retrospectively analyzed. The inclusion criteria were as follows: American Society of Anesthesiologists grade I to III, age >17 years, and ICU stay >24 hours. The exclusion criteria were severe hepatic insufficiency, severe renal insufficiency, and >20% missing data. Surgical procedures and anesthetic management were performed according to local protocol. The study was approved by the Ethical Committee of Dongyang People's Hospital (Dong Ren Yi 2021-YX-172).

2.2. Drug regimen

Patients who received butorphanol tartrate (National Medicine Permit No. H20020454) combined with sufentanil citrate (National Medicine Permit No. H20054171) were assigned to the treatment group. Butorphanol was administered with a 0.167 mg/h micro-pump and maintained for 48 hours. Sufentanil dosage was adjusted based on the pain level of the patients and maintained within a target critical-care pain observation tool (CPOT) score of 0 to 2. Those who received conventional analgesia with sufentanil (administered with a 0–0.5 μg/kg/h micro-pump) and maintained a target CPOT score of 0 to 2 were assigned to the control group.

2.3. Data collection and processing

Data were collected using a medical record information mining software program (Shanghai Le9 Healthcare Technology Co., Ltd., Shanghai, China). The data collected comprised basic demographics data, including age, sex, the severity of disease, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, history of smoking, history of alcoholism, and comorbidities. The operation-related data included type of valve surgery, operation time, cardiopulmonary bypass time, clamping time, vital signs within 48 hours of admission to the ICU, delirium, and cardiac arrhythmia after cardiac surgery. Prognosis data of patients included time on the ventilator, length of ICU stay, length of hospital stay, and hospitalization cost. Patients with missing values for >20% of these variables were excluded from the analysis. The missing values of variables with loss rates of <20% were replaced using multiple imputations. Outliers were detected using the interquartile range (IQR, i.e., the difference between the upper and lower quartiles) of the boxplot. We used 1.5 times of IQR as the standard, and points exceeding this criterion (the upper quartile +1.5 times of IQR or the lower quartile −1.5 times of IQR) were defined as outliers. The excluded outliers were handled as missing values.

2.4. Evaluation of analgesic efficacy

Analgesia was evaluated using the CPOT scoring system, with higher scores indicating worse pain. Nurses performed CPOT assessments every 6 hours and maintained a target CPOT score of 0 to 2. We record the CPOT scores and total dose of sufentanil 24 hours after surgery. Nausea, vomiting, abdominal distension, respiratory depression, and other adverse drug reactions were recorded.

2.5. Evaluation of hemodynamic effects

The vital signs of patients were collected within 48 hours after enrollment and comprised maximum heart rate, minimum heart rate, average heart rate, maximum systolic blood pressure, minimum systolic blood pressure, average systolic blood pressure, maximum diastolic blood pressure, minimum diastolic blood pressure, and average diastolic blood pressure. In addition, the variabilities in heart rate, systolic blood pressure, and diastolic blood pressure were calculated; this comprised measuring hourly variance in heart rate, systolic blood pressure, and diastolic blood pressure. Patients in both groups were provided the same blood transfusion strategy and the use of vasopressors for steady hemodynamics. Common vasopressors, including norepinephrine, epinephrine, dopamine, and dobutamine, were recorded. Vasopressors were converted to an equivalent dose of norepinephrine using the following equation[11]:

Norepinephrine equivalent = norepinephrine + epinephrine + phenylephrine/10 + dopamine/100 + metaraminol/8 + vasopressin × 2.5 + angiotensin II × 10

2.6. Statistical analysis

Normally distributed measurement data are expressed as mean ± standard deviation ($x \pm$ standard deviation) and were compared between groups using independent-sample t test. Meanwhile, non-normally distributed data are expressed as M (P25, P75) and were compared using the Mann–Whitney U test. Enumeration data are expressed as rate and percentage and were compared between groups using the χ^2 test. All statistical analyses were performed using the R statistical software (version 4.1.2, The R Foundation for Statistical Computing, Vienna, Austria). A P value of ≤.05 was considered statistically significant. Propensity score matching (PSM) was used to reduce the influence of selection bias and potential confounding factors. The input variables in the propensity model were sex, age, APACHE II score, type of valve surgery, and operation duration, and 1:1 nearest neighbor matching was performed. A histogram and jitter plot of the propensity score distribution were drawn to evaluate the efficacy of the matching. A total of 76 patients were included in the study after PSM. A biomedical statistician conducted all statistical reviews required in this study.

