Effects of dezocine and sufentanyl for postoperative analgesia on activity of NK, CD4+ and CD8+ cells in patients with breast cancer

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Abstract. The effects of dezocine and sufentanyl on the activity of natural killer (NK), $CD4^+$ and $CD8^+$ cells in patients with breast cancer undergoing postoperative analgesia after radical mastectomy were compared. The clinical data of 76 female patients undergoing radical mastectomy in the Fudan University Shanghai Cancer Center from January 2015 to October 2017 were analyzed retrospectively. Forty-two patients treated with dezocine were group D and 34 patients with sufentanyl were group S. Visual analogue scale (VAS) was used to evaluate the analgesic effect at 3, 12, 24, 48 h after surgery. There was no significant difference in VAS score, NK cells, $CD4^+$ cells, and $CD8^+$ cell vitality at 3 h postoperatively between the two groups (P>0.05), and VAS score at 12, 24 and 48 h postoperatively in the S group was significantly lower than that in group D (P<0.05). The activity of NK cells and $CD4^+$ cells at 3, 12, 24 and 48 h after surgery in group D was significantly higher than that in group S, and the difference was statistically significant (P<0.05). The activity of $CD8^+$ cells at 3, 12, 24 and 48 h after surgery in group D was significantly lower than that in group S, and the difference was statistically significant (P<0.05). The analgesic effect of dezocine was slightly worse than that of sufentanyl, but it was more beneficial to the recovery of early postoperative immune function.

Introduction

Postoperative pain, a physiological, psychological and behavioral stress state induced by surgical injury (1), is a natural phenomenon of resistance to foreign invasiveness, occurring during surgery and lasting to after surgery with pain reaching a peak (2). Postoperative analgesia can effectively increase oxygen content in subcutaneous tissue, accelerate wound healing and reduce the incidence of tissue edema and incision infection (3,4).

Postoperative pain can increase the stress response of the body and lead to the decrease of immune function, and then causing increased incidence of tumor metastasis, recurrence, postoperative infection and adverse reactions, which seriously affect the prognosis of patients (5). Studies have shown that the main form of antitumor immunity is cellular immunity. T lymphocyte subsets can resist viruses and regulate immunity, and NK cells also play a role in regulating the immune function and are an important immune factor in anti-infection and antitumor at the same time (6,7).

As a new opioid analgesic, the analgesic effect of dezocine is stronger than morphine, pentazocine and codeine (8). Studies have shown that dezocine has minimal side effects, and the common ones are drowsiness, nausea and vomiting (9). There is no significant respiratory inhibition in the normal dose range of dezocine, and both patients and physicians have better acceptance and satisfaction (10).

As sufentanyl has a stronger binding and lipid-solubility to receptor than fentanyl, it can rapidly spread to various tissues and penetrate the blood-brain barrier to reach the effective concentration in the brain (11). Sufentanyl has the advantages of strong analgesic intensity, long duration, low toxicity and wide safety range, but it also has side effects similar to other opioid drugs, and a higher incidence with the increase of dosage (12). At the same time of causing adverse reactions, analgesic drugs can also inhibit the proliferation and differentiation of T cells and the activation of macrophages, and further decrease the immune function of patients (13).

The purpose of this study was to compare the effects of dezocine or sufentanyl on the activity of natural killer (NK), $CD4^+$ and $CD8^+$ cells in patients with breast cancer undergoing postoperative analgesia after radical mastectomy, and to provide a theoretical basis for clinical choice of appropriate postoperative analgesia methods.

Patients and methods

General information. The clinical data of 76 female patients with an average age of 47.26±7.37 years and undergoing radical mastectomy in the Fudan University Shanghai Cancer Center (Shanghai, China) from January 2015 to October 2017

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were analyzed retrospectively. Forty-two patients treated with dezocine were group D and 34 patients with sufentanyl were group S. There was no significant difference in general information between the two groups (P>0.05). All the patients were ASA status I-II, and operated under general anesthesia and received intravenous analgesia after surgery. Patients with coagulation dysfunction, immune dysfunction, administration of immunological agents within 6 months and allergies to dezocine and sufentanyl were excluded. This study was approved by the Medical Ethics Committee of Fudan University Shanghai Cancer Center and informed consent was signed by patients or family members. General information is shown in Table I.

