Effect of intravenous lidocaine infusion on perioperative cellular immunity and the quality of postoperative recovery in breast cancer patients: a randomized controlled trial

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Background: Breast cancer has become the most common malignancy worldwide. Experimental and, retrospective, clinical data indicate that anaesthetic technique might influence the risk of metastasis after cancer surgery by modulating the immune system. The purpose of this study is to investigate the effect of perioperative lidocaine injection on immune cells such as T lymphocytes and natural killer cells (NK cells) and the quality of postoperative recovery in breast cancer patients and to propose new ideas and relevant theoretical evidence for the selection of anesthetic protocols for perioperative tumor patients.

Methods: Women (n=68) undergoing primary breast tumour resection were randomly assigned to received 2% lidocaine (n=34; group L) or placebo (normal saline; n=34; group S). Venous blood was collected thirty minutes before surgery (T0), after tumor removal (T1), immediately after surgery (T2), 24 h after surgery (T3), and 48 h after surgery (T4). The percentages of NK cells and T lymphocyte subsets (CD3$^+$, CD4$^+$, CD8$^+$, CD4$^+$/CD8$^+$) in peripheral blood were detected by flow cytometry. Patients' quality of recovery-15 (QoR-15) scores were recorded by questionnaire before and 24 h after the operation, as well as intraoperative propofol and remifentanil dosages, the frequency of 24 h postoperative remedial analgesia, and the incidence of nausea and vomiting, dizziness, and chest tightness.

Results: There were 62 patients included in the study, and 60 patients were finally analyzed. The difference in the changing trend of NK cell levels in the 2 groups over time was statistically significant (F=7.675, P=0.008). The intraoperative changing trends of CD3$^+$ T cells, CD4$^+$ T cells, and the CD4$^+$/CD8$^+$ ratio over time differed significantly between the 2 groups of patients (P<0.05), whereas the trends of CD8$^+$ T cells did not differ significantly (P>0.05). The QoR-15 score at 24 h after surgery was higher in Group L (128.50±20.25) than in Group S (117.50±19.50), and the difference was statistically significant (P=0.005). No adverse events such as cardiac arrhythmia and lidocaine toxicity occurred in both groups during the perioperative period.

Conclusions: Continuous intravenous pumping of lidocaine during the perioperative period has little effect on immune function in breast cancer patients and promotes postoperative recovery.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2100050445.

Keywords: Lidocaine; breast cancer; perioperative; tumor immunity

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Introduction

Breast cancer is a major global health problem, with more than 2 million new cases worldwide. It is both the most common malignancy and the leading cause of cancer death in women (1). Although surgical resection under general anesthesia is still the main treatment for breast malignancies, the perioperative immunosuppression induced by surgery and anesthesia can cause the immunologic escape of tumor cells and tumor metastasis (2). Studies have shown that local anesthetics can affect the apoptosis, proliferation, metastasis, and oncogene DNA demethylation of certain tumor cells to regulate the immune system (3-6). However, there are few clinical studies on the effects of local anesthetics on the perioperative cellular immunologic function of patients with malignancies (7,8). Despite surgical treatment, 6% of patients with local tumors and 22% of patients with lymphatic metastasis will be confronted with recurrence within 5 years (9). Accordingly, there is growing concern that the perioperative period contributes directly (i.e., through oncologic manipulation) or indirectly to the spread of tumors. On the one hand, tumor surgery is crucial in the treatment of solid tumors, as final resection can achieve a complete cure, while on the other hand, it may increase the risk of microproliferation and further clinical metastasis. The development of clinical metastasis also depends on the balance between the growth ability of cancer cells at the site of metastasis and the patient's ability to fight the tumor (i.e., the anti-tumor immunity of the host) (10). Therefore, the recovery of the patient's immunologic function after surgery is also crucial for tumor prognosis. A variety of anesthetic drugs are required during the perioperative period, and current studies have shown that opioids and inhalation anesthetics have immunosuppressive effects, weakening the resistance of tumor patients to invasion by residual tumor cells during the perioperative period, which may be detrimental to tumor prognosis. Local anesthetics and propofol can directly affect the growth and invasion of tumor cells, which may help to reduce tumor recurrence and improve patient prognosis (7). Among them, the effects of regional block anesthesia and local anesthetics on postoperative metastatic recurrence in tumor patients are of the most concern, which has promoted more studies of their potential mechanisms.

