

Effects of transcutaneous electrical acupoint stimulation on perioperative immune function and postoperative analgesia in patients undergoing radical mastectomy: A randomized controlled trial

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Abstract. Radical mastectomy may lead to suppression of cellular immune function in patients with malignant tumors. Transcutaneous electrical acupoint stimulation (TEAS) is widely used in clinical practice. However, there have been relatively few studies on the effects of TEAS on postoperative analgesia and immune function. The present study aimed to evaluate the effects of TEAS on postoperative pain and immune function in patients undergoing radical mastectomy. A total of 65 patients were enrolled and allocated to either receive TEAS or sham TEAS. TEAS was implemented on bilateral Hegu (LI4), Neiguan (PC6) and Zusanli (ST36) acupoints simultaneously for 30 min before induction of anesthesia at 4 and 12 h post-operation. The primary outcomes included visual analogue scale (VAS) scores at 4 h (T₁), 12 h (T₂), 24 h (T₃) and 48 h (T₄) post-operation, and serum levels of IL-2, IL-4, IFN- γ and the IL-2/IL-4 ratio at 30 min before TEAS (T₀), T₁, T₂, T₃ and T₄. Secondary outcomes included the cumulative time of rescue analgesia within 48 h post-surgery, as well as the incidence of postoperative nausea and vomiting (PONV) and pruritus. Compared with the sham TEAS group,

postoperative VAS scores at T₂ and T₃, the total consumption of opioids in the patient-controlled analgesia (PCA) pump, pressing times of the PCA pump and the incidences of PONV and headache were significantly lower in the TEAS group. The serum levels of IFN- γ at T₃ and T₄, and the serum levels of IL-2 and the IL-2/IL-4 ratio at T₂, T₃ and T₄ were higher in the TEAS group compared with the sham TEAS group. By contrast, the serum levels of IL-4 were lower at T₂, T₃ and T₄ in the TEAS group compared with the sham TEAS group. The results indicated that TEAS could improve postoperative analgesia, reduce postoperative consumption of opioids and alleviate postoperative side effects. Simultaneously, TEAS was able to reverse decreased serum levels of IL-2 and IFN- γ , reduce the level of IL-4 and restore the balance of Th1/Th2, thereby partially attenuating perioperative immune function depression in patients with breast cancer. The current trial was registered prior to participant enrollment at www.chictr.org.cn (Clinical Trial no. ChiCTR1800017768).

Introduction

Breast cancer is the most frequently diagnosed malignancy and ranks as the leading cause for cancer-related deaths among females worldwide, for which surgery has become the primary treatment strategy (1). Patients with malignant tumors often also display immune dysfunction (2). A number of factors may aggravate immune dysfunction during the perioperative period (3-5). Recently, there has been increasing interest in the influence of perioperative immune function secondary to the surgical stress response, anesthesia and postoperative acute pain (6). Perioperative immune dysfunction may predispose patients to infections, homeostasis disturbances, organ dysfunction and other related complications, including an increased mortality rate (7,8). Therefore, it is crucial to take measures to protect the immune function of patients during the perioperative period.

Postoperative pain may trigger a strong stress response, stimulate the release of inflammatory factors and inhibit

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Abbreviations: BIS, bispectral index; P_{ET}CO₂, pressure of end-tidal carbon dioxide; PCA, patient-controlled analgesia; TENS, transcutaneous electrical nerve stimulation; VAS, visual analogue scale

Key words: transcutaneous electrical acupoint stimulation, breast cancer, radical mastectomy, postoperative analgesia, immunity

immune function (9). Therefore, an ideal postoperative analgesic is conducive to the recovery of patients and shortening the length of hospital stay. Currently, opioids providing high analgesic efficacy are commonly used as effective postoperative analgesics (10). However, opioid-induced immunosuppressive effects and adverse reactions including nausea, vomiting, sedation, dizziness and decreased gut motility may delay patient recovery, which limits the application of opioids (11,12).

A recently published meta-analysis suggested that acupuncture is effective in alleviating cancer-related pain, particularly malignancy- and surgery-induced pain (13). Transcutaneous electrical acupoint stimulation (TEAS), as a novel non-invasive acupuncture alternative therapy, combines acupoint stimulation and transcutaneous electrical nerve stimulation (TENS), and displays similarities with traditional acupuncture and moxibustion (14). Due to the advantages of the non-invasive, convenient application and reduced number of side effects of TEAS, it has been increasingly applied in conventional medical settings (15). To date, there have been a few prospective studies comparing the effects of TEAS on postoperative analgesia control and postoperative recovery (16,17).

The concentration of immune cytokines and immunocyte in tumor tissues and plasma is closely related to the cellular immune response to malignant tumors, which may implicate the prognosis of malignant tumors (18,19). Immune cytokines are primarily secreted by T helper (Th)1 and Th2 cells, which are associated with the cellular immune responses to malignant tumors. Th1 cells release IFN- γ , IL-2 and TNF, which are essential for anti-inflammatory and antineoplastic processes (20,21), whereas Th2 cells secrete proinflammatory cytokines, primarily including IL-4, IL-6 and IL-10 (19,22). Therefore, the release and balance of cytokines during the perioperative period have substantial implications for alterations to immune function (23). The present study investigated the serum levels of IL-2, IFN- γ and IL-4, and estimated the balance of Th1/Th2 by calculating the IL-2/IL-4 ratio to explore whether TEAS could improve immune dysfunction. The present study aimed to identify the effects of TEAS on immune function and postoperative analgesia for patients undergoing radical mastectomy.