Anesthesia induction, maintenance and analgesia. All patients were prohibited from eating 8 h before surgery or using medication before surgery, and 0.5 mg atropine (Guangdong South Land Pharmaceutical Co., Ltd., Guangdong, China, SFDA approval no. H44024022), 1.0 g pentobarbital sodium (Shanghai Xinya Pharmaceutical Co., Ltd., Shanghai, China, SFDA approval no. H31020240) were injected intramuscularly before surgery. Non-invasive cuff pressure measurement, central venous pressure, electrocardiogram, blood pressure, heart rate, pulse and oxygen protection were established, and sodium lactated Ringer's solution (Hangzhou Minsheng Pharmaceutical Co., Ltd., Hangzhou, China, SFDA approval no. H33020035) was injected intravenously.

Oxygen was given by mask for 5 min before anesthesia induction, and intravenous injection of 0.05 mg/kg midazolam (Jiangsu Enhua Pharmaceutical Group Co., Ltd., Jiangsu, China, SFDA approval no. H10980025), 2 μg/kg fentanyl (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China, SFDA approval no. H20030197) and 1.5 mg/kg propofol (Sichuan Guorui Pharmaceutical Co., Ltd., Sichuan, China, SFDA approval no. H20030114) was conducted sequentially. Rocuronium 0.5 mg/kg (Hebei Baiqi Pharmaceutical Co., Ltd., Hebei, China, SFDA approval no. H20100069) was slowly injected intravenously after the patient fell asleep. The trachea catheter was inserted into the mandibular joint and the respiratory loop was connected after patients were completely relaxed, then machine was used to control the patient's breathing after the breath was symmetrical. Propofol (200-300 mg/h) was continuously pumped in during the surgery, and sevoflurane (Fujian Gutian Pharmaceutical Co., Ltd., Fujian, China, SFDA approval no. H35020148) was continuously inhaled at the same time, and 25 mg/h atracurium (Jiangsu Hengrui Pharmaceutical Co., Ltd., Jiangsu, China, SFDA approval no. H20060869) was continuously pumped in to keep the muscles relaxed.

Atracurium was stopped before closing the incision, and all anesthesia was stopped after the surgery, and analgesic treatment was performed after the patient recovered from anesthesia. In group D, 2.5 mg/kg dezocine (Yangtze River Pharmaceutical Group Jiangsu HaiCi Biological Medicine Co., Ltd., Jiangsu, China, SFDA approval no. H20080328), 6 mg navoban (Southwest Pharmaceutical Co., Ltd., Chongqing, China, SFDA approval no. H20041374) and 0.9% saline (Sichuan Kelun Pharmaceutical Co., Ltd., Sichuan, China, SFDA approval no. H51021156) were diluted to 150 ml; In group S, 2.5 μg/kg sufentanyl (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China, SFDA approval no. H20054172), 6 mg navoban and 0.9% saline were diluted to 150 ml. Both groups were given a dose of 0.075 ml/kg, background infusion of 2 ml/h, PCIA dose of 1 ml and a locking time of 15 min.

Observation index. The effect of postoperative analgesia was evaluated by visual analogue scale (VAS) (14) at 3, 12, 24 and 48 h after surgery. The score ranged from 0 to 10, and the higher the score, the higher the patient's pain index.

Venous blood was taken from patients before surgery and 3, 12, 24 and 48 h after surgery, respectively, then the activities of NK cells and T lymphocyte subsets, $CD4^+$, $CD8^+$ were determined by BD FACSCalibur flow cytometry (BD Biosciences, Franklin Lakes, NJ, USA) (15). Mouse anti-human CD3-FITC/CD (16+56)-PE, CD4FITC and CD8PE monoclonal antibodies (dilution, 1:100; cat. nos. 340300, 555346 and 560959, respectively) and homotypic control, hemolysin and fluorescence calibrated microsphere were purchased from BD Biosciences (San Jose, CA, USA). Fasting venous whole blood (2-3 ml) was drawn from patients to vacuum heparin anticoagulant tube before 9 a.m. NK cells (30 μl), $CD4^+$, $CD8^+$ detection kit, CD3-FITC/CD (16+56)-PE monoclonal antibody, CD4FITC, CD8PE antibody were fully mixed with 50 μl anticoagulant whole blood and stained in the dark for 15 min. RBC lysate (1 ml) was added and mixed gently, and the mixture was put in the dark for 10 min, and centrifuged at 1,580 x g for 5 min at 20˚C, and then the supernatant was discarded. Diluent (1 ml) was added and mixed gently, and the mixture was centrifuged at 1,580 x g for 5 min at 20˚C, and then the supernatant was discarded, and the last 50 μl was retained. The processed samples were kept in the dark. Detection was conducted by flow cytometry, and the sample tubes were fully mixed before detection.

