Original Article Clinical efficacy of dexmedetomidine preemptive analgesia in breast tumor resection

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Received July 15, 2024; Accepted November 12, 2024; Epub December 15, 2024; Published December 30, 2024

Abstract: Objective: To investigate the clinical efficacy of dexmedetomidine preemptive analgesia in patients undergoing mastectomy. Methods: A retrospective study was conducted, including 236 patients who underwent breast tumor resection. Of these, 131 patients in the control group received routine postoperative intravenous patientcontrolled analgesia, while 105 patients in the preemptive analgesia group received dexmedetomidine preemptive analgesia during surgery. Visual analog scale (VAS) scores, Ramsay sedation scores, clinical efficacy, pain mediator levels, renal function indices, immune function indices, and adverse effects were statistically analyzed. Results: The preemptive analgesia group had lower VAS scores and Ramsay scores postoperatively (both P < 0.05). The success rate of analgesia was significantly higher in the preemptive analgesia group compared to the control group (84.8% vs. 74.0%, P < 0.05). After surgery, the levels of pain mediators, including prostaglandin E2 (PGE2), substance P (SP), and neuropeptide Y (NPY), initially increased and then decreased, with lower levels observed in the preemptive analgesia group (all P < 0.05). Renal function indices, including creatinine (Cr), blood urea nitrogen (BUN), and neutrophil gelatinase-associated lipocalin (NGAL), showed a similar trend, with lower levels in the preemptive analgesia group (all P < 0.05). Immune function markers, such as CD3+, CD4+, CD8+, and CD4/CD8+ ratios, demonstrated smaller changes in the preemptive analgesia group compared to the control group (all P < 0.05). The total adverse reaction rate was lower in the preemptive analgesia group (P < 0.05). Conclusion: Dexmedetomidine preemptive analgesia demonstrates significant clinical benefits in patients undergoing breast tumor resection, including better analgesic efficacy, reduced pain mediator and renal function index levels, improved immune function preservation, and fewer adverse reactions.

Keywords: Dexmedetomidine, preemptive analgesia, breast tumor resection

Introduction

A breast mass, or lump, is a thickened or raised area of tissue that differs noticeably from the surrounding tissue and is frequently associated with breast disease [1]. Breast masses can be classified as malignant or benign. Malignant lesions typically refer to breast cancer, characterized by the abnormal proliferation of cells within breast tissue, while benign lesions include fibroadenoma, fibrocystic changes, breast cysts, and intraductal papilloma. Benign lesions are approximately 5 to 10 times more common than malignant ones, with up to 30% of women worldwide experiencing benign breast masses [2]. In the United States, an estimated

1.6 million women are diagnosed with breast lesions annually, 75% of which are benign [3]. Despite their non-malignant nature, benign breast lumps can affect the aesthetic and functional aspects of the mammary glands, increasing psychological stress. Furthermore, disease progression can lead to up to 30% of benign breast lumps developing into malignancies, emphasizing the importance of early diagnosis and treatment to slow disease progression.

Surgical intervention remains the most direct and effective treatment for breast lumps, including minimally invasive and traditional radial incision surgeries [4]. Each approach has distinct advantages and limitations. Minimally in-

vasive surgery typically involves a 3-5 mm skin incision that requires no suturing, resulting in minimal scarring, local anesthesia feasibility, and shorter recovery times. However, this method requires specialized equipment and is relatively costly. It may also be unsuitable for masses larger than 3 cm, those located near the nipple or axilla, or those with a bleeding tendency, necessitating traditional open surgery. Traditional surgery provides better exposure of the mass through surface incisions, but it may leave multiple scars if there are multiple lumps. Additionally, during healing, the incised skin, subcutaneous tissue, and mammary glands may form nodules. This technique is more invasive, with complications such as excessive bleeding, significant scarring, and postoperative pain being more common [5].

Postoperative pain is a major concern, particularly in patients awakening from anesthesia, as it can increase discomfort and delay recovery. Conventional analgesic strategies often rely heavily on opioids, posing risks of dependence and addiction. Moreover, standard analgesics can cause adverse effects such as bradycardia, dizziness, headache, nausea, vomiting, respiratory depression, and delirium. These regimens may inadequately manage postoperative pain and carry risks of renal and immune function impairment, further hindering recovery.

