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Effects of sufentanil on immune response, pain mediators and brain-sparing effect in patients with breast cancer undergoing radical mastectomy

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Abstract

Objective To investigate the effects of sufentanil on immune response, pain mediators and brain-sparing effect in patients with breast cancer undergoing radical mastectomy.

Methods This study was a single center retrospective cohort study. The 118 study subjects were diagnosed and treated in our hospital from the period of January 2020-October 2022, who planned to undergo radical surgery for breast cancer. According to the different surgical drugs, these subjects were divided into sufentanil group and the control group, with 59 cases each. The visual analog scores (VAS) of patients in two groups were compared at 24 hour and 48 hour after surgery. The immune response indexes (including CD3+, CD4+, CD8+, CD4+/CD8+), pain mediators (β-endorphin, substance P and 5-hydroxytryptophan), brain-sparing effect indexes [arterio-venous oxygen content difference (Da-jvO2), jugular bulb venous saturation (S-jvO2), cerebral oxygen uptake (CEO2) and the Mini Mental State Scale (MMSE)], and brain damage indexes [S100 calcium-binding protein B (S100B) and neuron-specific enolase (NSE)] in two groups were compared. The incidence of adverse reactions in two groups was compared.

Results VAS scores were obviously lower in the sufentanil group than the control group at 24 hour and 48 hour postoperatively ($P<0.001$). Compared with the control group, the sufentanil group had higher CD3+, CD4+, CD4+/CD8+, MMSE scores, and lower content of CD8+, β-Endorphins, substance P, 5-hydroxytryptophan, Da-jvO2, S-jvO2 and CEO2 at 24 hour and 48 hour postoperatively ($P<0.05$). Patients in the sufentanil group had lower levels of S100B and NSE than the control group on the 1st and 7th day after surgery ($P<0.01$). The incidence of gastrointestinal reactions, hypertension and chills was significantly lower in the sufentanil group than the control group ($P<0.05$).

Conclusion The application of sufentanil in breast cancer radical surgery effectively improved the immune function of the body, reduced pain response, alleviated brain damage, and had a certain brain-sparing effect.

Keywords Sufentanil, Radical mastectomy, Immune response, Pain mediators, Brain-sparing effect

Introduction

Breast cancer is still the most common cancer in the world and the second leading cause of cancer related death in the world. According to statistics, more than half of breast cancer occurs in developing countries, especially in China [1, 2]. Surgical resection is the main treatment method for breast cancer at present, but the

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modified radical mastectomy for breast cancer has a large wound and severe postoperative pain. Acute postoperative pain affects the respiratory and immune system functions of patients, increases the risk of complications in high-risk patients, and leads to prolonged hospital stay [3]. As breast cancer radical surgery is a kind of surgery with obvious body surface trauma, it has a significant impact on the patient's respiratory system and circulatory system [4]. Therefore, in clinical practice, it is necessary to choose an effective anesthetic and an efficient anesthesia method to achieve good analgesic effects.

Sufentanil belongs to a type of fentanyl and is a newly synthesized powerful opioid analgesic. The analgesic potency of sufentanil is 5-10 times that of fentanyl, and it has advantages such as wide safety range, fast onset, strong analgesic effect, long duration, good cardiovascular stability, short and weak respiratory inhibition, and no histamine release [5]. However, sufentanil has high fat solubility, and compared to intravenous administration, it needs a higher dose through epidural administration to produce the same postoperative analgesic effect. Therefore, intravenous infusion of sufentanil is recommended for postoperative analgesia [6]. Scholars such as Lomangino et al [7] have found that using sublingual sufentanil for patient-controlled analgesia can provide effective analgesia for patients undergoing thoracoscopic lobectomy surgery and reduce the need for additional drugs, making it a non-invasive alternative to traditional intravenous therapy. Research has also found that, the unique pharmacological properties, good analgesic effect, and fewer adverse reactions of sufentanil give it a unique advantage in postoperative analgesic applications, making it suitable for postoperative intravenous analgesia and playing an important role in promoting early recovery of patients [8, 9]. However, the effect of sufentanil on the immune response, pain and brain protection of patients after radical surgery for breast cancer is still unclear.

In this study, 118 patients who were diagnosed and treated in our hospital from January 2020 to October 2022, and who planned to undergo radical surgery for breast cancer were chosen as the study subjects. We aimed to explore the effects of sufentanil on immune response, pain mediators and brain-sparing effect in patients with breast cancer undergoing radical mastectomy, aiming to provide certain theoretical references for clinical applications.

Materials and methods

General materials

Although this study was a retrospective cohort study, the advantages of prospective study have been fully considered at the beginning of its design. However, a prospective study could not be implemented due to practical conditions and time constraints. This retrospective study aimed to explore the effect of sufentanil in radical mastectomy using existing medical records and surgical reports. In this retrospective study, the creation of the panel was based on 118 patients who were diagnosed and treated in our hospital between January 2020 and October 2022 and were scheduled for radical mastectomy. According to the different surgical medication, the patients were divided into sufentanil group and control group by reviewing the medical records and medication records, with 59 cases in each group. Inclusion criteria: (1) All patients were diagnosed as breast cancer by postoperative pathology; (2) The patient was evaluated as Grade I-II according to the American Society of Anesthesiologists (ASA) classification; (3) The patient received treatment in the hospital throughout the entire process, and did not receive radiotherapy, chemotherapy, or other hormone drugs before surgery, and had complete clinical data; (4) The patient had no previous neurological disorders or cognitive impairment. Exclusion criteria: (1) Patients with severe liver, kidney or heart diseases; (2) Patients with severe allergies to the drugs used in this study; (3) Patients with abnormal immune or coagulation functions; (4) Patients who used immunosuppressive drugs and analgesics before surgery. This study was ratified by the hospital Ethics Committee and complied with medical ethics. These inclusion and exclusion criteria were determined according to the purpose of the study and literature review [10, 11], combined with the actual clinical situation, aiming to ensure the homogeneity of the study subjects and the reliability of the results. These criteria were strictly followed during data screening to ensure the accuracy and validity of the study data.