Statistical analysis. The data was analyzed by SPSS 20.0 statistical software (Shanghai Cabit Information Technology Co., Ltd., Shanghai, China). Chi-square test was used for enumeration data. t-test was used for measurement data. One-way analysis of variance (ANOVA) and Dunnett's post hoc test was used for multi-group comparison, and repeated measures ANOVA was used for the comparison of different time within the group. P<0.05 represented that the difference was statistically significant.

Results

VAS score in the two groups. There was no significant difference in VAS score at 12, 24 and 3 h postoperatively in group D (P>0.05), and VAS score at 48 h postoperatively was significantly lower than that at 3, 12 and 24 h postoperatively (P<0.05). There was no significant difference in VAS score at 12 h postoperatively and 3 h postoperatively in group S (P>0.05); VAS score at 24 and 48 h postoperatively was significantly lower than that at 3 and 12 h postoperatively, and VAS score at 48 h postoperatively was significantly lower than that at 24 h postoperatively (P<0.05) (Table II).

There was no significant difference in VAS score between the two groups at 3 h after surgery (P>0.05), and the VAS score in group S was significantly lower than that in group D at 12,

Table I. General information [n (%)].

Factor	Group D (n=42)	Group S (n=34)	t/χ^2 value	P-value
Age (years)			2.623	0.138
≥40	32 (76.19)	20 (58.82)		
<40	10 (23.81)	14 (41.18)		
Body weight (kg)	64.52±8.26	62.68±6.34	1.068	0.289
Surgical duration (min)	152.58±14.62	150.22±14.01	0.713	0.478
Blood transfusion (ml)	2072.24±152.41	2065.91±160.25	0.176	0.861
Blood loss (ml)	452.85±77.68	448.35±82.46	0.244	0.808
Net infusion (ml)	1032.31±237.52	1108.72±241.73	1.383	0.171
ASA			1.066	0.354
I	37 (88.10)	27 (79.41)		
II	5 (11.90)	7 (20.59)		

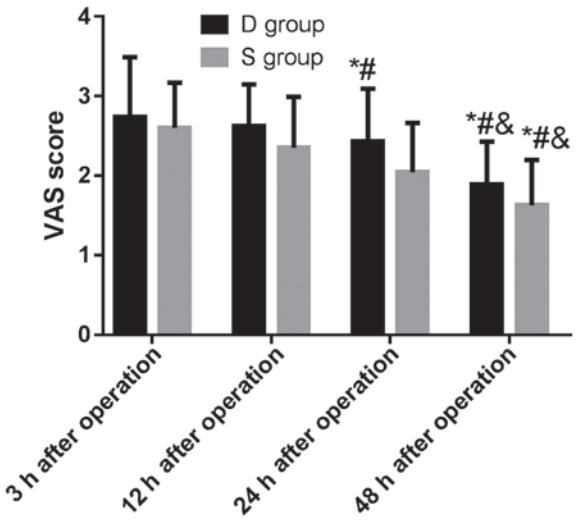

Figure 1. VAS score in patients of the two groups. There was no significant difference in VAS score between the groups at 3 h after surgery (P>0.05), and the VAS score in group S was significantly lower than that in group D at 12, 24 and 48 h after surgery, and the difference was statistically significant (P<0.05). There was statistical difference between groups D and S at each time-point after surgery (P<0.001). There was no significant difference in VAS score between 12 h, 24 h after surgery and 3 h after surgery in group D (P>0.05), and VAS score at 48 h after surgery was significantly lower than that at 3, 12 and 24 h after surgery, and the difference was statistically significant (P<0.05). There was no significant difference in VAS score between 12 and 3 h after surgery in group S (P>0.05), and VAS score at 24 and 48 h after surgery was significantly lower than that at 3 and 12 h after surgery, and 48 h after surgery was significantly lower than that 24 h after surgery, and the difference was statistically significant (P<0.05). *P<0.05 compared with 3 h after surgery; #P<0.05 compared with 12 h after surgery; &P<0.05 compared with 24 h after surgery.