Preemptive analgesia is an approach designed to reduce hyperalgesia and abnormal pain by preventing peripheral and central sensitization and minimizing nociceptive stimulation. Administering analgesics before pain onset can significantly alleviate postoperative pain and enhance patient comfort [6]. Dexmedetomidine, an effective $\alpha 2$ -adrenergic receptor agonist, has demonstrated significant analgesic properties. At appropriate doses, dexmedetomidine not only provides nerve blockade and sedation but also reduces side effects such as renal function impairment caused by other drugs and helps maintain immune system stability [7].

Zusman et al. reported that dexmedetomidine effectively enhances peripheral nerve blockade, prolonging postoperative pain relief, reducing adverse events, and achieving favorable clinical outcomes in female patients undergoing breast mass resection and biopsy [8]. These findings suggest that dexmedetomi-

dine preemptive analgesia may improve outcomes in mastectomy patients. However, its clinical effects in mastectomy remain underexplored, with limited studies conducted domestically or internationally. This study retrospectively examines the clinical impact of dexmedetomidine preemptive analgesia in 236 patients undergoing mastectomy for breast cancer.

Materials and methods

Case selection

This retrospective study included 236 patients with breast masses admitted to Tianjin Medical University Cancer Institute and Hospital from October 2020 to December 2023. Patients were divided into the preemptive analgesia group (n = 105) and the control group (n = 131). Clinical data were supplemented through telephone follow-ups. Ethical approval was obtained from the Tianjin Medical University Cancer Institute and Hospital Ethics Committee. The study workflow is illustrated in **Figure 1**.

Inclusion and exclusion criteria

Inclusion criteria: (1) Female patients aged ≥ 18 years; (2) Diagnosis of benign or malignant breast tumors confirmed through imaging techniques such as breast ultrasound or mammography, or histological examination (e.g., fineneedle aspiration or biopsy) [9]; (3) Classified as American Society of Anesthesiology (ASA) grade I-II [10]; (4) No history of allergic reactions; (5) Availability of complete clinical data.

Exclusion criteria: (1) Difficulty with intubation; (2) Severe heart or lung disease, mental illness history, significantly impaired liver or renal function; (3) Pregnancy or lactation; (4) Recent use of anticoagulants or coagulation disorders; (5) History of ipsilateral breast or chest wall radiotherapy.

Treatment methods

Patients in both groups fasted from food and medication for 8 hours before surgery. Upon entering the operating room, vital signs, including pulse oxygen saturation, electrocardiogram, and mean arterial pressure, were immediately monitored, and a bispectral index (BIS) electrode was attached. The patient's medical records were entered into a propofol closed-

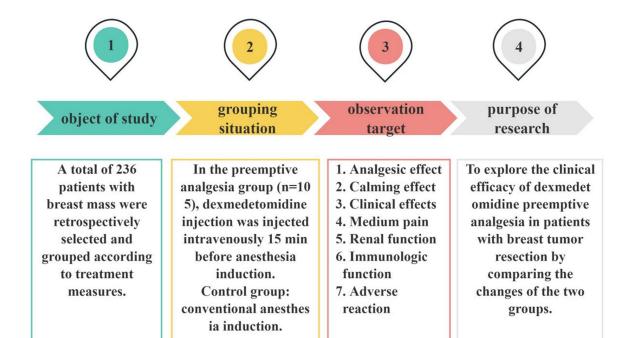


Figure 1. Basic flow of the study.

loop target-controlled infusion pump system, and the BIS value was maintained between 40 and 60.