Treatment methods

All patients undergoing radical breast cancer surgery received general anesthesia through endotracheal intubation, and 10 mg of diazepam and 0.5 mg of atropine were intramuscularly injected 30 minutes before surgery. After entering the operating room, a venous pathway was constructed, physiological saline was infused, and arterial blood pressure, pulse oxygen saturation, electrocardiogram, heart rate, and bispectral index (BIS) of electroencephalogram were routinely monitored. A mask was adopted to absorb oxygen for 1-2 L/min.

The sufentanil group: Based on the comprehensive consideration of multiple previous studies and clinical practice [12, 13], patients in the sufentanil group received intravenous injection of sufentanil 0.5 μg/kg within 30 minutes before surgery for pretreatment. During anesthesia induction, propofol (Sichuan Guorui Pharmaceutical Co., Ltd., batch number: 202000496, specification: 10 mL: 0.1 g) and sufentanil (Yichang

Humanwell Pharmaceutical Co., Ltd., batch number: 20194171, specification: 1 mL: 50 μg) with a dose of 0.2 μg/kg were intravenously injected for anesthesia induction. After about 1 minute of slow injection, intermittent intravenous injection of rocuronium (Zhejiang Xianju Pharmaceutical Co., Ltd., batch number: 20203188, specification: 2.5 mL: 25 mg) was administered. An anesthesia ventilator was adopted to control ventilation, with tidal volume set at 7 m/kg, respiratory rate of 10-12 breaths/min, and maintain an end-expiratory carbon dioxide partial pressure of 35-40 mmHg. During the operation, sevoflurane was used to maintain anesthesia, with an inhalation concentration of approximately 2% to 3% and a BIS value of 45-60 maintained. Stop injecting sufentanil 30 minutes before the end of the surgery, and discontinue sevoflurane after the surgery. The patient was sent into the anesthesia recovery room with a tracheal catheter. The tracheal catheter was removed after the patient's spontaneous breathing was restored and met the indications for extubation. Throughout the perioperative period, no other opioids other than sufentanil were used to suppress the stress response caused by tracheal intubation and intraoperative pain. All patients received patient-controlled intravenous analgesia (PCIA) with sufentanil 0.2 μg/kg plus normal saline, 100 mL in total. The total dose of sufentanil was 0.9 μg/kg, of which 0.5 μg/kg was used for preoperative conditioning, 0.2 μg/kg for induction of anesthesia, and 0.2 μg/kg for postoperative analgesia.

The control group: Patients in the control group received intravenous injection of equivalent dose of physiological saline within 30 minutes before surgery as placebo. During anesthesia induction, propofol and sufentanil with a dose of 0.2 μg/kg were intravenously injected for anesthesia induction. After about 1 minute of slow injection, intermittent intravenous injection of rocuronium was administered. An anesthesia ventilator was adopted to control ventilation, with tidal volume set at 7 m/kg, respiratory rate of 10-12 breaths/min, and maintain an end-expiratory carbon dioxide partial pressure of 35-40 mmHg. During the operation, sevoflurane was used to maintain anesthesia, with an inhalation concentration of approximately 2% to 3% and a BIS value of 45-60 maintained. Stop injecting sufentanil 30 minutes before the end of the surgery, and discontinue sevoflurane after the surgery. The patient was sent into the anesthesia recovery room with a tracheal catheter. The tracheal catheter was removed after the patient's spontaneous breathing was restored and met the indications for extubation. Throughout the perioperative period, no other opioids other than sufentanil were used to suppress the stress response caused by tracheal intubation and intraoperative pain. Postoperative analgesia with PCIA was not performed.