Local anesthetics can be applied alone or in combination with general anesthetics. The application of local anesthetics keeps down the demand for volatile anesthetics and opioids while alleviating the neuroendocrine stress response and perioperative immunosuppression. The results of Hu *et al.* found that ultrasound-guided erect spinal plane (ESP) block had little effect on immune function in patients undergoing radical mastectomy and promoted postoperative recovery (11). In recent years, intravenous lidocaine has attracted great interest from clinicians as part of the perioperative anesthetic regimen because of its analgesic, anti-hyperalgesia, and anti-inflammatory effects and its resultant shortened hospital stay. Lidocaine may also have the potential to reduce the risk of postoperative recurrence or progression in patients undergoing cancer surgery (12,13). A large number of *in vitro* experiments and some animal experimental evidence currently suggest that lidocaine may inhibit tumor recurrence, but there is still a lack of robust clinical studies demonstrating its benefit in patients undergoing tumor surgery (14). Wang *et al.* found that continuous intraoperative lidocaine infusion was protective of cell-mediated immune function in patients with cervical cancer undergoing radical hysterectomy (15). In the randomized, double-blind, placebo-controlled trial by Hou *et al.*, they randomly assigned 60 patients with early-stage non-small cell lung cancer (NSCLC) undergoing video-assisted thoracic surgery (VATS) to either a lidocaine group (n=30; intravenous push lidocaine 1.0 mg/kg, 1.0 mg/kg/h until surgery end of surgery) or saline control group (n=30). The primary outcome was serum IL-17 levels at 24 hours postoperatively. The results showed that intravenous lidocaine was associated with a decrease in serum IL-17 and cortisol after surgery in patients with early NSCLC (16). However, their studies all ignored the immune status of the preoperative organism and the effects of different degrees of surgical stress on the immune system. There are many factors that affect the immune function of the body during the perioperative period. In this study, we recorded preoperative leukocyte and lymphocyte counts, excluded patients who had received preoperative radiotherapy, and patients who had intraoperative blood transfusions, and all patients were operated on by the same surgical team. This study aims to investigate the effect of lidocaine on postoperative cellular immunity in patients with breast cancer, in order to provide a promising approach for improving postoperative prognosis. We present the following article in accordance with the CONSORT reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-134/rc).

Methods

This study is a prospective single-center, double-blind,

randomized controlled trial conducted in the Department of Anesthesiology of the Affiliated Hospital of Xuzhou Medical University. The study protocol was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (No. XYFY2019-JS017-02), with all patients or their family members signing informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Participants

A total of 62 female patients undergoing an elective modified radical mastectomy in our hospital from December 2019 to April 2021 were selected and divided into 2 groups according to a computer-generated random digit table in a 1:1 ratio, namely, the control group (Group S, n=31) and the lidocaine group (Group L, n=31).

❖ Inclusion criteria: 18–85 years old; female patients; proposed to undergo elective unilateral radical mastectomy; confirmed diagnosis of primary invasive breast cancer (TNM staging: T_{1-3}, N_{0-2}, M_0) on frozen pathological sections; agreed to participate in this study and signed the informed consent.

❖ Exclusion criteria: allergic to local anesthetics such as lidocaine; history of chemotherapy or radiotherapy and patients undergoing secondary surgery (recurrence or reconstruction); metastatic breast cancer and inflammatory breast cancer; BMI >30 kg/m^2; endocrine system diseases, autoimmune diseases, immunodeficiency diseases, other active cancers and recent (<1 month) history of infection, or patients with American Society of Anesthesiologists (ASA) status IV-V, leukemia, or the long-term use of immunosuppressive drugs; unable to cooperate with the researcher for any reason; hearing or a visual impairment, speech comprehension impairment, mental illness; pregnant or breastfeeding; comorbid central neuropathy, hepatic or renal dysfunction and hypotension (systolic blood pressure ≤90 mmHg); those who have participated in other studies.

❖ Rejection criteria: patients with perioperative transfusion of blood products; patients with intraoperative application of local anesthesia (epidural anesthesia, nerve block, local incision infiltration) or intraoperative application of chemotherapeutic drugs; those who voluntarily withdrew from the trial; emergency unblinding cases; those who did not obey the arrangement or agreement of the trial.

❖ Trial termination: breaking of blindness; ethics committee termination or suspension of the trial; emergency envelope unblinding rate exceeding 20%; mid-term finding of a significantly higher rate of complications or adverse events in the intervention group than in the control group.

Randomization, blinding, and allocation concealment

A simple randomization method was used to randomly group the subjects, and the subjects were randomly grouped at a ratio of 1:1 using random numbers generated by a computer probabilistic system. The preparation of the intravenous infusion drug for patients in both groups was performed independently by an anesthesia nurse who did not participate in this study. The syringes containing the preparation were labeled with the patient's name, date of preparation, and route of administration, hence the blinding staff could not determine whether the preparation belonged to the control group or test group based on the appearance of the preparation. Emergency envelopes were prepared at the same time as drug blinding, and an opaque emergency envelope was set up for each blind number, which contained the case medication number and drug name so that individual cases could be unblinded and resuscitated in case of emergency. After the unblinding, the corresponding case was treated as a shedding case. The emergency envelope was sent to the researcher along with the already-blinded drugs. This was a double-blind trial, and all the patients and their families, anesthesiologists, surgeons, study recorders, and evaluators were unaware of the grouping and the composition of the drugs dispensed. Additionally, neither the blood specimen monitoring personnel nor the intraoperative pathology staff had any knowledge of the trial groupings. A supervisor dedicated to coordinating and overseeing the entire research supervised the implementation of the blinding method, ensuring the safety of the subjects and the reliability of the results. This supervisor was responsible for distributing emergency envelopes, maintaining the blind codes, and unblinding at the end of the trial.