Control group: Anesthesia Induction: Intravenous administration of the following: Sufentanil (0.35 µg/kg, Yichang Renfu Pharmaceutical Co., Ltd., Sinopharm Approval No. H20054171. Specification: 1 ml:50 µg × 10/box). Midazolam (0.04 mg/kg, Jiangsu Enhua Pharmaceutical Co., Ltd., Sinopharm Approval No. H20031071, Specification: 5 ml:5 mg). BIS-guided, targetcontrolled infusion of propofol (Fresenius Kabi Deutschland GmbH, Sinopharm Approval No. H20170306, Specification: 50 ml:0.5 g), with an initial plasma concentration of 3 µg/ml. Once the patient became unconscious, cisatracurium besilate (0.15 mg/kg, Zhejiang Xianju Pharmaceutical Co., Ltd., Approval No. H2009-0202, Specification: 5 mg) was administered intravenously. After achieving muscle relaxation, oral visual intubation was performed, followed by mechanical ventilation. Ventilation parameters were set as: Respiratory rate: 10-15 breaths/min. Tidal volume: 4-8 ml/kg. Abdominal pressure: 12-14 mmHg. Carbon dioxide partial pressure: 30-45 mmHg. Anesthesia Maintenance: Plasma concentration was adjusted automatically using the closed-loop target-controlled infusion pump system. Remifentanil (Yichang Renfu Pharmaceutical Co., Ltd., Sinopharm Approval No. H20030197, Specification: 1 mg) was infused at a plasma concentration of 0.04-0.2 μ g/kg. The BIS value was maintained between 40 and 60. Intermittent injections of atracurium were administered as needed.

Preemptive analgesia group: Fifteen minutes before anesthesia induction, dexmedetomidine (Jiangsu Hengrui Pharmaceutical Co., Ltd., National Standard: H20090248, Specification: 2 ml:200 μ g) was administered intravenously. Dexmedetomidine was dosed at 0.5 μ g/kg and infused over 10 minutes. The methods for anesthesia induction and maintenance were identical to those in the control group.

Observation indicators

Analgesic effect: The visual analog scale (VAS) [11] was used to assess pain at 1, 6, 12, 24, and 48 hours postoperatively. The VAS score ranges from 0 to 10, where lower scores indicate more intense pain.

Sedation effect: The Ramsay sedation score [12] was used to evaluate sedation at 1, 6, 12, 24, and 48 hours postoperatively. Scores were defined as follows: 1: Irritability. 2: Quiet coop-

eration. 3: Drowsiness but responsive to instructions. 4: Sleep state, arousable. 5: Moderate sleep, slow response. 6: Deep sleep, unresponsive to stimuli. Scores of 2-4 indicated satisfactory sedation, while scores \geq 5 indicated excessive sedation.

Clinical efficacy [13]: Postoperative pain was graded 24 hours after surgery: Grade 0: No pain or mild pain with coughing. Grade 1: Mild, intermittent, tolerable pain not affecting sleep quality. Grade 2: Moderate, persistent, tolerable pain with poor sleep quality. Grade 3: Severe, intolerable, continuous pain requiring analgesics. The analgesic success rate was calculated as: Analgesic Success Rate = (Grade 0 + Grade 1)/Total Cases × 100%.

Pain mediator levels [14]: Levels of prostaglandin E2 (PGE2), substance P (SP), and neuropeptide Y (NPY) were measured using radioimmunoassay at the following time points: 1 day before surgery, and 12, 24, and 48 hours after surgery.

Renal function indices [15]: Renal function was assessed by measuring creatinine (Cr), urea nitrogen (BUN), and neutrophil gelatinase-associated lipocalin (NGAL) using enzyme-linked immunosorbent assay (ELISA). Measurements were taken 1 day before surgery and at 12, 24, and 48 hours postoperatively.

Immune function indices [16]: Venous blood samples (5 mL) were collected 1 day before surgery and at 12, 24, and 48 hours postoperatively. Levels of CD3+, CD4+, CD8+, and CD4+/CD8+ ratios were measured using a flow cytometer (BriCyte E6, Myriad BioMedical Electronics Co., Ltd., Shenzhen, China).

Adverse reactions: The incidence of adverse events, including bradycardia, dizziness, headache, nausea, and vomiting, was recorded for both groups.