24 and 48 h after surgery, and the difference was statistically significant (P<0.05).

There was no significant difference in VAS score between 12, 24 h after surgery and 3 h after surgery in group D (P>0.05), and VAS score at 48 h after surgery was significantly lower than that at 3, 12 and 24 h after surgery, and the difference was statistically significant (P<0.05).

There was no significant difference in VAS score between 12 and 3 h after surgery in group S (P>0.05), and the VAS score

Table II. VAS score in patients of the two groups.

Time	Group D (n=42)	Group S (n=34)	t value	P-value
3 h after surgery	2.74±0.75	2.60±0.57	0.925	0.358
12 h after surgery	2.63±0.52	2.35±0.64	2.059	0.043
24 h after surgery	2.43±0.66	2.04±0.62[a,b]	2.649	0.010
48 h after surgery	1.89±0.54[a-c]	1.63±0.57[a-c]	2.024	0.047
F value	12.42	20.36		
P-value	<0.001	<0.001		

[a]P<0.05 compared with 3 h after surgery; [b]P<0.05 compared with 12 h after surgery; [c]P<0.05 compared with 24 h after surgery.

at 24 and 48 h after surgery was significantly lower than that at 3 and 12 h after surgery, and 48 h after surgery was significantly lower than that 24 h after surgery, and the difference was statistically significant (P<0.05). The results showed that the analgesic effect of sufentanyl was slightly better than that of dezocine (Fig. 1).

Comparison of NK cell activity between the two groups. There was no significant difference in the activity of NK cells between the two groups before surgery (P>0.05), and the activity in group D was significantly higher than that in group S at 3, 12, 24 and 48 h after surgery, and the difference was statistically significant (P<0.05) (Table III).

There was no significant difference in the activity of NK cells between 48 h after surgery and before surgery in group D (P>0.05), and the activity at 3, 12 and 24 h after surgery was significantly lower than that before surgery. The activity of NK cells in group S at 3, 12, 24 and 48 h after surgery was significantly lower than that before surgery. The activity of NK cells in group D and S increased gradually 12 h after surgery, and the difference was statistically significant (P<0.05). These results indicated that the activity of NK cells in the patients after surgery was less inhibited and they recovered more quickly (Fig. 2).

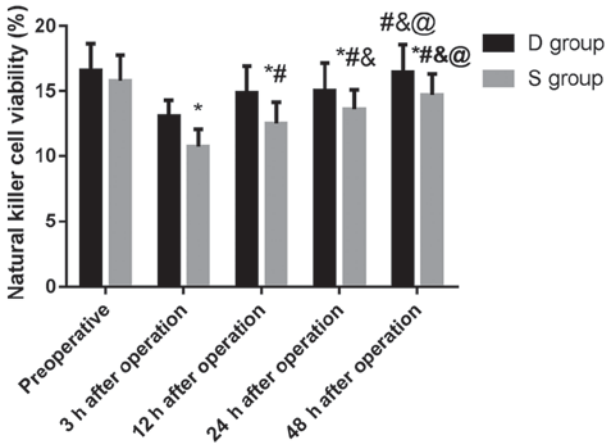

Figure 2. Comparison of NK cell activity between the two groups. Flow cytometry showed that the activity of NK cells in group D was significantly higher than that in group S at 3, 12, 24 and 48 h after surgery, and the difference was statistically significant (P<0.05). The activity of NK cells in group D at 3, 12 and 24 h after surgery was significantly lower than that before surgery, and the activity at 12, 24, 48 h after surgery was significantly higher than that at 3 h after surgery, and 24 h and 48 h after surgery was significantly higher than that at 12 h after surgery, and 48 h after surgery was significantly higher than that at 24 h after surgery, and the difference was statistically significant (P<0.05). The activity of NK cells in group S at 3, 12, 24 and 48 h after surgery was significantly lower than that before surgery, and the activity at 12, 24, 48 h after surgery was significantly higher than that at 3 h after surgery, and 24 h, 48 h after surgery was significantly higher than that at 12 h after surgery, and 48 h after surgery was significantly higher than that at 24 h after surgery, and the difference was statistically significant (P<0.05). *P<0.05 compared with before surgery; #P<0.05 compared with 3 h after surgery; &P<0.05 compared with 12 h after surgery; @P<0.05 compared with 24 h after surgery.