Anesthesia and post-anesthesia management

All patients were routinely requested to undergo solid food fasting and liquid fasting before surgery. The data collector

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visited the patients 1 day before surgery, explained the meaning and use of the visual analogue scale (VAS) to the patients. The scale consists mainly of a 10-cm line, with one end of the line indicating "no pain at all" and the other end indicating "the most severe pain imaginable", "pain to the extreme" etc. Patients are asked to mark the appropriate place on the line (with a dot or an "×", etc.) to represent the intensity of the pain they are experiencing at that time (17). After admission, all patients were monitored for non-invasive blood pressure (NIBP), electrocardiogram (ECG), and pulse oxygen saturation (SpO$_2$). Upper limb venous access was opened and an intravenous infusion of 8 mL/kg compound electrolytes was administered.

The bispectral index (BIS) was monitored by a brain state index monitor. General anesthesia was induced by 0.05 mg/kg intravenous midazolam, 0.05 µg/kg sufentanil, 0.9 mg/kg rocuronium, and 0.4 mg/kg etomidate, and the laryngeal mask was inserted when the patient's neck muscles were relaxed and the BIS value decreased to 40–60. Respiratory parameters were set as follows: the total flow of fresh gas was adjusted to 2 L/min (FiO$_2$ 0.5), tidal volume to 6–8 mL/kg, and respiratory rate to 12–14 times/min. Intraoperative respiratory parameters were adjusted according to the situation, maintaining End-expiratory carbon dioxide partial pressure (P$_{ET}$CO$_2$) at 35–45 mmHg (1 mmHg = 0.133 kPa). All patients were given 4 mg intravenous tropisetron before skin excision to prevent postoperative nausea and vomiting.

General anesthesia was maintained with propofol (4–6 mg/kg/h) and remifentanil to maintain BIS values between 40 and 60. The infusion volume of remifentanil was adjusted as needed to maintain the mean arterial pressure (MAP) within ±20% of baseline values. Hypotension was defined as exceeding or decreasing 20% of the baseline MAP, or MAP <65 mmHg for more than 30 s.

When hypotension occurred, 20 µg phenylephrine was administered. The intraoperative heart rate (HR) was maintained at 60–100 beats/min. When bradycardia (HR <50 beats/min) was present, 0.5 mg atropine was administered. A convective warming blanket was used to maintain the patient's intraoperative body temperature at 36–37 ℃. Anesthetics were stopped during skin suturing, then 0.04 mg/kg neostigmine, 0.02 mg/kg atropine, and 0.5 mg flumazenil were injected intravenously, and the patient was sent to the post-anesthesia care unit (PACU). When the patient was awake with spontaneous breathing, laryngeal reflex, and cough reflex restored, and the tidal

volume and minute respiratory volume normalized, the laryngeal mask could be removed and oxygen was administered with a face mask at 3 L/min. After observation in the PACU for about 1 h, the patient could return to the ward. All patients were given standard postoperative analgesia. If the postoperative VAS score exceeded 4 points, 50 mg flurbiprofen axetil would be injected intravenously. If the score was still greater than 4 points, 0.1 mg fentanyl would be injected intravenously.

Intervention

In addition to the standard intraoperative management described above, a loading dose of 1.5 mg/kg of 2% lidocaine was pumped intravenously into the patients of Group L 10 min before induction of anesthesia, followed by induction of anesthesia using mask ventilation for oxygen denitrogenation. After the induction of anesthesia, this drug was continued at a pumping rate of 2.0 mg/kg/h using a micropump until the end of surgery. In Group S, a loading dose of normal saline with pumping was applied in an equal volume.

Outcomes and data collection

The primary outcome indicator was the change in natural killer (NK) cell levels in peripheral blood during the perioperative period. The secondary outcome indicators were as follows: changes in T lymphocyte subset levels in peripheral blood during the perioperative period; patients' QoR-15 scores were recorded by questionnaire before and 24 h after the operation; intraoperative dosage of propofol and remifentanil; additional use of postoperative analgesics and the incidence of complications (postoperative nausea and vomiting, dizziness, and chest tightness). The safety indexes were the occurrence of intraoperative arrhythmias and lidocaine intoxication.

