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Original Article

The effects of remifentanil combined with propofol on the oxidative damage and the stress and inflammatory responses in cardiac surgery patients

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Abstract: Objective: This paper aims to explore the effects of remifentanil combined with propofol on the stress responses, oxidative damage, and inflammatory responses in cardiac surgery patients. Methods: One hundred and four patients who underwent cardiac surgery in our hospital from August 2017 to March 2019, were recruited as the study cohort and divided into control and observation groups. The 50 patients in the control group were anesthetized with fentanyl and propofol, and the 54 patients in the observation group were anesthetized with remifentanil and propofol. The general clinical data were observed and compared between the two groups. At different time points, changes in the oxidative stress response indicators (mean artery pressure (MAP) and heart rate (HR)) and in the cardiac function indexes (left ventricular ejection fraction (LVEF), stroke volume (SV), and cardiac output (CO)) were observed. The inflammatory cytokine levels (high-sensitivity C-reactive protein (hs-CRP), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α)) were analyzed using enzyme-linked immunosorbent assays (ELISA). The patients' postoperative recovery (time to spontaneous respiration, time to opening eyes, extubation time) and their Visual Analogue Scale (VAS) scores were observed. Their pain at half an hour and at 24 hours after the operation were observed, as well as their postoperative adverse reactions. Results: There were no differences in the general data between the two groups ($P>0.05$). Compared with the patients in the control group, the patients in the observation group had better oxidative stress levels and better cardiac function indexes ($P<0.05$), better postoperative inflammatory cytokine levels ($P<0.05$), better postoperative recovery ($P<0.05$), lower postoperative pain scores ($P<0.05$), and a lower total incidence of adverse reactions ($P<0.05$). Conclusion: Remifentanil combined with propofol can effectively reduce oxidative stress and inflammatory responses in cardiac surgery patients.

Keywords: Remifentanil, propofol, cardiac surgery, oxidative stress responses, inflammatory responses

Introduction

Clinically, heart diseases commonly seen in the department of cardiac surgery include congenital heart disease, valvular heart disease, coronary heart disease, cardiac tumors, etc. [1]. Their therapeutic methods are usually surgical treatment, such as coronary artery bypass graft surgery, surgery for congenital heart disease, and valve replacement [2]. However, cardiac surgery operations are difficult, and the complexity of the operation, coupled with the fact that some patients need to be operated on under extracorporeal circulation, make surgical anesthesia essential to the completion of the whole surgery [3]. In open surgery, the risk of surgery is exacerbated by the extracorporeal circulation of the blood, the need to control the coagulation parameters, and the restriction of the operating time, so keeping satisfactory intraoperative hemodynamics is crucial to the smooth completion of cardiac surgery [4]. Anesthetic drugs, however, affect the hemodynamics to a certain extent [5]. Moreover, with the rapid development of modern society and the changes in people's living habits, the number of patients with cardiac diseases is on the rise [6], so the number of those undergoing cardiac surgery has been gradually rising, and the shortage of medical resources (such as operating rooms and intensive care units) has become a major factor that restricts this surgery [7]. Therefore, the accurate depth of anesthesia and the accurate dosage of drugs provide great help for the patients and help conserve medical resources.

At present, opioids are one of the main drugs used in anesthesia [8]. It has been confirmed that remifentanil, an opioid, has a quick response, a short action time, intravenous infusion, and it can be administered intravenously at a variable administration rate [9]. This drug is usually used for anesthesia and sedation in clinical surgery because of its satisfactory anesthetic effect [10]. As a commonly used anesthetic drug, propofol is used for the induction and maintenance of general anesthesia [11], and it is usually used with analgesics, muscle relaxants and inhalation anesthetics [12]. Currently, the anesthetic effect of remifentanil combined with propofol in clinical surgery has been verified [13], but the effect in cardiac surgery remains controversial. To determine the best choice of anesthetic drugs in cardiac surgery and to improve patient prognosis, we explored the anesthetic effect of the combination in this surgery in this study, so as to provide a reference for clinical practice.