Outcome measures

(1) Immune response detection: The content of immune response indicators was measured by flow cytometry (purchased from Beckman Kurt International Trade (Shanghai) Co., Ltd., model: CytoFLEX SRT), including CD3+, CD4+, CD8+, and CD4+/CD8+ before, 24 hours after surgery and 48 hours after surgery in two groups of patients. The specific steps were as follows: (1) Extract peripheral blood mononuclear cells: Fresh anticoagulant whole blood was gently mixed with 1 ×washing solution (purchased from Wuxi Tiancui Biotechnology Co., Ltd., Liangxi District, Wuxi City, Jiangsu Province, China, product number YC-B05611) in a 1:1 ratio (aimed to reduce blood viscosity) for later use. An appropriate amount of mononuclear cell separation solution was added to the sterile centrifuge tube (purchased from Beijing Zeping Biotechnology Co., Ltd., Haidian District, Beijing, China, product number TF112-1000-Q). The diluted blood sample flat was spread above the liquid level of the separation solution (separation solution: diluted whole blood=1:2), keeping the interface between the two liquid levels clear. The blood sample was centrifuged at room temperature for 20-30 minutes at 800 g. After centrifugation, the plasma layer was discarded, and the PBMC layer (the white membrane layer) was carefully drawn and transferred to a 15 mL centrifuge tube. After centrifugation, the liquid level in the tube was sequentially divided into the diluted plasma layer, PBMC layer, separation liquid layer, and red blood cell layer from top to bottom. 10 mL of 1 × diluted detergent was added to a centrifuge tube to resuspend the cells, followed by centrifugation at room temperature for 10 minutes at 250 g. The supernatant was then discarded. This step was repeated for 1-2 times for subsequent experiments. The cell suspension was centrifuged at room temperature of 600 g for 10 minutes and the supernatant was then discarded. 6 mL 1 ×red blood cell lysate was added to the centrifuge tube to fully suspend cells, and then the mixture was stood at room temperature for 5 minutes. The cells were washed twice with 20 mL PBS, centrifuged at room temperature of 600 g for 5 minutes. The supernatant was then discarded. N equal cell sample (1×10^6 cells) were removed and transferred to N different 1 mL centrifuge tubes for labeling. 100 μL FACS buffer containing antibodies (PBS, 0.5% BSA, 0.02%

NaN3) was added into the tubes for resuspension and the tube was incubated at room temperature in dark for 20-40 minutes. After incubation, the cells were washed twice with 1 mL of cold FACS buffer. The supernatant was discarded and the cells were resuspended with 0.5 mL FACS buffer for flow cytometry detection. The flow cytometry was purchased from Beckman Coulter International Trading (Shanghai) Co., Ltd. (Brand: BECKMAN COULTER; product number: 01).

(2) Pain score: The visual analogue scale (VAS) was used to evaluate the pain level of patients 24 and 48 hours after surgery, with a score range of 0-10 points. The more obvious the pain was, the higher the VAS score was.

(3) Pain mediator detection: Enzyme-linked immunosorbent assay was used to detect pain mediator indicators in two groups before, 24 hours after surgery, and 48 hours after surgery, including β-Endorphins, substance P, 5-hydroxytryptamine. The specific steps were as follows: The venous blood was extracted from two groups of patients, and centrifuged at 3000 r/min for 10 minutes. The supernatant was collected and stored at -20℃ for testing. Before testing, reagents and samples should be placed at room temperature (20℃-25℃) for more than 20 minutes to ensure sufficient reaction temperature for antigen and antibody in subsequent steps. The antigen peptide segments were prepared into 1 mg/ml antigen reserve solution using coated buffer and stored in a -20℃ refrigerator. The antigen peptide segments were diluted to 1 μg/ml using the coating buffer and the mixture was added into a 96-well ELISA plate with 50 μl/well during coating. The plated was incubated at 4℃ overnight (for 6-8 hour). 0.1 mL diluted sample was added to the coated reaction well and incubated at 37℃ for 1 hour. Then, the wells were washed (the blank holes, negative control holes, and positive control holes were set simultaneously). 0.1 mL of freshly diluted enzyme-linked antibodies (diluted after titration) was added to each reaction well, incubated at 37℃ for 0.5-1 hour, and then washed. Then, 0.1 mL of the temporarily prepared TMB substrate solution was added to each reaction well and was stood at 37℃ for 10 to 30 minutes. Finally, 0.05 mL of 2 M sulfuric acid was added to each reaction well for termination. The results could be directly observed with the naked eye on a white background: the darker the color inside the reaction hole was, the stronger the positive degree was. The negative reaction was colorless or extremely light. The result could also be determined by detecting the OD value on an ELISA detector at 450 nm. The reagent kits were all purchased from Jiangxi Aiboyin Biotechnology Co., Ltd. in Jiangxi Province, China.

(4) Detection of brain-sparing effect indicators: A blood gas analyzer (Beijing Bayun Tong Medical Equipment Co., Ltd., model: IRMATRUPOINT) was used to detect the levels of brain-sparing effect indicators in two groups before, 24 hours after surgery and 48 hours after surgery. Related indicators included cerebral arterio venous differences of oxygen content (Da-vO2), internal jugular vein bulb blood oxygen saturation (S-jvO_2) and cerebral extraction of oxygen (CEO2). The Mini mental state examination (MMSE) scale was used to evaluate changes in cognitive function in patients. The MMSE score included 7 items, including directional ability, attention and computational ability, and language, with a total score of 30 points. The score was directly proportional to the patient's cognitive function.

(5) Brain injury indicators: Peripheral venous blood was collected from patients before and 1 and 7 days after surgery. Blood samples were centrifuged and the supernatant after centrifugation was taken. Quantitative detection of S100 Calcium Binding Protein B (S100B) and neuron specific enolase (NSE) was performed using an enzyme-linked immunosorbent assay kit, following the same steps as (3).

(6) Adverse reactions: The occurrence of postoperative adverse reactions, including tachycardia, gastrointestinal reactions (such as nausea and vomiting), hypertension, pruritus and shivering, were observed. These adverse reactions were recorded for safety analysis.