Blood specimens

A volume of 3 mL of venous blood from the contralateral elbow of the enrolled patients was collected 30 min before surgery (T0), after tumor resection (T1), immediately after surgery (T2), 24 h after surgery (T3), and 48 h after surgery (T4). Whole blood samples were anticoagulated with heparin, stored at room temperature, and sent for examination within 4 h.

Flow cytometry

For the preparation of phosphate buffered saline (PBS), 16.00 g NaCl, 0.40 g KCl, 2.88 g NaH_2PO_4, and 0.48 g K_2HPO_4 were weighed then dissolved in 1,800 mL of tri-distilled water. The pH was adjusted to 7.4 with HCl, then tri-distilled water was added to a constant volume of 2,000 mL. The solution was autoclaved and stored at room temperature. For the preparation of tris-NH4Cl (erythrocyte lysate), 7.47 g of NH_4Cl (ammonium chloride) and 1.3 g of Tris (trihydroxymethyl aminomethane) were weighed and dissolved in 1,000 mL of water, then the solution was stored at 4 ℃.

A volume of 200 μL of venous blood was added into a flow tube (Nanjing Beyotime Biotechnology Co., Ltd.), then the appropriate amount of antibody was added [PerCP/Cyanine5.5 anti-human CD4; APC anti-human CD8a; FITC anti-human CD3; PE anti-human CD56 (NCAM); PE anti-human CD16; PE/Cyanine7 anti-human CD45; PE Mouse IgG2a, κ Isotype Ctrl; PE Mouse IgG1, κ isotype Ctrl; Biolegend, USA]. After mixing well and incubating in the dark for 20 min, 2 mL of erythrocyte lysate was added and mixed well to lyse the erythrocytes. Then, 2 mL of PBS was added and mixed well, followed by centrifugation at 2,000 r/min (Beckman Coulter, USA). After washing 3 times, 200 μL of PBS was finally added and mixed well. Samples were placed in the dark at 4 ℃ for experiments, and the results were recorded after detection by flow cytometry (FACS Calibur flow cytometer, Becton, Dickinson and Company, USA).

Sample size

Based on the results of the preliminary experiment (unpublished data, n=20), the sample size was estimated using repeated measurement data. To prove that the mean discrepancy of NK cell percentage was 2%, the standard deviation was 4.2%, and the autocorrelation coefficient between adjacent measurement points of the same tester was 0.3, a two-sided test was adopted, with a test efficacy of 0.05 and a 90% certainty. PASS 15.0 (NCSS, LLC, Kaysville, USA) was applied for calculation, the sample size was 30 cases per group, and an expulsion rate of 10% would be taken into consideration. Eventually, 68 cases of breast cancer patients were to be recruited for this study.

Statistical analysis

For continuous data, the normality test was carried out first, and if each group met the normality criteria and the variances between the 2 groups were equal, the *t*-test would be adopted for comparisons between groups; otherwise, a nonparametric Wilcoxon rank-sum test was considered. For grouped data, the chi-square test was used for unordered outcomes, while the nonparametric Wilcoxon rank-sum test was adopted for ordered data. In this study, due to the multiple repeated measurements, we used repeated measurement analysis of variance (ANOVA) for comparisons of continuous variables and variables of the compound normal distribution; otherwise, we used a generalized estimating equation for comparison. The groups were compared separately to determine statistical differences between groups and time points, and the interaction terms between groups and time points were analyzed to explore whether there were differences in the changing trend between groups. If the interaction terms were statistically significant, a simple effects analysis would be performed to analyze the trend of change over time for each group. All statistical analyses were performed using a two-sided test, with P<0.05 representing a statistically significant difference. All statistical analyses were conducted using SPSS 25.0 (SPSS, Inc., Chicago, IL, USA).

Results

Female patients undergoing elective modified radical mastectomy in our hospital from December 2019 to April 2021 were selected. There were 68 primary screening patients, among which 6 (9%) did not meet the inclusion criteria or met the exclusion criteria, and 2 refused to participate in the study. At first, a total of 62 (91%) patients were enrolled. One patient in Group S voluntarily withdrew from the trial, while 1 patient's blood sample in Group L did not meet the requirements, and they were lost to follow up. Finally, 60 (88%) patients were statistically analyzed, with 30 patients in each group (*Figure 1*). The general information of the patients in both groups was well balanced (*Table 1*).