Materials and methods

Collection of the patients' data

One hundred and four patients who underwent cardiac surgery in Qinghai Provincial People's Hospital from August 2017 to March 2019, were recruited as the study cohort and divided into a control group and an observation group. The 50 patients in the control group were anesthetized with fentanyl and propofol, and the 54 patients in the observation group were anesthetized with remifentanil and propofol.

Inclusion and exclusion criteria

Inclusion criteria: Patients who were confirmed to have cardiac diseases in our hospital and who could undergo cardiac surgery, patients who were operated on for the first time, patients who had complete case data, patients who agreed to participate in the investigation conducted by the medical staff in our hospital, and patients older than 18 years old.

Exclusion criteria: Patients suffering from other critical illnesses, patients who had taken sedative drugs for a long time, patients with hepatic or renal insufficiencies, patients with poor self-awareness, patients who were allergic to the drugs used in this study.

All of the above patients agreed to and signed the agreement. This experiment was approved by the Ethics Committee of our hospital.

Anesthesia methods

Observation group: At 30 min before the operation, the patients in this group were given scopolamine (0.3 mg) and diazepam (10 mg). After entering the operating room, they were connected with various measurement instruments, with the peripheral venous access opened. After an invasive arterial puncture was performed, their invasive blood pressure and central venous pressure were continuously monitored. After inhaling oxygen through masks for 3 min, they were intravenously injected with midazolam (0.2 mg/kg) and vecuronium (0.1 mg/kg) and then infused with remifentanil (2 μg/kg). Mechanical ventilation was performed after the endotracheal intubation. Next, they were intravenously administered remifentanil (1 μg/kg/min) and propofol (2 mg/kg/h) to maintain the anesthesia. During the operation, the patients' conditions were closely monitored, and their anesthetic doses were adjusted. The injection of propofol was stopped at 10 min before the end of the operations, but the administration of remifentanil continued until the end. Control group: The patients in this group were given fentanyl (5 μg/kg) instead of remifentanil, and then mechanical ventilation was performed after the endotracheal intubation. The target-controlled infusion of propofol was conducted to maintain anesthesia, and the fentanyl was intermittently infused. Drugs were no longer administered at half an hour before the end of the operation.

Outcome measures

At different time points, changes in the oxidative stress response indicators (mean artery pressure (MAP) and heart rate (HR)) and in the cardiac function indices (left ventricular ejec-

Table 1. Baseline data sheet

Groups	Observation group (n=54)	Control group (n=50)	t or X^2 value	*P* value
Age	68.5±5.4	69.8±5.6	1.205	0.231
Gender			0.048	0.826
Male	26 (48.15)	23 (46.00)		
Female	28 (51.85)	27 (54.00)		
History of smoking			0.227	0.633
Yes	23 (42.59)	19 (38.00)		
No	31 (57.41)	31 (62.00)		
History of alcoholism			0.193	0.661
Yes	15 (27.78)	12 (24.00)		
No	39 (72.22)	38 (76.00)		
BMI (kg/m^2)	22.89±3.34	23.08±3.27	0.283	0.770
Place of residence			0.237	0.626
City	37 (68.52)	32 (64.00)		
Countryside	17 (31.48)	18 (36.00)		
Nationality			0.195	0.659
Han	44 (81.48)	39 (78.00)		
Ethnic minorities	10 (18.52)	11 (22.00)		
Course of disease (Years)	2.32±0.47	2.26±0.37	0.720	0.474
Past medical history			0.016	0.992
Hypertension	10 (31.03)	9 (34.78)		
Diabetes	9 (27.59)	8 (26.09)		
No	35 (41.38)	33 (50.72)		
Family history			0.023	0.880
Yes	7 (14.89)	8 (16.00)		
No	40 (85.11)	42 (84.00)		

tion fraction (LVEF), stroke volume (SV), cardiac output (CO)) were observed. The inflammatory cytokine levels (high-sensitivity C-reactive protein (hs-CRP), interleukin-10, (IL-10), and tumor necrosis factor-α (TNF-α)) were analyzed using enzyme-linked immunosorbent assays (ELISA). The patients' postoperative recovery (time of spontaneous respiration, time of opening eyes, extubation time) and their Visual Analogue Scale (VAS) scores were observed. Their pain levels at half an hour and at 24 hours after the operations and their postoperative adverse reactions were also observed.