Statistical Analysis

The enumeration data in this study was represented by [cases (%)] and compared using χ^2 test. Immune indicators and other measurement data were tested for normal distribution, and all were in accordance with normal distribution. The measurement data were shown in the form of ($\bar{x}\pm s$), and measurement data between two groups were compared using independent sample t-tests; The overall comparison of various observation indicators at different time points before and after surgery between the same group was conducted using repeated measurement bivariate analysis of variance. Multiple comparisons between different time points or between different time points in each group were conducted using LSD-t-test. In this study, SPSS24.0 software was used for statistical data analysis, and it was considered that the statistical result $P<0.05$ was statistically significant.

Results

Patient inclusion process and general data analysis

The inclusion process of 118 patients with breast cancer was shown in Figure 1. According to different anesthetic drugs, all subjects were divided into sufentanil group and control group, with 59 cases each. There existed no statistically significant difference between the two groups in terms of age, lesion length, surgical time, pathological grading and ASA grading (P>0.05, Table 1).

Analysis of postoperative immune response indicators in patients

Analysis of variance for repeated measurements of immune response indicators before surgery and at 24 and 48 hours after surgery in two groups of patients was conducted. The results found that the interaction effects between different drug groups and time factors were statistically significant (P<0.05). Further analysis of the individual effects of different drug groups showed that compared with the control group, the sufentanil group

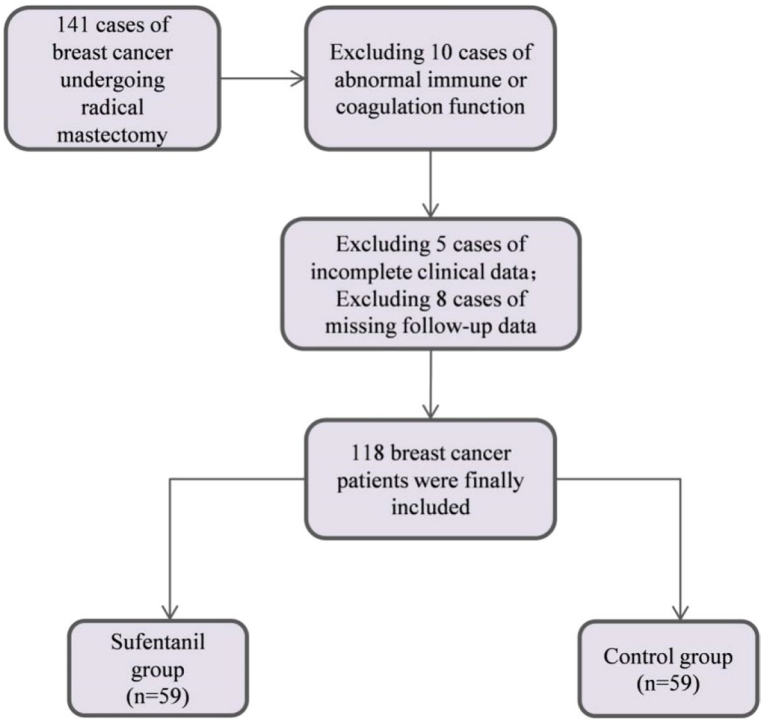

Fig 1 General data selection flow chart.

Table 1 Comparison of general information between two groups ($\bar{x}\pm s$, %)

General data	Sufentanil group (n=59)	Control group (n=59)	t/χ^2	P
Age (year)	41.28±5.39	42.33±4.89	1.108	0.27
BMI (kg/m^2)	22.15±1.36	21.87±1.05	1.252	0.213
Lesion length (cm)	3.27±1.15	3.18±1.34	0.392	0.696
Operative time (min)	111.24±13.29	115.62±12.74	1.827	0.070
Pathological grading			0.719	0.698
Grade I	18 (30.51)	20 (33.90)		
Grade II	24 (40.68)	26 (44.07)		
Grade III	17 (28.81)	13 (22.03)		
ASA grading			0.546	0.460
Grade I	30 (50.85)	34 (57.63)		
Grade II	29 (49.15)	25 (42.37)		

had higher levels of CD3+, CD4+, CD4+/CD8+and lower levels of CD8+at 24 and 48 hours after surgery (P<0.05). Further analysis was conducted on the individual effects of different time factors. Compared with preoperative, the levels of CD3+, CD4+, CD4+/CD8+ were significantly lower and the levels of CD8+ were significantly higher in the two groups 24 hours after surgery. Compared with 24 hours after surgery, the levels of CD3+, CD4+, CD4+/CD8+ were significantly higher and the levels of CD8+ were markedly lower at 48 hours after surgery (P<0.05, Table 2).

Analysis of postoperative pain scores for patients

The of patients in the sufentanil group had much lower VAS scores than the control group at 24 and 48 hours after surgery (P<0.001, Table 3)

Analysis of postoperative pain mediator levels in patients

Analysis of variance for repeated measurements of β-endorphins, substance P and serotonin before surgery and at 24 and 48 hours after surgery in two groups of patients was conducted. The results found that there were no differences in the levels of β-endorphin, substance P, and serotonin between the two groups before surgery (P>0.05, Table 4). However, the levels of β-endorphin, substance P and serotonin in sufentanil group were significantly lower than those in control group 24 and 48 hours after surgery (P<0.001, Table 4). In addition, compared with pre-operation, the levels of β-endorphin, substance P and serotonin in sufentanil group were increased 24 hours after surgery (P<0.001, Table 4). The levels of all three indexes were decreased at 48 hours compared with 24 hours after surgery (P<0.001, Table 4). The levels of these pain mediators first rose and then fell after surgery might be due to the metabolism of anesthetic drugs in the body and the analgesic effect of anesthetic drugs.