Statistical methods

SPSS 26.0. (IBM, USA) was used for statistical analysis. Measured data were analyzed using a t test, and expressed as $\overline{x} \pm \text{sd.}$ counted data were analyzed using a chi-square (χ^2) test, and expressed as n [%]. Ordinal data were assessed by a rank sum test. Multiple time points were compared using repeated measures ANOVA. A

P-value < 0.05 was considered a significant difference.

This retrospective case-control study used the following formula for sample size calculation:

$$n = \frac{\left[Z_{1-\alpha/2}\sqrt{2P(1-P)} + Z_{1-\beta}\sqrt{P_0(1-P_0) + P_1(1-P_1)}\right]^2}{(P_0-P_1)^2}. \text{ n rep-}$$

resented the sample size of each group. The values of $Z_{1-\alpha/2}$ and $Z_{1-\beta}$ were 1.96 and 1.28, respectively. PO and P1 were the incidence rates in the exposed and non-exposed groups, respectively, set at 0.4 and 0.2, respectively. The calculation yielded n = 109 per group, requiring a minimum of 218 patients in total. The study included 236 patients, meeting the statistical requirements.

Results

Comparison of baseline data

The baseline characteristics, including age, BMI, history of hypertension and diabetes, disease duration, pathologic types, tumor diameter, ASA classification, operation time, and surgical methods, showed no significant differences between the two groups (all P > 0.05). See **Table 1**.

Comparison of VAS scores

Both groups showed a downward trend in VAS scores at 12 h after surgery (P < 0.05) compared to 1 h after surgery. At 1, 6, 12, 24, and 48 h after surgery, the VAS scores in the preemptive analgesia group were significantly lower than those in the control group (all P < 0.05) (**Figure 2**).

Comparison of Ramsay sedation scores

Ramsay sedation scores in both groups decreased significantly at 12 hours postoperatively compared to 1 hour (P < 0.05). At 1, 6, 12, 24, and 48 h after surgery, the Ramsay sedation score in the preemptive analgesia group were significantly lower than those in the control group, P < 0.05 (Figure 3).

Comparison of clinical efficacy

The analgesic success rate of the preemptive analgesia group (84.8%) was higher than that of the control group (74.0%), P < 0.05 (**Figure 4**).

Table 1. Comparison of baseline data $[\bar{x} \pm s, n (\%)]$

Item	n ·	Preemptive analgesia group	Control group	.24	Р
		(n = 105)	(n = 131)	χ ² /t	
Age		47.1±4.5	47.9±4.7	-1.283	0.201
BMI (kg/m²)		24.6±4.1	25.0±4.2	-0.788	0.432
Hypertension history [n (%)]				0.137	0.711
Yes	36 (15.3)	15 (14.3)	21 (16.0)		
No	200 (84.7)	90 (85.7)	110 (84.0)		
History of diabetes [n (%)]				0.195	0.659
Yes	48 (20.3)	20 (19.0)	28 (21.4)		
No	188 (79.7)	85 (81.0)	103 (78.6)		
Duration of disease (month)		21.3±9.0	20.1±9.7	1.006	0.315
Pathologic classification $[n \ (\%)]$				0.529	0.467
Malignant	24 (10.2)	9 (8.6)	15 (11.5)		
Benign	212 (89.8)	96 (91.4)	116 (88.5)		
Mass diameter (cm)		2.9±0.6	2.9±0.6	0.381	0.703
ASA classification				0.005	0.942
1	123 (52.1)	55 (52.4)	68 (51.9)		
II	113 (47.9)	50 (47.6)	63 (48.1)		
Time of operation (min)		62.2±18.1	61.2±17.8	0.427	0.669
Operation method				0.345	0.842
Modified type I	99 (41.9)	42 (40.0)	57 (43.5)		
Modified type II	71 (30.1)	32 (30.5)	39 (29.8)		
Standard radical operation	66 (28.0)	31 (29.5)	35 (26.7)		

Notes: BMI: Body Mass Index; ASA: American Society of Anesthesiology.