Statistical methods

The results of this experiment were statistically analyzed using SPSS 24.0. The count data was expressed as (rate), and chi-square tests were used for the comparisons between groups. The measurement data were expressed as (mean ± standard deviation), and a t test was used for the comparisons between groups, with one-way analysis of variance and LSD post hoc tests used for the comparisons between multiple groups. When P<0.05, the difference was considered statistically significant.

Results

General clinical data

There were no differences between the observation and control groups with respect to age, gender, history of smoking, history of alcoholism, body mass index (BMI), place of residence, nationality, course of disease, past medical history, or family history (P>0.05), as shown in **Table 1**.

The oxidative stress responses at the different time points

The changes in the patients' HR and MAP levels were observed before the induction of the anesthesia (t0), after the induction of the anesthesia (t1), immediately after the endotracheal intubation (t2), during the skin incision (t3), and at 10 min after the operation (t4). At t0, the changes in the two indicators were not significantly different between the two groups (P>0.05). At t2 and t3, the HR levels were lower in the observation group (P<0.05). At t1, the MAP levels were higher in the observation group (P<0.05), but at t3 and t4, this indicator was lower in this group (P<0.05). More details are shown in **Figure 1**.

Changes in the cardiac function indices at the different time points

The changes in the cardiac function indices at the different time points were compared between the two groups. At t0 and t4, there were no statistically significant differences in LVEF, SV, or CO between both groups (P>0.05). At t1, t2, and t3, the three indices were higher in the observation group (P<0.05). More details are shown in **Figure 2**.

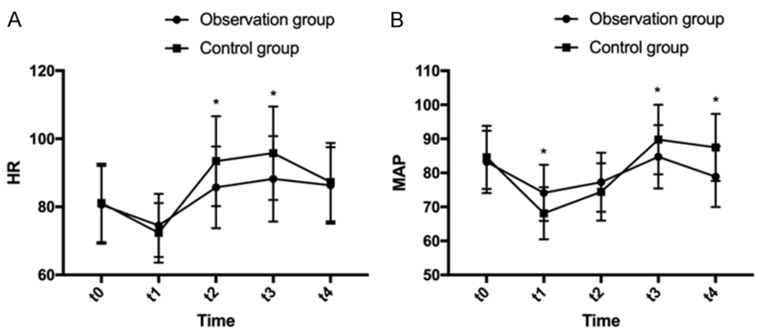
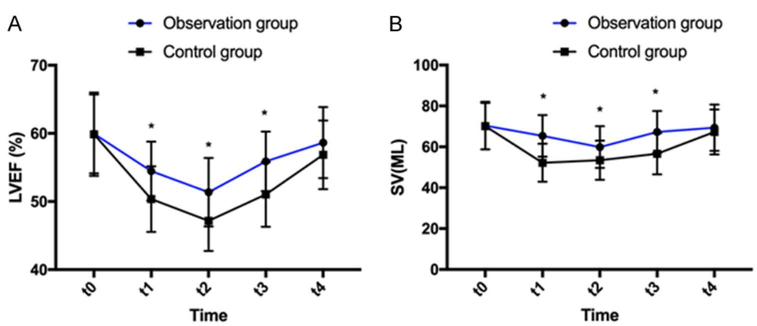


Figure 1. The oxidative stress responses at different time points. A. The changes in the HR at the different time points in both groups. B. The changes in the MAP at the different time points in both groups. Note: *indicates P<0.05.