As shown in *Figure 2*, there was a significant difference in the percentage of NK cells between the 2 groups (F=7.675, P=0.008), and the percentage of NK cells in Group S was lower than that in Group L. The measurement time also had an impact (F=32.766, P<0.001). The percentage of perioperative NK cells in both groups began to decline at T1 and then showed a downward trend over time to the lowest level at T2. Then, they presented an upward trend at T3, but the upward trend of Group S during the T2-
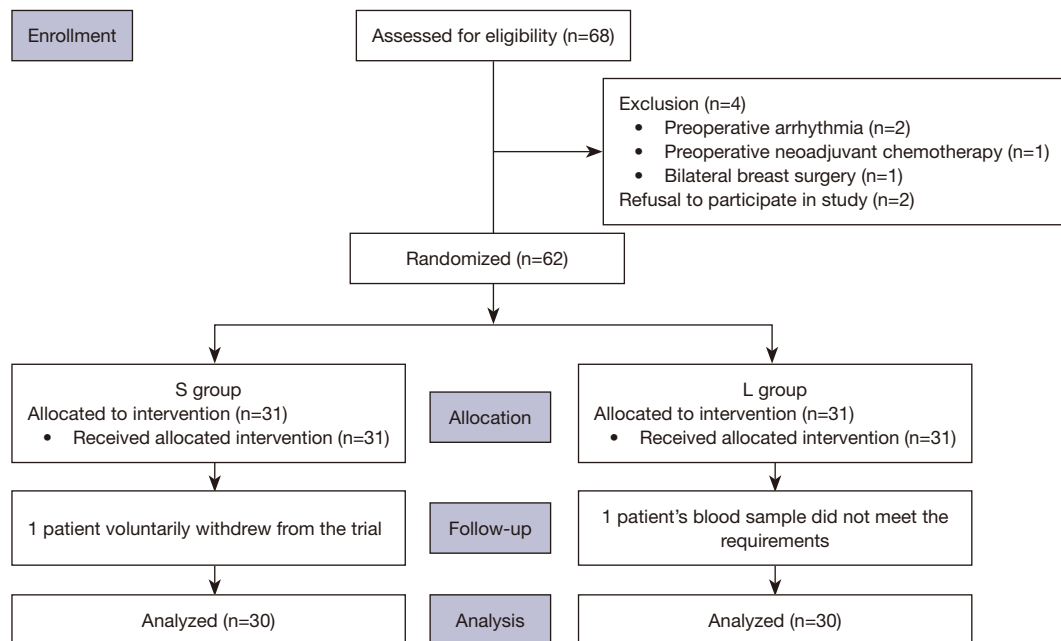
Figure 1 Flow diagram of the study.

Table 1 Comparison of patients' general information

Variables	Group L	Group S	P value
Age (years)	50.02±9.47	50.67±8.54	0.842
BMI (kg/m^2)	24.53±2.25	24.44±2.29	0.875
ASA classification			0.756
I	23 (77%)	24 (80%)	
II	7 (23%)	6 (20%)	
TNM stage			0.829
I	7 (23%)	7 (23%)	
II	21 (70%)	22 (73%)	
III	2 (7%)	1 (4%)	
Preoperative total lymphocyte count (×10^9/L)	2.05±0.62	2.12±0.58	0.690
Preoperative white blood cell count (×10^9/L)	6.09±1.20	5.94±1.11	0.616
Surgery types (%)			0.595
Breast-conserving surgery	10 (33%)	12 (40%)	
Unilateral modified radical mastectomy	20 (67%)	18 (60%)	
Surgery time (min)	147.03±63.02	143.27±55.86	0.807
Intraoperative fluid infusion volume (mL)	1,322.27±365.12	1,301.80±364.14	0.829
Blood loss (mL)	106.80±19.90	108.57±21.56	0.593

Data are presented as mean ± SD or n (%). BMI, body mass index; ASA, American Society of Anesthesiologists; TNM, Tumor Node Metastasis.
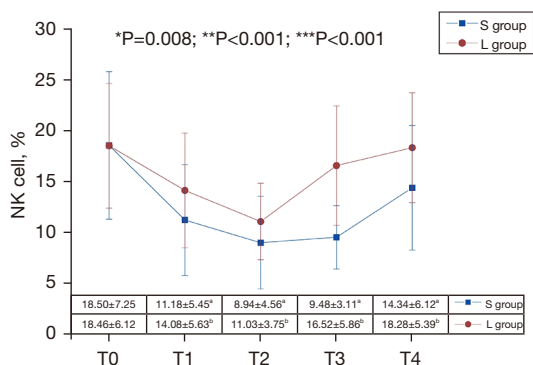
Figure 2 Changes in patient's NK cell levels at different time points. All indicators did not satisfy the covariance matrix or sphericity test; thus, MANOVA was adopted when making comparisons within one group. Simple effect analysis was conducted for two-way comparisons if there was a significant interaction effect between time and group. If there was no significant difference between the time and group interaction term, the main effect analysis would be performed. *, comparison among groups; **, comparison at different points in time; ***, the interaction of groups with time; [a], compared with T0 of the same group, P<0.05; [b], compared with Group S at the same time point, P<0.05. T0, 30 min before anesthesia induction; T1, 30 min after surgery; T2, at the end of surgery; T3, 24 h after surgery; T4, 48 h after surgery; NK, natural killer; MANOVA, multivariate analysis of variance.