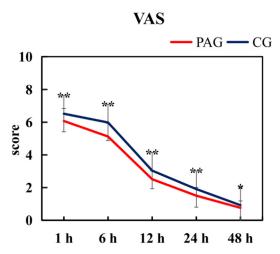


Figure 2. Comparison of visual analog scale (VAS) scores. PAG: Preemptive analgesia group; CG: Control group.

Comparison of pain mediators

Before treatment, there were no significant differences in the levels of pain mediators PGE2, SP, and NPY between the two groups (all P >

Ramsay

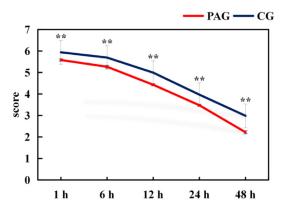


Figure 3. Comparison of Ramsay sedation scores. PAG: Preemptive analgesia group; CG: Control group.

0.05). At 12 h after treatment, the levels of PGE2, SP and NPY in both groups were increased compared to those before treatment (all P < 0.05). However, the preemptive analgesia group showed smaller increases than the control group (all P < 0.05). At 24 and 48 hours

Curative effect Preemptive analgesia group control group 90 80 $Z = -2.425, \quad P = 0.015$ 70 Number (%) 60 50 40 30 20 10 Moderate pain 0 Success rate of analyzein Şiight pain

Figure 4. Comparison of clinical efficacy.

after treatment, PGE2, SP, and NPY levels in the preemptive analgesia group were significantly lower than those in the control group, with levels continuing to decline at 48 hours (all P < 0.05, **Figure 5**).

Comparison of Renal function indices

Before treatment, there were no significant differences in the levels of renal function indices (Cr, BUN, and NGAL) between the groups (all P > 0.05). At 12 h after treatment, the levels of Cr, BUN, and NGAL in both groups increased (all P < 0.05). However, the increase in the preemptive analgesia group was lower than that in the control group (all P < 0.05). At 24 and 48 hours after treatment, Cr, BUN, and NGAL levels in the preemptive analgesia group were significantly lower than those in the control group, with levels continuing to decline at 48 hours (all P < 0.05, **Figure 6**).

Comparison of immune function indices

Before treatment, there were no significant differences in the levels of immune function indicators (CD3+, CD4+, CD8+, CD4/CD8+, CD4/CD8+) between the groups (all P > 0.05). At 12 h after treatment, the levels of CD3+, CD4+, and CD4/CD8+ in both groups decreased (all P < 0.05). However, at 24 and 48 hours after

treatment, the levels of CD3+, CD4+, CD8+, and CD4/CD8+ in the preemptive analgesia group remained significantly higher than those of the control group (all P < 0.05, **Figure 7**).

Comparison of adverse reactions

The preemptive analgesia group had lower total incidence of adverse reactions than the control group (86.7% vs. 65.5%), P < 0.05 (Table 2).

Discussion

Surgery remains a cornerstone in the treatment of breast lumps, with continuous efforts by breast surgeons to refine incision techniques and procedures to improve patient

satisfaction. However, mastectomy often involves the removal of nerves in the breast, possibly leading to postoperative pain. Additionally, the size, number, and location of the mass can significantly influence the surgical approach. For instance, axillary lymph node dissection may damage intercostal nerves, causing sensory disturbances in the chest wall, axilla, and inner upper arm skin, thereby increasing the risk of postoperative pain [17, 18]. Furthermore, conventional opioid-based analgesic regimens not only elevate the risk of adverse reactions but also often fail to provide sufficient pain relief, ultimately affecting clinical outcomes. Thus, effective analgesic strategies are critical to minimizing postoperative pain and improving treatment outcomes in mastectomy patients.

This study retrospectively evaluated the therapeutic impact of dexmedetomidine preemptive analgesia in patients undergoing breast tumor resection. The findings demonstrated that dexmedetomidine preemptive analgesia effectively reduced VAS and Ramsay scores, improved analgesic success rates, and decreased the incidence of adverse reactions. These results align with the findings of Goneppanavar et al. [19], who reported significant reductions in postoperative pain and enhanced sedation in patients receiving dexmedetomidine preemptive analgesia after general anesthesia [19].