3. Results

3.1. Comparison of general characteristics and clinical outcomes

A flowchart of the study process is shown in Figure 1. A total of 221 patients who underwent heart valve surgery were included, comprising 68 cases of aortic valve surgery (30.8%), 139 cases of mitral valve replacement (62.9%), and 14 cases of double valve replacement (6.3%).

Table 1 shows the general and clinical characteristics of the butorphanol-combined-with-sufentanil and the control groups. Before PSM, the proportion of men in the treatment group was 68.4%, and the severity of the disease was relatively high; the APACHE II score was higher in the treatment group than in the control group ($P = .051$). The treatment group had a higher body weight and a larger proportion of patients with a smoking history than the control group ($P < .05$ for both). No significant differences were observed in the proportion of patients with hypertension, diabetes, surgery time, cardiopulmonary bypass time, clamping time, and preoperative ejection fraction between the 2 groups ($P > .05$).

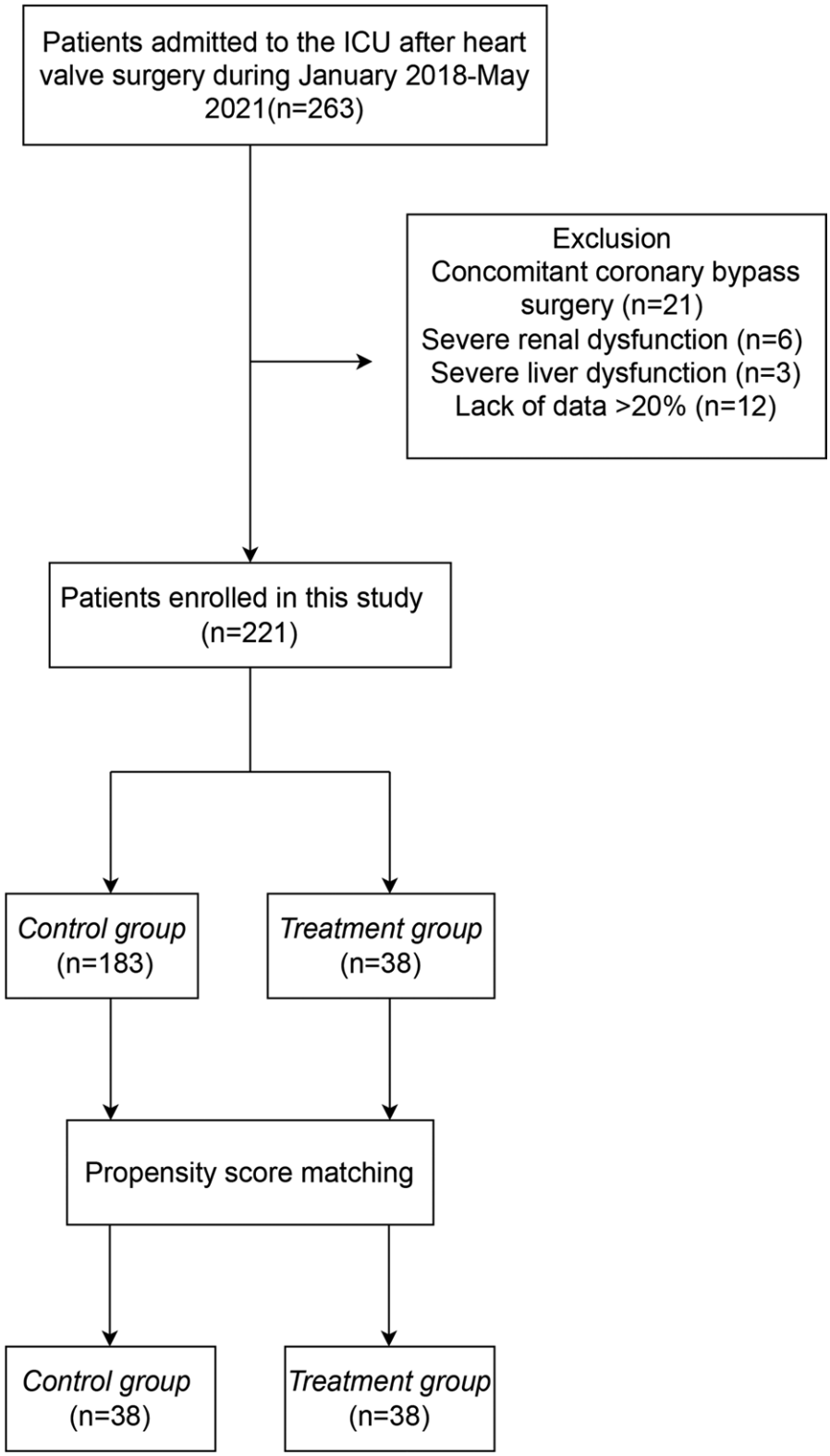

Figure 1. Flow chart of the study process.

After PSM, no significant differences were found in any of the indicators. Figure 2 shows the histogram of the propensity score distribution. After matching, the propensity score of the treatment group changed from unbalanced to balanced and became similar to that of the control group, indicating good matching. Figure 3 shows the jitter plot of the propensity score distribution. The 1:1 nearest neighbor matching result shows that the matched individual propensity scores were relatively close, indicating good matching.