T3 period was not significant (the differential value was 0.54, 95% CI: –1.67 to 2.75, P=0.999). The upward trend during T3-T4 was greater (the differential value was 4.86, 95% CI: 2.44 to 7.27, P<0.001), but the percentage of perioperative NK cells during this period did not restore to the initial level. In Group L, the restoration of NK cells was obvious during T2-T3 (the differential value was 5.49, 95% CI: 3.28 to 7.70, P<0.001), and reached baseline level at T3 (the differential value was –1.94, 95% CI: –5.20 to 1.32, P=0.602), but the trend slowed down during T3–T4 (the differential value was 1.75, 95% CI: –0.65 to 4.17, P=0.324). Furthermore, there was an interaction effect between group and time (F=7.328, P<0.001). As measurement time increased, the decrease in the percentage of NK cells and the recovery trend differed between the 2 groups. After comparing the 2 groups, the percentage of NK cells of Group L was significantly higher than that of Group S at T3 (the differential value was 7.04, 95% CI: 4.57 to 9.51, P<0.001) and T4 (the differential value was 3.94, 95% CI: 0.91 to 6.97, P=0.012). At T1 and T2, though the

percentage of NK cells in Group L was higher than that of Group S, the difference was not statistically significant (P>0.05).

Different counts of perioperative CD3+ T cells (F=19.903, P<0.001), CD4+ T cells (F=4.515, P=0.038), and the CD4+/CD8+ value (F=4.400, P=0.040) between the 2 groups were statistically significant. The data in Group S were lower than that in Group L, and there was an interaction effect between group and time. The influence of lidocaine on the counts of CD3+ T cells, CD4+ T cells, and the CD4+/CD8+ value changed with time, whereas no significant difference was found between the 2 groups in terms of CD8+ T cells (F=1.936, P=0.169) and time and group interaction. The counts of CD3+ T, CD4+ T, and CD8+ T cells differed at different times (P<0.001). At T1, the counts of the CD3+ T, CD4+ T, and CD8+ T cells of both groups began to decline and decreased to the lowest level at T2 (P<0.05). At T3, they showed an upward recovery trend. In contrast, the CD4+/CD8+ value in Group S showed a declining trend at T1 and T2 then went up at T3 and T4, reaching the baseline level at T4 (P>0.05). However, the CD4+/CD8+ value in Group L showed an increasing trend at T1, T2, T3, and T4, with a faster increase at T1 and T2 (P<0.05) and a slower increase at T3 and T4 (P>0.05). The percentage of CD3+ T cells in Group S was significantly lower than that in Group L at T1, T2, T3, and T4 (P<0.05). The percentage of CD4+ T cells and the CD4+/CD8+ value in Group L were significantly higher than those in Group S at T2, T3, and T4 (P<0.05). However, at T1, though not significantly, the percentage of CD4+ T cells and the CD4+/CD8+ value in Group L were also higher than those in Group S, but there was no statistical significance (P>0.05). The difference in CD8+ T cells between the 2 groups was statistically significant at T5 (P<0.05), but not at other time points (P>0.05). Details are revealed in *Figure 3*.

The preoperative QoR-15 scores were 133.50 (12.50) in group S and 136.00 (11.50) in group L. The preoperative QoR-15 score in the two groups was not statistically significant (P=0.134). The QoR-15 scores were significantly higher in the group L than in the group S on the 24 h postoperative. It was 128.50 (20.25) in group L and 117.50 (19.50) in group S (*Table 2* and *Figure 4*). The difference was statistically significant (P=0.005).