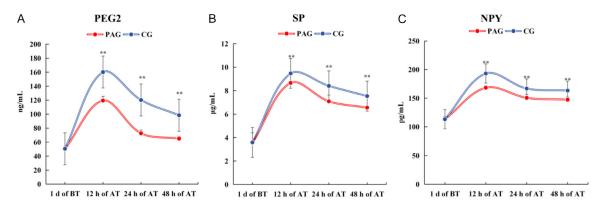


Figure 5. Comparison of pain mediators. Note: Comparison of pain mediators before and after treatment between the two groups. A: Level of prostaglandin E2 (PGE2); B: Level of substance P (SP); C: Level of neuropeptide Y (NPY). PAG: Preemptive analgesia group; CG: Control group; BT: before treatment; AT: after treatment. **P < 0.01.

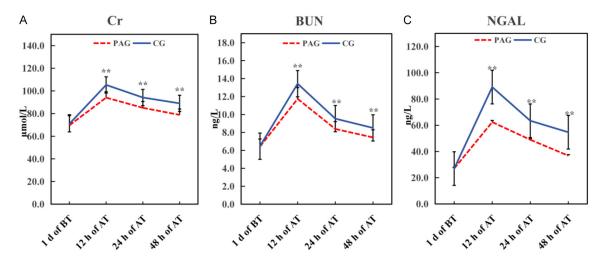


Figure 6. Comparison of renal function indexes before and after treatment between the two groups. A: Level of creatinine (Cr); B: Level of blood urea nitrogen (BUN); C: Level of neutrophil gelatinase-associated lipocalin (NGAL). PAG: Preemptive analgesia group; CG: Control group; BT: before treatment; AT: after treatment. **P < 0.01.

The possible mechanisms underlying these effects are as follows:

Peripheral nerve blockade: Dexmedetomidine locally blocks function-dependent cation currents in C-type and small myelinated nerve fibers, inducing a hyperpolarized state in these fibers. This prevents the formation of new currents, enhancing analgesic effects.

Central sedative action: Dexmedetomidine exerts sedative and hypnotic effects by acting on $\alpha 2$ receptors in the locus coeruleus and activating endogenous sleep-promoting pathways. This state reduces pain perception.

Opioid-sparing effect: Dexmedetomidine's analgesic properties reduce opioid requirements,

thereby mitigating opioid-related adverse effects such as nausea and vomiting [20, 21].

These findings highlight the potential of dexmedetomidine preemptive analgesia as an effective and safe approach to improving postoperative outcomes in patients undergoing breast tumor resection.

PGE2 is an important biologically active medium.

PGE2 is a key bioactive mediator belonging to the prostaglandin family. It is synthesized from arachidonic acid through the cyclooxygenase pathway and is involved in various physiological and pathological processes, including pain, inflammation, and immune responses. PGE2

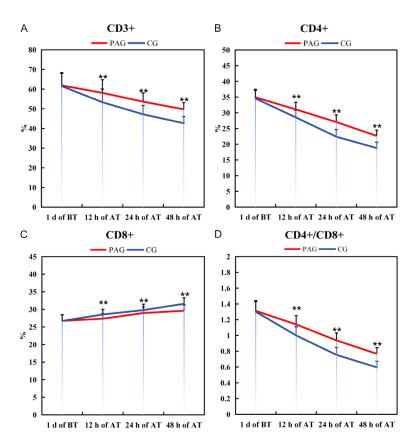


Figure 7. Comparison of immune indexes before and after treatment between the two groups. A: Level of CD3+; B: Level of CD4+; C: The level of CD8+; D: Level of CD4/CD8+. PAG: Preemptive analgesia group; CG: Control group; BT: before treatment; AT: after treatment. **P < 0.01.

plays a critical role in postoperative pain by lowering the activation threshold of pain receptors, allowing stimuli that would not normally cause pain to induce it. This mechanism makes PGE2 a significant contributor to postoperative pain [14].