A total of 6 patients died during the study, and 1 patient died after PSM. As the case fatality rate was low, no further analysis was performed. A comparison of the prognosis of the 2 groups

Table 1

Comparisons of baseline characteristics and prognosis between the treatment and control groups.

	Before PSM			After PSM		
Variables	**Control group (n = 183)**	**Treatment group (n = 38)**	***P* value**	**Control group (n = 38)**	**Treatment group (n = 38)**	***P* value**
Male [n (%)]	91 (49.7)	26 (68.4)	.055	25.0 (65.8%)	26.0 (68.4%)	.8
Age (yr)	60.5 ± 10.3	59.5 ± 11.5	.616	59.9 ± 9.4	59.5 ± 11.5	.887
APACHE-II score	14.2 ± 5.1	15.9 ± 4.9	.051	15.6 ± 5.5	15.9 ± 4.9	.775
Body height (cm)	162 ± 6.2	163.1 ± 5.3	.262	164.1 ± 6.1	163.1 ± 5.3	.446
Body weight (kg)	59.5 ± 10.6	63.3 ± 9.3	.031	61.8 ± 12.6	63.3 ± 9.3	.563
Smoking [n (%)]	56 (30.6)	20 (52.6)	.016	16 (42.1)	20 (52.6)	.491
Alcohol drinking [n (%)]	63 (34.4)	19 (50)	.104	18 (47.4%)	19 (50)	.818
Hypertension [n (%)]	52(28.4)	10 (26.3)	.949	8(21.1)	10 (26.3)	.889
Diabetes [n (%)]	23 (12.6)	4 (10.5)	.938	6 (15.8)	4 (10.5)	.734
Type of valve surgery			.064			.750
Aortic valve	62 (34%)	6 (16%)		8 (21%)	6 (16%)	
Mitral valve	110 (60%)	29 (76%)		26 (68%)	29 (76%)	
Double valve	11 (6.0%)	3 (7.9%)		4 (11%)	3 (7.9%)	
Ejection fractions (%)	58.8 ± 13	62.7 ± 15.6	.149	57.1 ± 13.1	62.7 ± 15.6	.153
Surgery time (h)	6.3 ± 2	6.2 ± 1.2	.755	5.4 (4.6, 7.0)	6.2 (5.6, 6.6)	.085
Cardiopulmonary bypass time (min)	101.6 ± 27.8	108.2 ± 25.4	.159	100.5 ± 26.3	108.2 ± 25.4	.2
Clamping time (min)	81.3 ± 20.9	79.9 ± 19.2	.694	87.4 ± 23.5	79.9 ± 19.2	.129

APACHE = Acute Physiology and Chronic Health Evaluation, PSM = propensity score matching.

showed no significant differences in the time on the ventilator, length of ICU stay, length of hospital stay, and total hospitalization cost ($P > .05$) (Table 2).