Analysis of postoperative brain-sparing effect indicators in patients

Analysis of variance for repeated measurements of MMSE score and Da-jvO2, S-jvO2 and CEO2 level before surgery and at 24 and 48 hours after surgery in two groups was conducted. The results found that the interaction effects between different drug groups and time factors were statistically significant (P<0.05). Further analysis of the individual effects of different drug groups showed that compared with the control group, the sufentanil group had higher MMSE score and lower levels of Da-jvO2, S-jvO2 and CEO2 at 24 and 48 hours after surgery (P<0.05). Further analysis was conducted on the individual effects of different time factors. Compared with preoperative, the MMSE score was much lower and the levels of Da-jvO2, S-jvO2 and CEO2 were significantly higher at 24 hours after surgery. Compared with 24 hours after surgery, the MMSE score was significantly higher and the levels of Da-jvO2, S-jvO2 and CEO2 were markedly lower at 48 hours after surgery (P<0.05, Table 5).

Comparison of postoperative brain injury indicators between two groups

Analysis of variance for repeated measurements of S100B and NSE level before surgery and at 24 and 48 hours after surgery in two groups was conducted. The results found that the interaction effects between different drug groups and time factors were statistically significant (P<0.05). Further analysis of the individual effects of different drug groups showed that compared with the control group, the sufentanil group had lower S100B and NSE level at 1d and 7d after surgery (P<0.05). Further analysis was conducted on the individual effects of different time factors. Compared with preoperative, the S100B and NSE level was much higher at 1d after surgery. Compared with 1d after surgery, the S100B and NSE level was significantly lower at 7d after surgery (P<0.05, Table 6).

Safety analysis

There existed no significant difference in tachycardia and skin itching between the sufentanil group and the control group (P>0.05). The sufentanil group had much lower incidence of gastrointestinal reactions, hypertension and chills than the control group (P<0.05, Table 7).

Discussion

Breast cancer not only brings considerable burden to patients, but also has a significant impact on physical and mental health, health care system and the whole society. Breast cancer radical surgery is an important method to treat breast cancer. However, due to factors such as short surgical time, general anesthesia is often used for rapid anesthesia in clinical practice, which brings significant physical harm to patients and affects their nervous system [14, 15]. The combined use of anesthetic drugs is a commonly used method of general anesthesia, but the synergistic or antagonistic effects can cause changes in drug efficacy, making it difficult to control the effect [16, 17]. Therefore, this study aimed to explore the effects of sufentanil on the immune response, pain mediators and brain-sparing effect of patients, so as to monitor its application in breast cancer radical surgery, and avoid or reduce the occurrence of adverse reactions in patients.

Radical surgery for breast cancer has a wide range of operations and serious trauma, which can cause acute or chronic pain in patients. In addition, due to the long-term consumption of body energy by the disease, the immune function of breast cancer patients is significantly

Table 2 Analysis of postoperative immune response indicators in patients (`$x \pm s$)

Group	n	CD3+ (%)			CD4+ (%)		
		Before surgery	24 hours after surgery	48 hours after surgery	Before surgery	24 hours after surgery	48 hours after surgery
The sufentanil group	59	84.27±6.14	66.68±7.86***	80.24±5.52##	46.38±5.84	35.35±6.36**	42.33±5.47##
The control group	59	82.41±5.92	58.15±5.86***	67.62±5.25###	45.79±4.41	27.95±5.38***	33.49±5.86###
$F_{\text{Treatment value}}/P_{\text{Treatment value}}$			4.634/0.031			7.442/0.016	
$F_{\text{Time value}}/P_{\text{Time value}}$			4.501/0.034			6.305/0.025	
$F_{\text{Treatment×Time value}}/P_{\text{Treatment ×Time value}}$			7.236/0.017			9.771/0.008	
Groups	n	CD8+ (%)			CD4+/CD8+ (%)		
		Before surgery	24 hours after surgery	48 hours after surgery	Before surgery	24 hours after surgery	48 hours after surgery
The sufentanil group	59	30.86±5.87	36.33±5.35***	33.02±3.57##	1.78±0.35	1.26±0.27***	1.45±0.35###
The control group	59	31.68±3.75	41.26±3.52***	30.17±2.58#	1.68±0.39	0.98±0.30***	1.12±0.17###
$F_{\text{Treatment value}}/P_{\text{Treatment value}}$			3.256/0.045			8.521/0.011	
$F_{\text{Time value}}/P_{\text{Time value}}$			5.221/0.030			7.852/0.018	
$F_{\text{Treatment×Time value}}/P_{\text{Treatment ×Time value}}$			4.555/0.028			10.321/0.001	

Note: $^{**}P<0.01$ and $^{***}P<0.001$ compared with preoperative data; $^{\#}P<0.05$, $^{\#\#}P<0.01$ and $^{\#\#\#}P<0.001$ compared with postoperative 24 hours.