SP, a neuropeptide of the tachykinin family, is essential for pain transmission. After surgery, tissue damage activates nociceptors, triggering the release of SP. Binding of SP to its receptor, neurokinin-1 receptor (NK-1R), facilitates the transmission of pain signals to the spinal cord and brain, resulting in pain perception [22]. Similarly, NPY modulates pain perception by interacting with specific G protein-coupled receptors [23].

Kim et al. reported that preemptive analgesia with dexmedetomidine can inhibit the expression of pain mediators such as PGE2 [24]. Consistent with this, our study observed a sharp increase in PGE2, SP, and NPY levels within 12

hours postoperatively, followed by a significant decline at 24 hours. The decrease in the dexmedetomidine preemptive analgesia group was more pronounced. This could be attributed to tissue injury leading to an initial surge in PGE2, SP, and NPY levels, which is subsequently suppressed by the prolonged efficacy of dexmedetomidine, effectively inhibiting the production of pain mediators.

This study examined the impact of dexmedetomidine preemptive analgesia on renal function in patients undergoing breast tumor resection. The findings revealed significant reductions in Cr. BUN, and NGAL levels between 12 and 24 hours postoperatively, with a more pronounced decrease in the dexmedetomidine group. These results suggest that dexmedetomidine effectively enhances renal function and improves therapeutic outcomes in these patients.

Previous animal studies have shown that dexmedetomidine inhibits inflammatory responses in renal ischemia-reperfusion injury models in a dose-dependent manner, thereby mitigating kidney damage. Loomba et al. also demonstrated that dexmedetomidine improves Cr, BUN, and NGAL levels, supporting its potential postoperative renal protective effects [25].

Renal impairment typically leads to increased Cr, BUN, and NGAL levels. Cr is a byproduct of muscle metabolism, while blood urea nitrogen (BUN) results from protein metabolism; both are primarily filtered and excreted by the kidneys [26]. When renal filtration is impaired, Cr and BUN excretion decreases. NGAL, a glycoprotein secreted by renal tubular epithelial cells, is an early biomarker of kidney injury. Elevated NGAL levels in blood and urine indicate early-stage renal damage.

The possible mechanism underlying dexmedetomidine's renoprotective effects may involve

Table 2. Comparison of adverse reactions

Group	Bradycardia	Dizziness	Headache	Nausea	Emesis	Adiaphora	χ^2	P
Preemptive analgesia group	2 (1.9)	4 (3.8)	4 (3.8)	3 (2.9)	1 (1.0)	91 (86.7)	14.554	0.012
Control group	10 (7.6)	9 (6.9)	12 (9.2)	8 (6.1)	6 (4.6)	86 (65.6)		

its ability to inhibit hypoxia/reoxygenation injury in human renal cortical proximal tubular epithelial cells, reduce apoptosis, suppress cyclosporine D acetylation, and downregulate silent information regulator 3 expression, ultimately reducing cellular activity and damage [27].

This study also assessed the effect of dexmedetomidine on immune function in patients undergoing mastectomy. Results showed that while levels of CD3+, CD4+, CD8+, and CD4/CD8+ ratios changed in both groups, the degree of change was less pronounced in the dexmedetomidine group, indicating its positive effect on preserving immune function.

T-cell subsets are central to cellular immunity. The percentage of CD3+ T-cells reflects overall cellular immunity; CD4+ T-cells support other immune cells, while CD8+ T-cells suppress immune responses. A decrease in the CD4+/ CD8+ ratio indicates a state of immunosuppression [28-31]. Dexmedetomidine's ability to preserve immune function may enhance the postoperative recovery of cellular immunity in mastectomy patients.

However, this study primarily focused on the analgesic, renal, and immune function indices in this patient population, leaving the precise mechanisms of dexmedetomidine's action unclear. Future research should expand the scope of observational indicators to further elucidate the clinical therapeutic effects and mechanisms of dexmedetomidine preemptive analgesia in patients undergoing breast tumor resection.

In conclusion, dexmedetomidine preemptive analgesia demonstrates significant analgesic and sedative effects in patients undergoing breast tumor resection. It effectively reduces levels of PGE2, SP, and NPY, improves renal function, and helps maintain immune system stability.

Disclosure of conflict of interest

None.

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