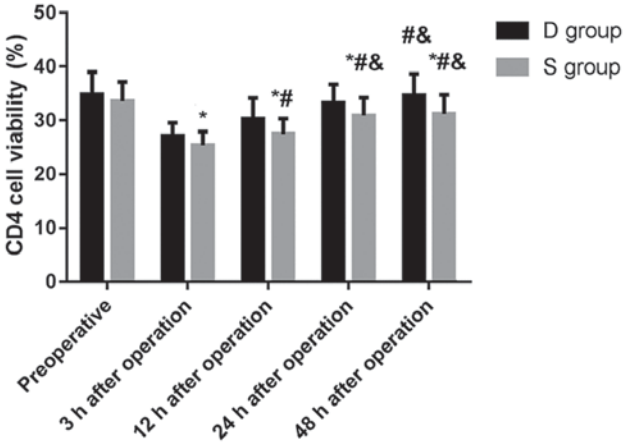

Figure 3. Comparison of CD4+ cell activity between the two groups. Flow cytometry showed that the activity of CD4+ cells in group D was significantly higher than that in group S at 3, 12, 24 and 48 h after surgery, and the difference was statistically significant (P<0.05). The activity of CD4+ cells at 3, 12, 24 h after surgery was significantly lower than that before surgery in group D, and 12, 24, 48 h after surgery was significantly higher than that 3 h after surgery, and 24 h, 48 h after surgery was significantly higher than that 12 h after surgery, and the difference was statistically significant (P<0.05). The activity of CD4+ cells at 3, 12, 24 h after surgery was significantly lower than that before surgery in group S, and 12, 24, 48 h after surgery was significantly higher than that 3 h after surgery, and 24, 48 h after surgery was significantly higher than that 12 h after surgery, and the difference was statistically significant (P<0.05). *P<0.05 compared with before surgery; #P<0.05 compared with 3 h after surgery; &P<0.05 compared with 12 h after surgery.

Table III. Comparison of NK cell activity between the two groups (%).

Time	Group D (n=42)	Group S (n=34)	t value	P-value
3 h after surgery	13.05±1.26[a]	10.76±1.32[a]	7.712	<0.001
12 h after surgery	14.86±2.07[a,b]	12.51±1.64[a,b]	5.389	<0.001
24 h after surgery	15.04±2.11[a-c]	13.62±1.47[a-c]	3.323	0.001
48 h after surgery	16.47±2.09[b-d]	14.71±1.58[a-d]	4.059	<0.001
F value	23.19	49.53		
P-value	<0.001	<0.001		

[a]P<0.05 compared with before surgery; [b]P<0.05 compared with 3 h after surgery; [c]P<0.05 compared with 12 h after surgery; [d]P<0.05 compared with 24 h after surgery.

Comparison of CD4+ cell activity between the two groups. There was no significant difference in the activity of CD4+ cells between the two groups before surgery (P>0.05), and the activity of CD4+ cells in group D was significantly higher than that in group S at 3, 12, 24 and 48 h after surgery, and the difference was statistically significant (P<0.05) (Table IV).

There was no significant difference in the activity of CD4+ cells between 48 h after surgery and before surgery, 24 h after surgery in group D (P>0.05), and the activity of CD4+ cells at 3, 12 and 24 h after surgery was significantly lower than that before surgery. The activity of CD4+ cells in groups D and S was gradually increased 12 h after surgery, with statistically significant difference (P<0.05). The results indicated that the activity of CD4+ cells in the patients after surgery was less inhibited and recovered more quickly (Fig. 3).

Table IV. Comparison of CD4+ cell activity between the two groups (%).