Table 3 Analysis of postoperative pain scores for patients ($\bar{x}\pm s$)

Groups	Cases	VAS score		*t*	*P*
		24 hours after surgery	48 hours after surgery		
The sufentanil group	59	2.32±0.92	1.98±0.77	2.177	0.032
The control group	59	3.55±1.82	3.01±1.60	1.7142	0.090
t		4.633	4.456		
P		<0.001	<0.001		

reduced [18]. Research has shown that persistent severe pain can also cause severe stress reactions in patients, affecting normal physiological functions [19]. Delayed treatment can prolong postoperative hospitalization, hinder postoperative recovery, and increase medical expenses. Therefore, opioid drugs should be used during perioperative anesthesia and analgesia to reduce stress reactions and pain, especially in cancer patients, in order to maintain normal immunity. Sufentanil is a powerful opioid analgesic, which has high selectivity for μ Agonists and clear analgesic effects [20]. According to relevant data [21], under the same analgesic effect, sufentanil has a stronger effect on Treg cells in vitro than fentanyl. In addition, sufentanil may reduce the CD4+/CD8+ratio and increase the frequency of Treg cells [22]. In this study, the changes in immune function indicators and pain mediators in patients were observed. The results showed that the levels of CD3+, CD4+, CD4+/CD8+significantly increased at 24 and 48 hours after surgery, and CD8+and β- The levels of endorphins, substance P, and serotonin were largely reduced. These above results indicated that sufentanil played an important role in improving patient immune function and reducing patient pain. As important markers of T cells, CD3+ and CD4+ play a crucial role in cellular immune response. CD3+ is a marker on the surface of all T cells, and an increase in its number means an increase in the overall number of T cells, which usually reflects an enhanced immune response of the body [23]. CD4+ is a marker of helper T cells, which can activate other immune cells and promote the generation of immune response [23]. Therefore, the increase of CD3+ and CD4+ usually means the improvement of the immune function of the body. The changes of CD4+ and CD8+ ratio reflect the balance between T cell subsets. Under normal circumstances, a certain balance is maintained between CD4+ and CD8+ cells, which is crucial for maintaining the immune homeostasis of the body [24]. In the present study, the increase in the ratio of CD4+ and CD8+ at 48 hours after surgery indicated that the balance between the T cell subsets of patients in the sufentanil group was improved, which contributed to the accelerated recovery of immune function. The present study also found that the levels of β-endorphin, substance P, and serotonin were all significantly reduced after surgery. These pain mediators play an important role in pain transmission and regulation. β-endorphin is an endogenous analgesic substance, and a reduction in its levels may mean a reduction in pain perception. Substance P and serotonin, on the other hand, are closely related to pain perception and transmission, and their reduction may also contribute to reduced pain perception. The changes of these pain mediators are not only related to pain management, but also related to immune regulation [25]. Pain stress can affect the body's immune function, and the reduction of pain mediators may help to alleviate this stress response and protect the immune function. The expression of appropriate receptors by immune cells, such as μ receptors and Toll like receptors. Opioid drugs are associated with μ receptor binding to regulate the immune system. Sufentanil has high affinity with μ1 opioid receptors, and they are most closely related to analgesia. However, sufentanil has opposite binding selectivity with μ2 receptors, and is related to adverse reactions such as gastrointestinal reactions, hypertension and shivering. Therefore, sufentanil has a stronger analgesic effect and lower adverse reactions [26]. As a potent opioid analgesic, the immunomodulatory effect of sufentanil may be related to its binding to opioid receptors on immune cells. The previous study has shown that opioids can affect the activity and function of immune cells by binding to receptors on immune cells such as μ receptors, thereby regulating the immune response of the body [27]. According to data [28], sufentanil may improve the immune status of the body by inhibiting the excessive activation of immune cells and reducing the release of inflammatory factors. This immunoregulatory effect may be particularly important for breast cancer patients, because both surgery and cancer itself may have a negative impact on the immune function of patients.

Da-jvO2, S-jvO2 and CEO2 are indicators of brain oxygen metabolism and have an important relationship with brain tissue oxygen supply. The higher the levels of Da jvO2, S-jvO2 and CEO2 are, the lower the brain oxygen supply is [29]. S100B is a calcium-binding protein produced mainly by astrocytes, which can be released from damaged cells into the cerebrospinal fluid and peripheral blood after brain injury. NSE is an enzyme mainly present in neurons and neuroendocrine cells. When neurons are damaged, NSE will also be released from the damaged cells and enter the cerebrospinal fluid and peripheral blood [30]. Therefore, the levels of S100B and NSE can be used as an effective index for evaluating the severity of brain injury and judging the range and degree

Table 4 Analysis of postoperative pain mediator levels in patients ($\bar{x}\pm s$)

Groups	n	β-endorphins (ng/L)			Substance P (ng/L)			Serotonin (pg/mL)		
		Before surgery	24 hours after surgery	48 hours after surgery	Before surgery	24 hours after surgery	48 hours after surgery	Before surgery	24 hours after surgery	48 hours after surgery
The sufentanil group	59	179.74±29.72	201.28±31.75***	72.61±28.74###	264 .38±29.27	341.09±31.28***	303.29±33.19###	183.38±23.50	307.88±35.09***	209.18±29.29###
The control group	59	175.14±25.30	229.52±34.39***	146.15±19.14###	274.15±26.17	408.85±39.64***	322.79±38.18###	184.66±24.03	359.16±29.71***	250.74±36.19###
$F_{\text{Treatment value}}/P_{\text{Treatment value}}$		10.326/0.001			5.264/0.030			9.778/0.000		
$F_{\text{Time value}}/P_{\text{Time value}}$		9.526/0.001			6.520/0.020			6.528/0.020		
$F_{\text{Treatment×Time value}}/P_{\text{Treatment×Time value}}$		10.397/0.001			9.442/0.000			4.025/0.041		

Note: **P<0.01 and ***P<0.001 compared with preoperative data; ###P<0.001 compared with postoperative 24 hours.