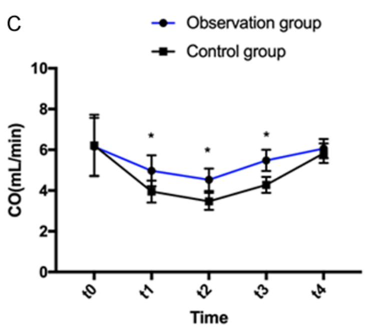


Figure 2. The changes in the cardiac function indices at the different time points. A. The changes in the LVEF at the different time points in both groups. B. The changes in the SV at the different time points in both groups. C. The changes in the CO at the different time points in both groups. Note: *indicates P<0.05.

The postoperative inflammatory cytokine levels

The postoperative serum hs-CRP, IL-10, and TNF-α levels were compared between the two groups. The three postoperative levels in the observation group were lower than they were in the control group (P<0.05). More details are shown in **Figure 3**.

Postoperative recovery

The spontaneous respiration times, the eye opening times, and the extubation times in both groups were observed. The times in the observation group were all shorter than the times in the control group (P<0.05). More details are shown in **Figure 4**.

VAS scores

The patients' pain levels at half an hour and at 24 hours after the operations were observed. At the two time points, the VAS scores in the observation group were lower than they were in the control group (P<0.05). More details are shown in **Figure 5**.

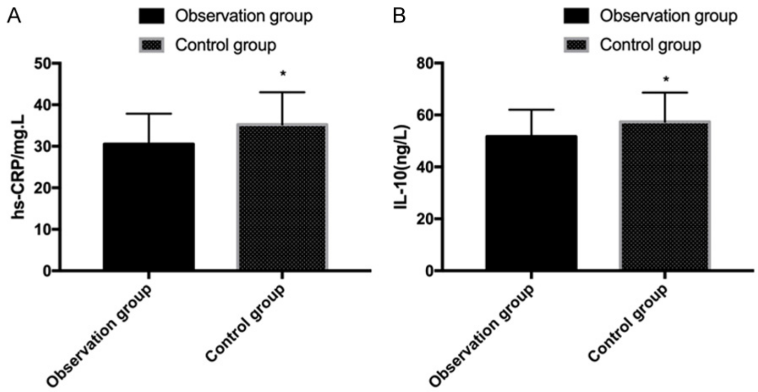
Postoperative adverse reactions

The incidences of postoperative adverse reactions in the two groups were observed. The number of adverse reactions in the observation group was 3 (5.56), which was significantly lower than the 10 (20.00) in the control group (P<0.05). More details are shown in **Table 2**.

Discussion

As a common surgery in clinical practice, cardiac surgery is performed frequently [14], so determining how to reduce the oxidative stress injuries and the inflammatory responses in patients undergoing this surgery is a major clinical focus [15]. With the deepening of research, more scholars believe that the use of different anesthetic and sedative drugs has different intervention effects on the surgical effects [16]. The application value of remifentanil combined with propofol in cardiac surgery has not yet been determined. Therefore, in this study, the influences of the combination on patients undergoing this surgery were explored, in order to provide a reliable reference for future clinical practice.

First of all, we intervened in the treatment of the patients with remifentanil combined with propofol, and we compared the HR and MAP level changes during the surgery in the two groups. At t0-t4, the two indicators in both groups exhibited great changes and similar fluctuations, but the changes were smaller in the observation group. This suggests that the