The intraoperative propofol dosage was 934.17 (531.72) mg in Group S and 908.16 (430.14) mg in Group L. The results showed no significant difference between the 2 groups (P=0.836). The intraoperative remifentanil dosage was 1,385.69 (674.88) μg in Group S and 1,145.00 (531.25) μg
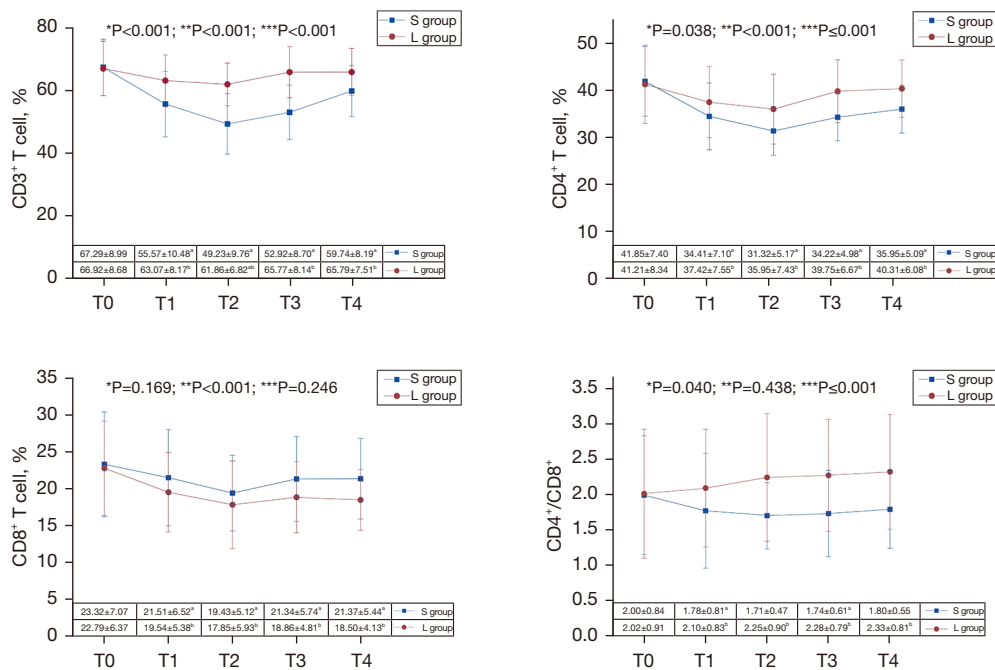
Figure 3 Changes in T-lymphocyte subset levels in patients at different time points. All indicators did not satisfy the covariance matrix or sphericity test; thus, MANOVA was adopted when making comparisons within one group. Simple effect analysis was conducted for two-way comparisons if there was a significant interaction effect between time and group. If there was no significant difference between the time and group interaction term, the main effect analysis would be performed. *, comparison among groups; **, comparison at different points in time; ***, the interaction of groups with time; [a], compared with T0 of the same group, P<0.05; [b], compared with Group S at the same time point, P<0.05. NK, natural killer; T0, 30 min before anesthesia induction; T1, 30 min after surgery; T2, at the end of surgery; T3, 24 h after surgery; T4, 48 h after surgery; MANOVA, multivariate analysis of variance.

Table 2 Comparison of QoR-15 scores, anesthetic dosage, and complications between the 2 groups

Variables	Group L (n=30)	Group S (n=30)	P value
Preoperative QoR-15 scores	136.00 (11.50)	133.50 (12.50)	0.134
QoR-15 scores at 24 h after surgery	128.50 (20.25)	117.50 (19.50)	0.005
Intraoperative propofol dosage (mg)	908.16 (430.14)	934.17 (531.72)	0.836
Intraoperative lidocaine dosage (mg)	257.50 (176.23)	0	0.000
Intraoperative remifentanil dosage (µg)	1,145.00 (531.25)	1,385.69 (674.88)	0.014
Frequency of using analgesics	0 (1.00)	1 (1.00)	0.022
Postoperative nausea and vomiting	2 (6.67%)	5 (16.67%)	0.436
Vertigo	3 (10.00%)	9 (30.00%)	0.098
Chest distress	6 (20.00%)	9 (30.00%)	0.226

Data are presented as M (IQR) or n (%). QoR-15, quality of recovery-15.
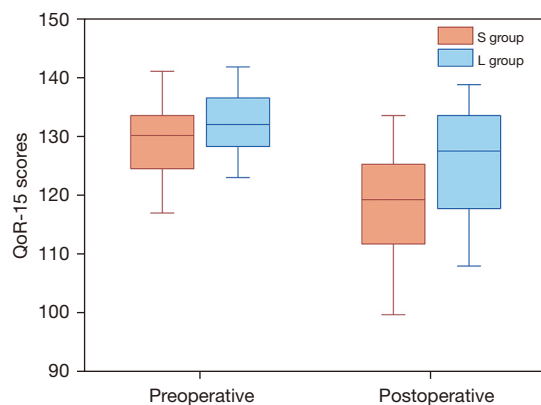
Figure 4 Comparison of QoR-15 scores at 24 h before and after surgery between the 2 groups. QoR-15, quality of recovery-15.

in Group L, presenting a significant difference (P=0.014). There was a significant difference between the 2 groups in the frequency of using analgesics (P=0.022). In Group S, 5 patients experienced postoperative nausea and vomiting, and 9 patients experienced vertigo and chest distress. In Group L, 2 patients had postoperative nausea and vomiting, 3 patients had vertigo, and chest distress occurred in 6 patients. The results showed no significant difference in the incidence of nausea and vomiting, vertigo, and chest distress between the 2 groups (P=0.436, P=0.098, P=0.226). More details are shown in *Table 2*. No perioperative adverse events such as cardiac arrhythmias and lidocaine toxicity occurred in either group.