Table 3 shows the comparison of vital signs and vasopressor use within 48 hours of enrollment in the ICU between the treatment and control groups. Between the treatment and control groups, the minimum systolic blood pressure was higher (105.8 ± 15.9 mm Hg vs 98.9 ± 9.2 mm Hg, respectively; $P = .024$); heart rate variability was lower (3.7 ± 3.1 beats/min vs 5.5 ± 4.6 beats/min, respectively; $P = .049$); and minimum diastolic blood pressure was higher (52.6 ± 7.7 mm Hg vs 49.6 ± 7.5 mm Hg, respectively; $P = .088$) in the treatment group. The maximum and average systolic blood pressure; maximum and average diastolic blood pressure; and maximum, minimum, and average heart rate were similar between the 2 groups. However, the total dose of vasopressors 24 hours or 48 hours after surgery was not significantly different between the 2 groups ($P > .05$).

Table 4 shows the analgesia scores and adverse drug reactions in the patients in the treatment and control groups. The analgesic efficacy was better in the treatment group, and the CPOT scores and the dose of sufentanil 24 hours after surgery were lower than those in the control group; the difference between the 2 groups was significant ($P < .05$). The incidence of vomiting was lower in the treatment group than in the control group (5.3% vs 26.3%, respectively; $P < .028$); nausea, abdominal distension, respiratory depression, serum creatinine levels, and liver enzyme levels did not differ significantly between the 2 groups ($P > .05$).

4. Discussion

Our study found that the use of butorphanol combined with sufentanil after heart valve surgery resulted in better analgesic efficacy, more stable postoperative vital signs, and a lower incidence of adverse drug reactions.

Postoperative pain is difficult to control effectively with a single analgesic. Previously published research showed that butorphanol reduced sufentanil-induced cough[12] and stabilized the hemodynamic condition in patients. Better control of postoperative pain can be achieved by combining butorphanol with other opioids, such as tramadol[13] and meperidine.[14] Our study found the CPOT scores and the consumption of sufentanil were lower in the butorphanol-combined-with-sufentanil group. As most ICU patients cannot express pain, we selected CPOT, which is an objective index that can be used in patients under mechanical ventilation. Therefore, combined analgesia may be a future direction for postoperative analgesia therapy.

Hemodynamic instability often develops in patients after cardiac surgery.[1] Most patients develop myocardial dysfunction and reduced ventricular compliance in the early stages after cardiac surgery, which causes fluctuations in the heart rate and blood pressure and results in poor outcomes. The present study showed that the combination treatment group had a lower risk of hypotension and better heart rate stability 48 hours after enrollment in the ICU than the control group, indicating better hemodynamic stability. However, the dose of vasopressors used 24 hours and 48 hours after surgery did not decrease.

Animal and human studies have shown that opioid-mediated myocardial protection may be associated with improving ischemia-reperfusion injury.[15–17] The 3 different opioid receptor subtypes, κ, μ, and δ, appear to play different roles in producing these effects.[18] The combination of butorphanol and sufentanil may make the protective effect on the myocardium more significant.

Notably, opioid analgesics are the cornerstone of postoperative pain management but are often associated with nausea, vomiting, and other adverse reactions.[19] Butorphanol is a derivative of morphinan, which partially antagonizes α-opioid receptors and reduces the incidence of nausea, vomiting, and other postoperative side effects.[20] In a randomized controlled trial of gastrointestinal endoscopic analgesia,[21] butorphanol reduced postoperative nausea and vomiting, possibly due to reduced gastrointestinal motility and smooth muscle spasm, which in turn reduced the incidence of vomiting.

5. Limitations

The present study had some limitations. First, the sample size of the study was small, particularly after PSM matching. The differences in the variables between the 2 groups were not significant; for example, the minimum systolic blood pressure was significantly higher in the treatment group, whereas the minimum diastolic blood pressure did not differ significantly ($P = .088$), even though it was higher in the treatment group. It is believed that the difference between the 2 groups would be more significant if the sample size were increased. Second, the