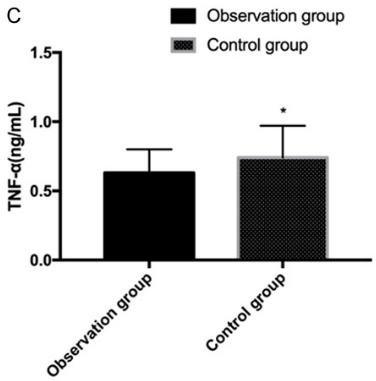
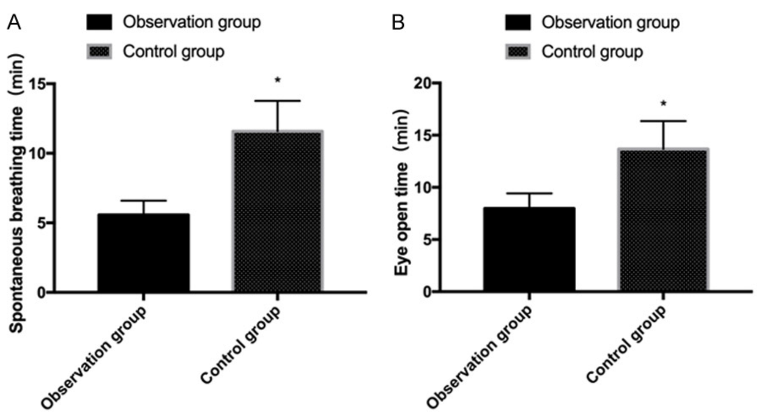


Figure 3. The postoperative inflammatory cytokine levels. A. The postoperative hs-CRP levels in both groups. B. The postoperative IL-10 levels in both groups. C. The postoperative TNF-α levels in both groups. Note: *indicates P<0.05.



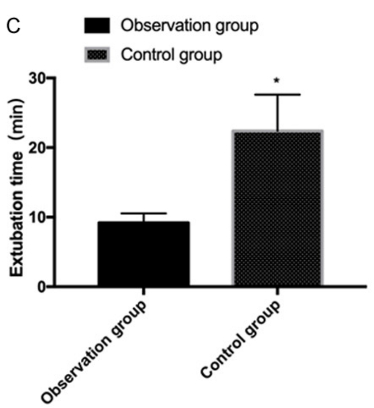


Figure 4. Postoperative recovery. A. The spontaneous respiration times after the operations in both groups. B. The times of opening the eyes after the operations in both groups. C. The extubation times after the operations in both groups. Note: *indicates P<0.05.

HR and MAP levels in the observation group were more stable, indicating that the combination has a better effect on maintaining the patients' vital signs, which is in line with the effects of the combination in previous research [17] and supports our experimental results. In our study, there were differences in the LVEF, SV, and CO levels at the different time points between the two groups, and they were higher in the observation group. The above results show that the cardiac function of the patients was better in the observation group, which suggests that the combination can protect the cardiac function more significantly. During cardiac surgery, it is usually necessary to perform a tracheotomy, sternum and skin incisions, and other operations, which cause sympathetic nerves to be excited and hemodynamics to fluctuate violently [18], and this is consistent with our research results above. It is precisely because of these fluctuations that there is a great potential for the impairment of cardiac function and the negative effects on the surrounding organs and tissues [19]. Therefore, maintaining the hemodynamic stability and the blood supply capacity of the cardiac function is crucial for reducing the fluctuations of the hemodynamics [20]. We speculate that the influence of remifentanil combined with propofol has a great relationship with the principle of remifentanil. With a molecular weight of 412.9 Da, remifentanil belongs to the methyl propionate hydrochloride family and is mainly combined with μ receptors, so it has all the analgesic and sedative characteristics of μ receptor agonists in pharmacodynamics [21]. However, this drug also has opiate side effects, such as respiratory depression, brady-