Discussion

Surgical stress can exacerbate malignancy-induced immunosuppression, which may facilitate cancer recurrence (2). Perioperative risk factors for cancer recurrence include postoperative residual cancer cells, cancer-free margin, cancer cell characteristics, and immune function (18). The management of the tumor during surgery may boost metastasis. Other factors associated with tumor recurrence are anesthetic drugs, anesthetic techniques, acute pain, and the use of opioids. There is growing evidence that anesthetic techniques and anesthetic drugs may influence the long-term proliferation and recurrence of tumors (19). Perioperative use of anesthetic/analgesic techniques with protective effects against metastatic immune responses may slow tumor progression. The effects of different anesthetic drugs on immune cell function are different, and the anesthetic drugs that have the least effect on

cellular immune function may optimize the prognosis of patients. Moreover, in *in vitro* and retrospective studies, the anti-metastatic effects and protective effects of lidocaine on immune function have received extensive attention. Therefore, this study examined the effects of perioperative intravenous infusion of lidocaine on cellular immune function and the quality of postoperative recovery.

Cellular immunity of NK cells and T lymphocyte subsets plays a crucial role in the body's anti-tumor immune effect (20,21). NK cells are broad-spectrum killer cells that play an important role in inhibiting tumor proliferation and growth, and produce cytokines that regulate phagocytosis. They are also important immunomodulatory cells that regulate T lymphocytes, B lymphocytes, and bone marrow stem cells, among others, by releasing lymphokines (IFN, IL-2), preventing the spread of circulating tumor cells and inhibiting the viability of microscopic cancer foci that are freed during surgery (22). Therefore, the NK cell level reflects the immune status of the body to a certain extent. Some studies have shown that NK cell levels are higher in breast cancer patients before surgery than after surgery (23-25). The increase in the percentage of NK cells can improve the immune function of the body, giving it the ability to kill tumor cells. The results of our study showed that the percentage of NK cells, CD3$^+$ cells, and CD4$^+$ cells and the CD4$^+$/CD8$^+$ values were significantly higher in patients in Group L than in Group S patients at T1–T4, and the recovery time of immune cells was shorter in Group L than in Group S, indicating that perioperative intravenous pumping of lidocaine improved the cellular immune function in patients with primary invasive breast cancer after surgery. The overall immune function of the body was consistent with the level of CD3$^+$ cells. By secreting a large number of cytokines that assist CD8$^+$ cells in killing tumor cells, CD4$^+$ cells played a vital role in anti-tumor immunity (26). When the postoperative cellular immune function was severely impaired, the counts of CD4$^+$ and CD8$^+$ cells changed between the 2 groups, disrupting the balance. Cellular immune dysfunction occurred with a decrease in immune cells, and several anesthetic drugs such as sufentanil, remifentanil, and sevoflurane caused suppression of cellular immune function, suggesting that cellular immune function was related to anesthesia (27). Therefore, the choice of the appropriate anesthetic drug was crucial for patients undergoing malignant tumor resection. Previous studies have demonstrated the benefits of propofol in anesthesia for patients with malignant tumors, and lidocaine has been shown to have antitumor effects (28,29). In this study, both

methods of anesthesia had a suppressive effect on cellular immune function in patients with primary invasive breast cancer after surgery, but the results showed that continuous intravenous pumping of lidocaine had a less suppressive effect on NK cell and T cell immune function. Therefore, perioperative intravenously pumped lidocaine may be a better option for patients with primary invasive breast cancer.

Another important finding was that the quality of postoperative recovery was significantly higher in Group L than in Group S. In addition, the study also found a lower incidence of adverse events in Group L than in Group S, suggesting that perioperative intravenous pumping of lidocaine was effective and safe in primary invasive mastectomy. It is known that pain is an important risk factor for the recurrence of cancer metastasis (30). Based on these findings, this study provided further evidence that perioperative intravenous pumping of lidocaine helped improve the quality of patients' postoperative recovery and reduce postoperative adverse reactions.

However, the small sample sizes and short follow-up periods of this study, which failed to record long-term prognostic indicators for patients, did not provide stronger evidence for our findings. Therefore, more evidence should be explored in further studies with larger sample sizes and longer follow-up periods. How to better preserve T lymphocyte and NK cell activity to reduce surgery-mediated neuroendocrine stress, maintain the homeostasis of the body's microenvironment, and potentially enhance host immune function against tumor cells is the challenge for perianesthesia management for oncology surgery. An effective response to the suppression of the immune system by anesthetic drugs is a guarantee of a balanced perioperative microenvironment and provides the best prognosis for the patient. Maximizing the protection of the microenvironment and immune function in oncology surgery patients and optimizing patient prognosis are some of the directions and tasks for future studies in the field.

Conclusions

To sum up, continuous intravenous infusion of lidocaine promoted postoperative cellular immune function, reduced the amount of intraoperative remifentanil administered, improved the quality of patients' postoperative recovery, and mitigated postoperative pain and adverse reactions. Therefore, it can be used for immune function protection in patients with primary invasive breast cancer with a better

therapeutic effect, thereby improving the quality of the patient's recovery.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-134/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-134/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (No. XYFY2019-JS017-02), with all patients or their family members signing informed consent.

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