Table 5 Analysis of postoperative brain-sparing effect indicators in patients ($\bar{x}\pm s$)

Groups	n	MMSE (score)			Da-jvO_2(ml/L)		
		Before surgery	24 hours after surgery	48 hours after surgery	Before surgery	24 hours after surgery	48 hours after surgery
The sufentanil group	59	29.32±1.31	24.38±2.47***	27.85±2.77#	41.18±7.14	63.63±7.37***	54.25±5.11##
The control group	59	29.36±1.48	21.28±3.03***	25.03±2.16###	42.41±5.05	67.76±6.85***	68.76±6.18###
$F_{\text{Treatment value}}/P_{\text{Treatment value}}$			4.196/0.041			5.513/0.013	
$F_{\text{Time value}}/P_{\text{Time value}}$			4.738/0.038			4.973/0.034	
$F_{\text{Treatment×Time value}}/P_{\text{Treatment×Time value}}$			3.976/0.046			9.254/0.001	
Groups	n	S-jvO_2(%)			CEO_2(%)		
		Before surgery	24 hours after surgery	48 hours after surgery	Before surgery	24 hours after surgery	48 hours after surgery
The sufentanil group	59	72.83±5.25	61.24±4.17***	66.16±4.24##	20.74±3.69	26.91±2.84***	21.28±3.18#
The control group	59	73.53±5.38	65.65±4.23***	68.14±3.17##	21.07±3.69	29.47±4.35***	25.25±3.03###
$F_{\text{Treatment value}}/P_{\text{Treatment value}}$			4.689/0.030			9.778/0.001	
$F_{\text{Time value}}/P_{\text{Time value}}$			6.836/0.027			10.326/0.001	
$F_{\text{Treatment×Time value}}/P_{\text{Treatment×Time value}}$			10.201/0.001			12.785/0.001	

Note: ***P<0.001 compared with preoperative data; #P<0.05, ##P<0.0 and ###P<0.001 compared with postoperative 24 hours.

Table 6 Comparison of postoperative brain injury indicators between two groups ($\bar{x}\pm s$)

Groups	n	S100B (μg/L)			NSE (μg/L)		
		Before surgery	1 day after surgery	7 days after surgery	Before surgery	1 day after surgery	7 days after surgery
The sufentanil group	59	0.20±0.03	0.51±0.08***	0.46±0.05***	5.26±0.70	7.26±1.35***	6.20±0.95***
The control group	59	0.21±0.04	5.30±0.68	0.69±0.10***	5.30±0.68	9.75±1.70***	6.83±1.56***
$F_{\text{Treatment value}}/P_{\text{Treatment value}}$			8.863/0.003			6.191/0.033	
$F_{\text{Time value}}/P_{\text{Time value}}$			5.844/0.016			9.899/0.001	
$F_{\text{Treatment×Time value}}/P_{\text{Treatment×Time value}}$			8.996/0.002			10.153/0.001	

Note: ***P<0.001 compared with preoperative indicators

of nerve injury. In this study, the effects of sufentanil on brain oxygen metabolism and brain injury indicators were analyzed. The results showed that the postoperative MMSE score of the sufentanil group was largely increased, while the levels of Da jvO2, S-jvO2, and CEO2 were obviously reduced. The levels of S100B and NSE were much lower than those of the control group. It indicated that sufentanil could improve postoperative nerve damage in patients and had a certain degree of brain protective function. The present study found that sufentanil could improve cognitive function and reduce brain damage by improving oxidative status in the brain. Cerebral oxidative stress is one of the important causes of brain tissue damage, and sufentanil may reduce the damage of oxidative stress to brain tissue through its antioxidant effect. This antioxidant effect may be related to its ability

Table 7 Analysis and comparison of adverse reactions [cases (%)]

Groups	Cases	Tachycardia	Gastrointestinal reactions	Hypertension	Skin itching	Chills
The sufentanil group	59	4 (6.78)	0 (0.00)	3 (5.08)	2 (3.39)	0 (0.00)
The control group	59	5 (8.47)	5 (8.47)	8 (13.56)	1 (1.69)	4 (6.78)
χ^2		0.120	5.221	4.624	0.678	4.140
P		0.729	0.022	0.032	0.410	0.042