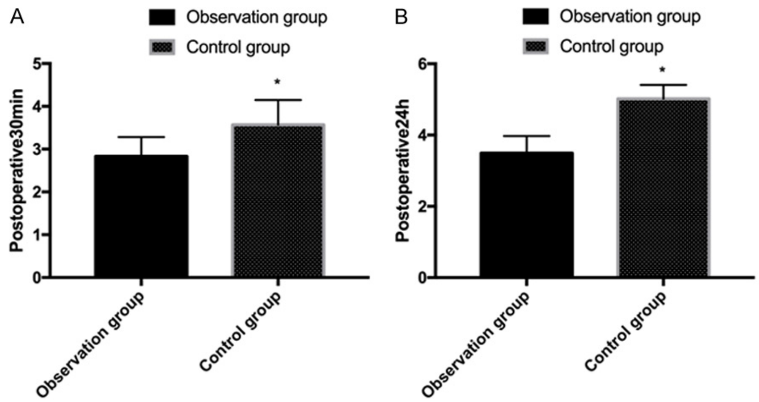


Figure 5. The VAS scores. A. The VAS scores at half an hour after operations in both groups. B. The VAS scores at 24 hours after the operations in both groups. Note: *indicates P<0.05.

cardia, and hypotension, but the side effects can be reduced using propofol and other adjuvant drugs [22]. Unlike traditional fentanyl, which is hydrolyzed by nonspecific blood and tissue esterases, 90% of the drug occurs in the urine as its metabolite. Erythrocytes are the main metabolic sites of remifentanil. After esterification, this drug forms a carboxylic acid metabolite-remifentanil acid (GI90291) with relatively weak activity, also a μ receptor agonist [23]. Additionally, this drug is highly fat-soluble and its time of onset is extremely fast, so its action intensity is higher than that of fentanyl [24]. It is widely distributed outside blood vessels, and its distribution volume is much smaller than the distribution volume of other opioids in a steady state [25]. For this reason, in this study, the vital signs and the cardiac function in the observation group were better than they were in the control group. In addition, the hs-CRP, IL-10, and TNF-α levels were lower in the observation group, which further suggests that remifentanil combined with propofol has a certain influence on the patients' inflammatory cytokines. As we all know, an increase in the inflammatory cytokines is caused by the severe necrosis or injury of tissues, cells, or nerves [26]. In our study, the reasons for their decrease in the observation group may also be similar to the results of the above analysis. The protective effect of the combination on the cardiac function can reduce the damage caused by intraoperative invasive operations, thus decreasing the inflammatory cytokines. Then, we compared the rehabilitation times between the two groups and found that the time was lower in the observation group. Such results reveal that the combination can not only improve the patients' cardiac function and inflammatory cytokines, but it can also greatly improve their rehabilitation cycles, which is consistent with the findings of Olesen and others [27]. Finally, we compared the incidences of adverse reactions between the two groups and found that the incidence was also lower in the observation group. This is possibly due to the results of the above analysis. Remifentanil has a strong and fast effect, and 90% of it can be completely metabolized in the urine, causing little damage to human body. Therefore, we speculate that remifentanil combined with propofol may have a potential application value for other types of clinical surgery in the future.

In summary, remifentanil combined with propofol can effectively reduce oxidative stress and the inflammatory responses in cardiac surgery patients.

However, there are still shortcomings to this experiment, such as the short duration of the experiment, the failure to conduct a long-term follow-up survey on the two groups of patients, and the small sample size in the experiment. In addition, only the two anesthetic methods with higher application rates were used in the experiment, so the differences between them and the other anesthetic methods could not be ruled out. The above limitations will also be the focus of our future research, and we will carry out a more complete and effective experimental analysis on the application of anesthesia in cardiac surgery to provide more precise clinical references.

Disclosure of conflict of interest

None.

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Table 2. The incidences of postoperative adverse reactions

	Observation group (n=54)	Control group (n=50)	X^2	P
Urinary retention	1 (1.85)	2 (4.00)		
Respiratory depression	0 (0.00)	2 (4.00)		
Nausea and vomiting	1 (1.85)	3 (4.08)		
Headache	1 (1.85)	2 (4.00)		
Restlessness during the recovery period	0 (0.00)	1 (2.00)		
Total incidence (%)	3 (5.56)	10 (20.00)	4.952	0.026

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