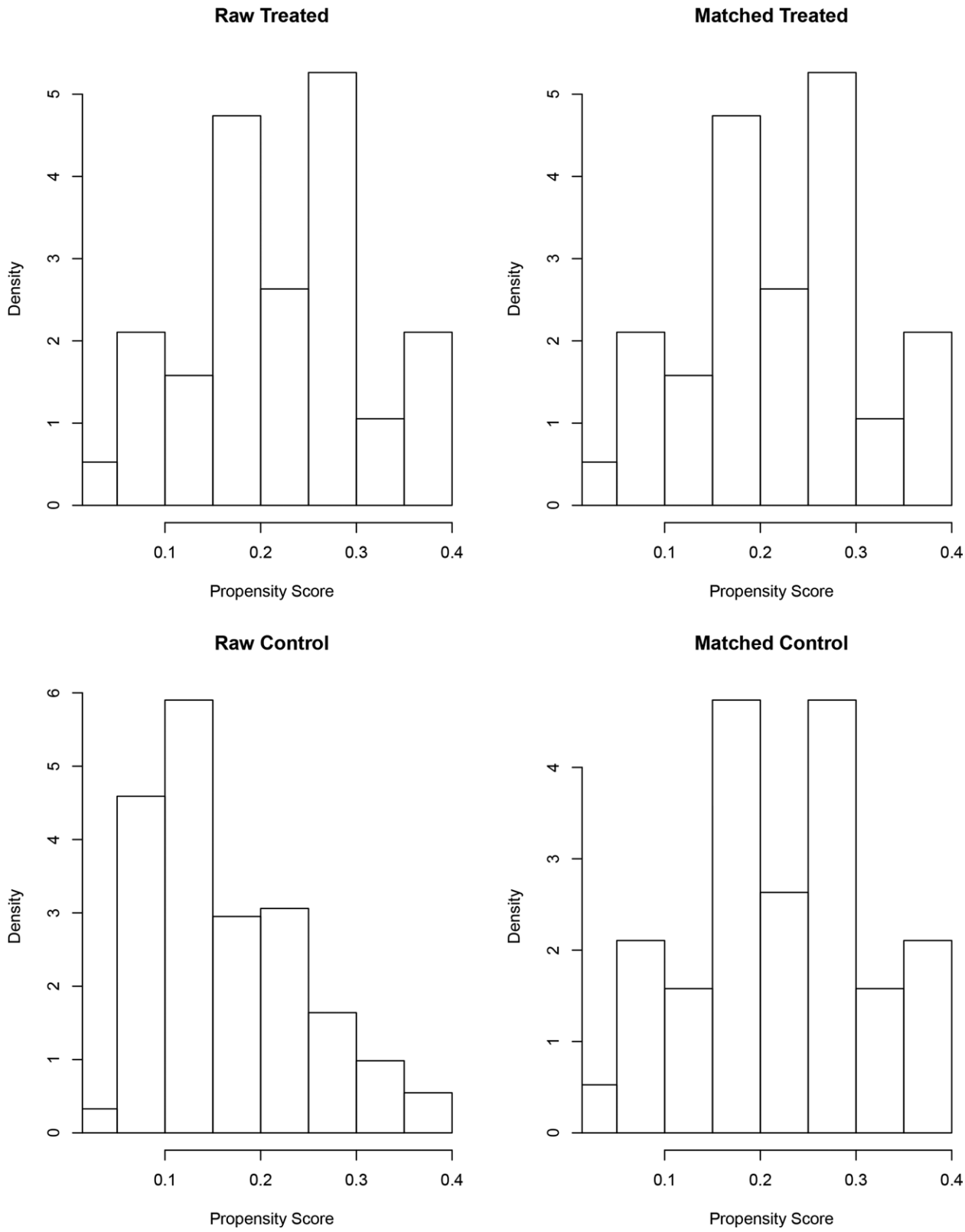

Figure 2. Histogram of distribution of propensity scores.

dose of butorphanol in the present study was fixed. The optimal dose of butorphanol combined with sufentanil is unclear. Future research can investigate how the ratio of the 2 doses can be adjusted to achieve optimal analgesic efficacy. Finally, this was a retrospective study, and some data were missing. For further research, we are currently conducting prospective trials.

6. Conclusions

Butorphanol combined with sufentanil has significant analgesic efficacy in patients after heart valve replacement and may increase hemodynamic stability. In addition, this combination therapy can effectively reduce adverse drug reactions, such as vomiting, making it a promising regimen for managing postoperative pain.