to stabilize peripheral vascular resistance and improve the microcirculation state of brain tissue, thus helping to maintain the balance of oxygen supply and consumption in brain tissue [31]. Regarding how improving brain oxidation specifically affects cognitive function and brain damage, we believe that it may be related to the following aspects [32, 33]: Firstly, the antioxidant effect can reduce the production and accumulation of free radicals, thereby mitigating the direct damage to brain cells. Secondly, by improving the microcirculation of brain tissue, sufentanil can promote the delivery of nutrients and the discharge of metabolic wastes, providing a better environment for the normal function of brain cells. Finally, antioxidant effects may also indirectly affect cognitive function by regulating the activity of neurotransmitters and neural networks. One aspect of concern is the effect of sufentanil on the blood-brain barrier (BBB). As a key barrier between the brain and blood circulation, the functional status of BBB directly affects the stability of the internal environment of the brain. Sufentanil may act on specific receptors or signaling pathways on the BBB to maintain the integrity of the BBB by regulating the expression and function of molecules such as tight junction proteins [34]. Secondly, the regulation of sympathetic nervous system by sufentanil is also an important way for sufentanil to exert cerebral protection. Excessive activation of the sympathetic nervous system tends to cause vasoconstriction, increase blood pressure, and increase the risk of brain injury. Sufentanil may inhibit the activity of the sympathetic nervous system and reduce the sensitivity of blood vessels to neurotransmitters, thereby dilating blood vessels and improving microcirculation. This effect may involve the binding of sufentanil to opioid receptors in the central nervous system, and then trigger a series of signal transduction processes, and finally affect the function of the sympathetic nervous system [35]. In addition, the neuroprotective effect of sufentanil may also be related to its ability to affect brain inflammation or oxidative stress. Inflammation and oxidative stress are two important links in the process of brain injury, which promote each other and jointly lead to brain tissue damage. Sufentanil may reduce the inflammatory response and oxidative damage in brain tissue by inhibiting the release of inflammatory mediators and the occurrence of oxidative stress. This effect may involve multiple aspects such as the regulation of immune cells by sufentanil, the inhibition of inflammatory signaling pathways, and the enhancement of antioxidant enzyme activity [36]. Zhang et al. [37] found through animal experiments that sufentanil pretreatment had a certain protective effect on brain injury in rats undergoing cardiopulmonary bypass (CPB). Wang et al. [38] found in their research that sufentanil could alleviate cerebral ischemia-reperfusion injury in rats by inhibiting inflammation and protecting the blood-brain barrier. Clinical trials have confirmed [39] that sufentanil has better analgesic and sedative effects than fentanyl, bringing in faster patient recovery and lower incidence of postoperative cognitive impairment. Thus, sufentanil was recommended for elderly patients undergoing open surgery. The brain protective function of sufentanil may be related to its ability to stabilize peripheral vascular resistance, stimulate the central nucleus of the vagus nerve, block the sympathetic nervous system, improve the microcirculation of brain tissue, stabilize hemodynamics, and maintain brain oxygen supply balance, thereby improving cognitive function [40]. Therefore, it could be considered that sufentanil belongs to the fentanyl family as an anesthetic with faster onset and shorter maintenance time. Although this study found that the levels of Da-jvO2, S-jvO2, CEO2 and other indicators in the sufentanil group were significantly decreased after surgery, this is not necessarily directly equivalent to the reduction of cerebral ischemia, and the changes of these indicators may reflect more the regulatory effect of sufentanil on the balance of oxygen supply and oxygen consumption in brain tissue. Therefore, future studies using more sensitive brain injury assessment methods, such as neuroimaging examination or more specific biochemical markers, are needed to further verify the mechanism of brain protection by sufentanil.

In general, the application of sufentanil in breast cancer radical surgery effectively improved the immune function of the body, reduced pain response, alleviated brain damage, and had a certain brain-sparing effect with high safety. However, this study also has certain limitations. The design and reliability of retrospective

studies essentially depend on the accuracy and completeness of the documents provided in electronic medical records and surgical reports. Therefore, it is recommended to conduct a further study with larger sample size and longer study time in the future to comprehensively evaluate the accuracy of the study. In addition, for other potential confounding factors, the specific control measures and explanations of this study are as follows:

(1) Control measures: All operations were performed by the same surgical team under standardized conditions to reduce the influence of surgical procedure differences on the results.

Interpretation: By standardising surgical procedures and team consistency, we sought to ensure similarity of surgical procedures, thereby reducing the interference of this confounding factor on the results.

Individual differences in patients:

(2) Control measures: We selected patients with similar baseline characteristics through strict inclusion and exclusion criteria.

Interpretation: Baseline characteristics of patients such as age, weight, and ASA classification were matched in this study, which helped to reduce the potential influence of individual differences on the results.

Differences in postoperative care and rehabilitation:

(3) Control measures: All patients received a standardized care and rehabilitation program after surgery.

Interpretation: Standardized postoperative care and rehabilitation programs help to ensure patient consistency in the postoperative recovery process, thereby reducing the interference of this confounding factor on the results.

Interactions of sufentanil with other drugs:

(4) Control measures: During the study period, we recorded all medications used by the patients and analyzed their potential interactions with sufentanil.

Interpretation: By careful medication documentation and interaction analysis, we were able to assess and control for possible interactions between sufentanil and other drugs, thereby reducing the potential impact of this confounding factor on the results.

Differences in postoperative pain management:

(5) Control measures: We used a uniform pain assessment method and analgesic protocol, and closely monitored patients' pain during the study.

Interpretation: With uniform pain management and close monitoring, we were able to ensure patient consistency in postoperative pain control, thereby reducing the interference of this confounding factor on the results.

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Authors' contributions
Weicheng Jin confirmed the authenticity of all the raw data and edited the manuscript, Jie Wang and Hui Cao collected data and processed the data. Xiaoping Shen and Yang Yang conducted the statistics. Lanqing Lv reviewed and revised the article. All authors read and approved the final manuscript.

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

Declarations

Ethics approval and consent to participate
This study was approved by The Ethics Committee of The Ninth People's Hospital of Suzhou. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
Written informed consent was obtained from all individual participants included in the study.

Consent for publication
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Competing interests
The authors declare no competing interests.

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