Time	Group D (n=42)	Group S (n=34)	t value	P-value
3 h after surgery	27.13±2.42[a]	25.36±2.57[a]	3.084	0.003
12 h after surgery	30.36±3.79[a,b]	27.48±2.87[a,b]	3.660	0.001
24 h after surgery	33.24±3.46[a-c]	30.92±3.28[a-c]	2.974	0.004
48 h after surgery	34.68±3.97[b,c]	31.21±3.51[a-c]	3.988	<0.001
F value	35.01	35.54		
P-value	<0.001	<0.001		

[a]P<0.05 compared with before surgery; [b]P<0.05 compared with 3 h after surgery; [c]P<0.05 compared with 12 h after surgery.

Comparison of CD8+ cell activity between the two groups. There was no significant difference in the activity of CD8+ cells between the two groups before surgery (P>0.05), and the activity of CD8+ cells in group D was significantly lower than that in group S at 3, 12, 24 and 48 h after surgery, and the difference was statistically significant (P<0.05) (Table V).

There was no significant difference in the activity of CD8+ cells in group D between 3 h and 12 h after surgery

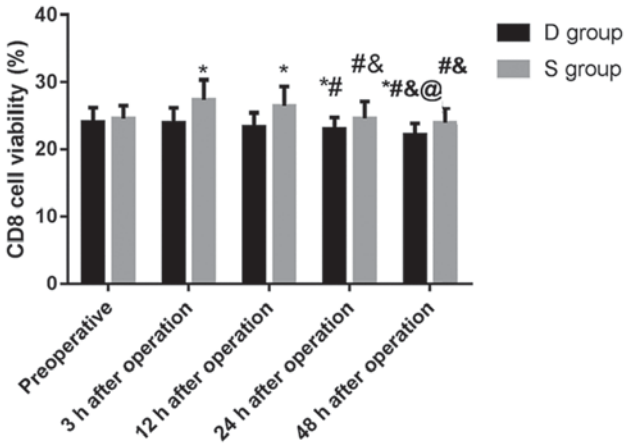

Figure 4. Comparison of CD8+ cell activity between the two groups. Flow cytometry showed that the activity of CD8+ cells in group D was significantly lower than that in group S at 3, 12, 24 and 48 h after surgery, and the difference was statistically significant (P<0.05). The activity of CD8+ cells at 24 and 48 h after surgery was significantly lower than that before surgery and 3 h after surgery in group D, and the activity at 48 h after surgery was significantly lower than that at 12 and 24 h after surgery, and the difference was statistically significant (P<0.05). The activity of CD8+ cells at 3 and 12 h after surgery was significantly lower than that before surgery in group S, and the activity at 24 and 48 h after surgery was significantly lower than that at 3 and 12 h after surgery, and the difference was statistically significant (P<0.05). *P<0.05 compared with before surgery; #P<0.05 compared with 3 h after surgery; &P<0.05 compared with 12 h after surgery; @P<0.05 compared with 24 h after surgery.

Table V. Comparison of CD8+ cell activity between the two groups (%).

Time	Group D (n=42)	Group S (n=34)	t value	P-value
Before surgery	24.08±2.08	24.57±1.89	1.063	0.291
3 h after surgery	23.95±2.16	27.32±2.98[a]	5.710	<0.001
12 h after surgery	23.34±2.07	26.41±2.94[a]	5.332	<0.001
24 h after surgery	23.01±1.74[a,b]	24.62±2.47[a-c]	3.328	0.001
48 h after surgery	22.16±1.68[a-d]	23.96±2.11[b,c]	4.142	<0.001
F value	6.631	10.84		
P-value	<0.001	<0.001		

[a]P<0.05 compared with before surgery; [b]P<0.05 compared with 3 h after surgery; [c]P<0.05 compared with 12 h after surgery; [d]P<0.05 compared with 24 h after surgery.

and before surgery (P>0.05), between 12 h after surgery and 3 h after surgery P>0.05), and between 24 h after surgery and 12 h after surgery (P>0.05). The activity of CD8+ cells at 24 and 48 h after surgery was significantly lower than that before surgery and 3 h after surgery, and the activity at 48 h after surgery was significantly lower than that at 12 and 24 h after surgery, and the difference was statistically significant (P<0.05).