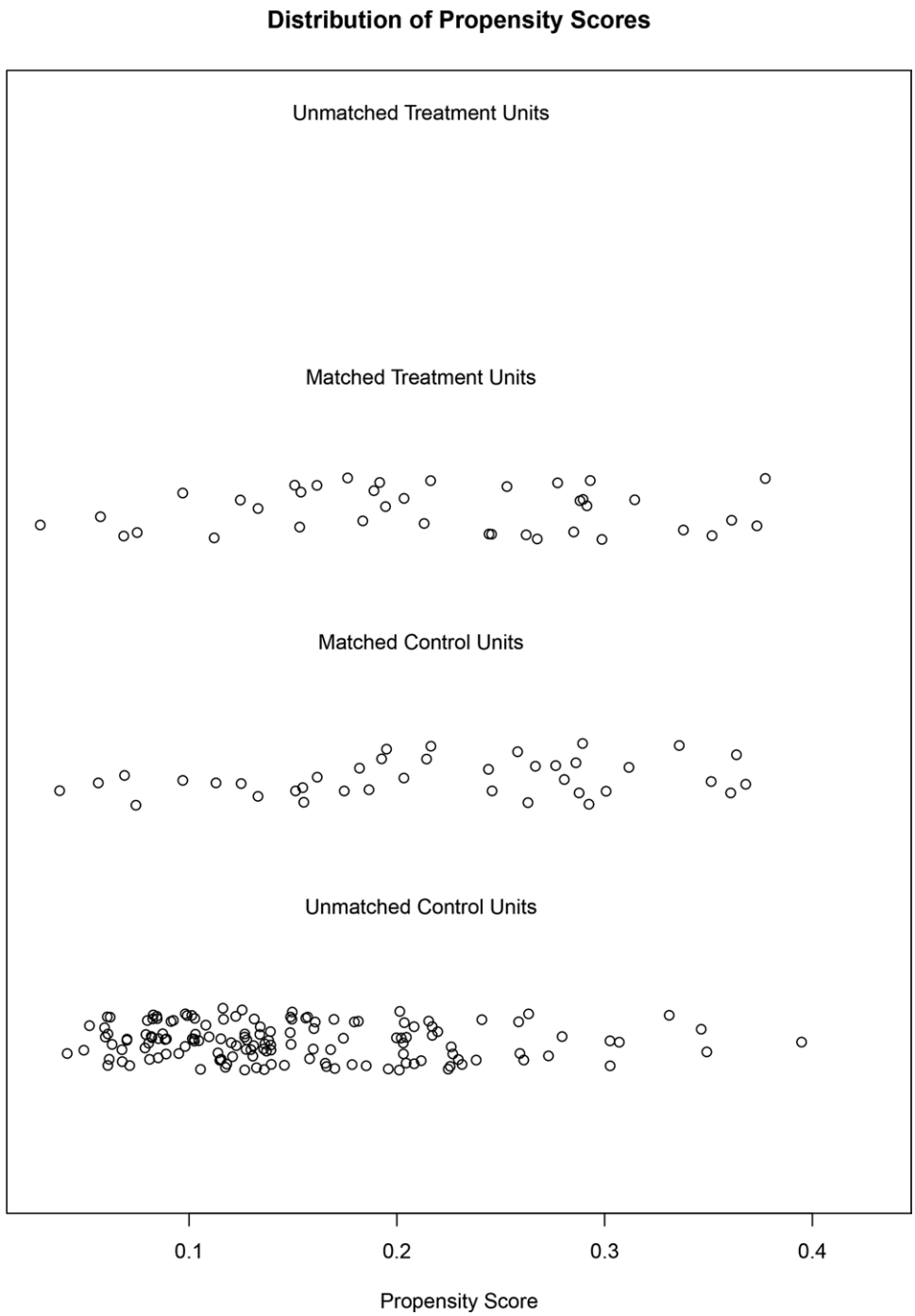

Figure 3. Jitter plot of propensity scores.

Table 2

Comparisons of prognosis between the treatment and control groups.