There was no significant difference in the activity of CD8+ cells in group S between 24 h and 48 h after surgery and before surgery (P>0.05), between 12 h after surgery and 3 h after surgery (P>0.05), and between 24 h after surgery and 48 h after surgery (P>0.05). The activity of CD8+ cells at 3 and 12 h after surgery was significantly lower than that before surgery, and the activity at 24 and 48 h after surgery was significantly lower than that at 3 and 12 h after surgery, and the difference was statistically significant (P<0.05). This suggests that dezocine can inhibit the activity of CD8+ cells, and the activity of CD8+ cells can increase in patients with sufentanil 3 h after surgery, and then gradually recover (Fig. 4).

Discussion

According to literature reports, sufentanyl, dezocine and other analgesic drugs may have a certain degree of damage to postoperative immune function, and natural killer (NK) cells play an inhibitory role in tumor immune-associated cells (16). Inhibition of NK cell activity may increase the incidence of tumor metastasis or recurrence after surgery (17). Tumor development is usually accompanied by low immune function. Radical mastectomy can activate inflammatory stress and suppresses immune cells during tumor resection (18). In T lymphocyte subsets, CD4+ plays a major role in assisting the body in antitumor immunity and CD8+ mainly inhibits the immune response of the body (19). Therefore, the cellular immunity can be reflected by NK cells and T lymphocyte subsets.

This study showed that there was no significant difference in VAS score between the two groups at 3 h after surgery (P>0.05), and VAS score in group S was significantly lower than that in group D at 12, 24 and 48 h after surgery, and the difference was statistically significant (P<0.05).

Combined with the above results, VAS scores in both groups decreased with the increase of time, but the postoperative analgesic effect of sufentanyl was slightly better than that of dezocine. However, in mouse models of neuropathic pain, dezocine has been shown to alleviate hypersensitivity to both thermal and mechanical pain by activation of progenitor receptor agonist and inhibition of norepinephrine reuptake (20,21). In addition, dezocine is an adjuvant analgesic currently used in clinical practice with minimal side effects and low dependence tendency (22,23). Soleimani *et al* (10) found however, that there was no significant difference in VAS score between dezocine and sufentanyl after cesarean section. The reason may be the small number of subjects and standard deviation included in their study resulting in the statistical difference.

In this study, there was no significant difference in the activity of NK cells, CD4+, CD8+ cells between the two groups before surgery (P>0. 05), and the activity of NK cells and CD4+ cells in group D was significantly higher than that in group S at 3, 12, 24 and 48 h after surgery, and the activity of CD8+ cells in group D was significantly lower than that in group S at 3, 12, 24 and 48 h after surgery, and the difference was statistically significant (P<0.05). There were significant differences in the activity of NK cells, CD4+, CD8+ cells in groups D and S at each time-point before and after surgery (P<0.001). Feng *et al* (24) showed that dezocine can play a role in the immune system by regulating the secretion of IL-12 and IL-10 and affecting the lymphocyte activity during tissue injury, which may also contribute to the analgesic effect. These results showed that the activity of NK cells and CD4+ cells

in both groups was lower than that before surgery, which indicated that the body's immune function could be suppressed by surgical trauma and stress response. However, both groups began to recover gradually from 12 h after surgery, but the recovery rate of immune function in patients with dezocine was faster within 48 h after surgery. The variation tendencies of NK cells and T lymphocyte subsets were basically consistent with the results of previous studies (25,26).

In conclusion, the postoperative analgesic effect of sufentanyl was slightly better than that of dezocine. Dezocine can reduce the inhibitory effect on the activity of NK cells and $CD4^+$, and inhibit the activity of $CD8^+$ cells, and is more beneficial to the recovery of patients' immune function. This study analyzed the advantages and disadvantages of postoperative analgesic drugs for patients, and suggested that dezocine is more appropriate for the recovery of patients' physical function and long-term consideration.

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Availability of data and materials

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

Authors' contributions

FW, XZ and HW conceived and designed the study. FW, HW and YL collected and interpreted the data. FW completed the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center (Shanghai, China). Patients who participated in this study or their guardians, signed an informed consent and had complete clinical data.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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