	Before PSM			After PSM		
Variables	**Control group (n = 183)**	**Treatment group (n = 38)**	***P* value**	**Control group (n = 183)**	**Treatment group (n = 38)**	***P* value**
Cost ($\times 10^3$, yuan)	132.85 ± 40.94	131.19 ± 36.13	.801	126.54 ± 40.19	131.79 ± 37.573	.558
Ventilation duration (d)	0.8 (0.72, 0.89)	0.79 (0.74, 0.82)	.458	0.8 (0.8, 0.9)	0.8 (0.7, 0.8)	.178
ICU length of stay (d)	3.8 (2.82, 5.59)	4.15 (3.73, 5.6)	.502	4.7 (3.7, 5.7)	4.2 (3.7, 5.6)	.629
Duration of hospital stays (d)	23 (19, 30)	25 (18.25, 31.75)	.722	22.0 (19.2, 30.2)	25.0 (18.2, 31.8)	.700

ICU = intensive care unit, PSM = propensity score matching.

Table 3

Comparison of vital signs and vasopressors in 2 groups of of enrolment after propensity score matching.

Variables	Control group (n = 38)	Treatment group (n = 38)	*P* value
SBPmin (mm Hg)	98.9 ± 9.2	105.8 ± 15.9	.024
SBPmax (mm Hg)	139.6 ± 11.5	143.7 ± 19.0	.205
SBPavg (mm Hg)	117.6 ± 10.7	121.7 ± 11.4	.057
SBPvariance	7.7 ± 2.8	8.0 ± 5.0	.747
DBPavg (mm Hg)	61.4 ± 7.7	61.1 ± 7.7	.897
DBPmin (mm Hg)	49.4 ± 7.5	52.6 ± 7.7	.088
DBPmax (mm Hg)	74.2 ± 9.5	91.3 ± 100.5	.493
DBPvariance	4.9 ± 2.3	4.7 ± 2.9	.403
Pmax (beats/min)	108.9 ± 32.9	103.1 ± 18.8	.925
Pmin (beats/min)	77.8 ± 10.8	78.7 ± 15.5	.636
Pavg (beats/min)	87.9 ± 10.7	90.4 ± 9.8	.273
Pvariance	5.5 ± 4.6	3.7 ± 3.1	.049
Vasopressors 24 h (μg/kg)	120.3 (102.8, 163.9)	147.6 (86.0, 243.2)	.596
Vasopressors 48 h (μg/kg)	219.0 (169.5, 312.5)	207.1 (154.6, 317.2)	.755

avg = average, DBP = diastolic blood pressure, max = maximum, min = minimum, P = heart rate, SBP = systolic blood pressure.

Table 4

Pain score the consumption of sufentanil and adverse drug reactions within 24 hours of enrolment after propensity score matching.

Variables	Control group (n = 38)	Treatment group (n = 38)	*P* value
CPOT score (6 h)			.005
0	9 (24%)	1 (2.6%)	
1	21 (55%)	33 (87%)	
2	7 (18%)	4 (11%)	
4	1 (2.6%)	0 (0%)	
CPOT score (12 h)			.009
0	5 (13%)	0 (0%)	
1	24 (63%)	35 (92%)	
2	8 (21%)	3 (7.9%)	
3	1 (2.6%)	0 (0%)	
CPOT score (18 h)			.003
0	5 (13%)	0 (0%)	
1	23 (61%)	35 (92%)	
2	10 (26%)	3 (7.9%)	
CPOT score (24 h)			.045
0	4 (11%)	0 (0%)	
1	26 (68%)	34 (89%)	
2	8 (21%)	4 (11%)	
Sufentanil 24 h (μg)			.016
100	8.0 (21.1%)	18.0 (47.4%)	
200	30.0 (78.9%)	20.0 (52.6%)	
Serum creatinine (mmol/L)	95.2 ± 35.6	89.8 ± 36.8	.518
Serum alanine aminotransferase (U/L)	97.9 ± 302	145.3 ± 521.9	.629
Serum aspartate aminotransferase (U/L)	99.5 ± 71.9	96.7 ± 64	.855
Respiratory depression [n (%)]	0 (13.2)	2 (5.3)	.493
Delirium [n (%)]	5 (13.2)	3 (7.9)	.709
Cardiac arrhythmia [n (%)]	8 (20.1)	11 (28.9)	.596
Nausea [n (%)]	7 (18.4)	4 (10.5)	.514
Vomiting [n (%)]	10 (26.3)	2 (5.3)	.028
Bloating [n (%)]	4 (10.5)	1 (2.6)	.358

CPOT = critical care pain observation tool.

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Writing – original draft: Xuandong Jiang.
Writing – review & editing: Xuping Cheng, Weimin Zhang.

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