Materials and methods

Participants. The present study was based on the Declaration of Helsinki and the Guidelines on Good Clinical Practice (24). The present study was approved by the Ethics Committee of Human Research of Tangshan People's Hospital (approval no. RMY-YWLL-2017-1110; Tangshan, China). The trial was also registered prior to participant enrollment at www.chictr.org.cn (clinical trial no. ChiCTR1800017768). Written informed consent was obtained from each patient. Adult female patients (age, 20-65 years) with American Society of Anesthesiologists physical status I or II (25), who were scheduled to undergo elective radical mastectomy of breast cancer in the Department of Anesthesiology, Tangshan People's Hospital and Tangshan Cancer Hospital, North China University of Science and Technology (Tangshan, China) between August 2018 and December 2019, were enrolled in the present study. The exclusion criteria were as follows: i) Body mass index >30 kg/m²; ii) severe cardiac or respiratory diseases,

significant renal or hepatic impairment or immune disorders; iii) history of immunosuppressive therapy (chemotherapy or radiation) or previous acupuncture/TAES therapies; iv) history of chronic pain, steroid or opioid administration, or alcohol or illegal substance abuse; v) high levels of C-reactive protein or leukocytosis ($>10,000$ /ml) prior to surgery; and vi) puncture site infection or systemic infection.

Randomization and blinding. A total of 70 patients were enrolled and randomly allocated to the TEAS group or the sham TEAS group using sequentially-numbered sealed envelopes and a random number generator. The allocation ratio between the two groups was 1:1. The envelopes were prepared and distributed by an assistant who was not involved in the present study. An experienced acupuncturist, who was independent of the present study, performed the corresponding interventions. All surgeries were performed by the same group of surgeons. Similarly, a blinded anesthesiologist provided anesthesia implementation and perioperative care. A second anesthesiologist, who was also blinded to the treatment regimen and was not involved in the data analysis, conducted the anesthesia follow-ups.

Study protocol. For patients in both groups, the application of TEAS was implemented at bilateral Hegu (LI-4), Neiguan (PC-6) and Zusanli (ST-36) acupoints simultaneously. The acupoints were identified according to the traditional anatomical location (Fig. 1). LI-4 Hegu is located at the radial side of the dorsum surface of the hand, between the first and second metacarpal bones. ST-36 Zusanli is located at 3 cun below the patella, outside of the anterior crest of the tibia. PC-6 Neiguan is located at 2 cun above the transverse crease of the wrist, between the palmaris longus tendons and the flexor carpi radialis. After acupoint selection and skin disinfection, the electrodes were attached to the target acupoints. A constant electrical stimulation was applied for 30 min each time with a dense-and-disperse frequency of 2/100 Hz (26) via a HANS LH-202 electrical stimulator (Nanjing Jisheng Medical Technology Co., Ltd.). The optimal intensity was set to mild twitching of the surrounding muscle and individual maximum tolerance (5-10 mA for upper limbs; 10-30 mA for lower limbs) (27,28). The TEAS effect was confirmed by *de qi* sensation (27,29). Participants in the sham TEAS group underwent electrode attachment on the target acupoints without electronic stimulation.

TEAS was performed for 30 min prior to the induction of anesthesia. Postoperative TEAS was performed for 30 min each time at 4 and 12 h post-surgery on the day of surgery, and administrated three times (8 a.m., 2 p.m. and 8 p.m.) daily at postoperative days 1 and 2. Participants in each group were also provided with a patient-controlled analgesia (PCA) pump for postoperative pain control, which was maintained for 48 h post-surgery. The PCA consisted of 1.5 μ g/kg sufentanil (cat. no. 81A09131; Yichang Humanwell Pharmaceutical Co., Ltd.), diluted to 150 ml with normal saline. The basal infusion rate was set to 2 ml/h, with a bolus dose of 0.5 ml and a lockout interval of 15 min.

Standardized anesthesia. Upon arrival in the operating room, all patients were continuously monitored with

electrocardiography, and the following parameters: Blood pressure, pulse oximetry, pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) and bispectral index (BIS) (cat. no. MG8001; Sichuan Kehong Medical Equipment Co., Ltd.) were monitored (30). Before anesthesia induction, all patients received midazolam (1-2 mg; cat. no. 20190108; Jiangsu Nhwa Pharmaceutical Co., Ltd.) intravenously. General anesthesia was induced using intravenous sufentanil (0.3-0.5 μ g/kg; cat. no. 81A09131; Yichang Humanwell Pharmaceutical Co., Ltd.), propofol (2-3 mg/kg; cat. no. 1809208; Fresenius Kabi) and cisatracurium (0.2 mg/kg; cat. no. 18082021; Jiangsu Hengrui Medicine Co., Ltd.). After intubation, ventilation was adopted with an 8 ml/kg tidal volume and $P_{ET}CO_2$ was maintained at 35-40 mmHg. Propofol and remifentanyl (cat. no. 80A06221; Yichang Humanwell Pharmaceutical Co., Ltd.) were titrated to maintain hemodynamic stability intraoperatively by using a target-controlled infusion. During the surgery, the BIS value was maintained at 40-60. Muscle relaxation was facilitated by the intermittent administration of cisatracurium according to surgical requirements. After surgery, muscle relaxation was antagonized with 1 mg neostigmine (cat. no. 1810605; Shanghai Xinyi Pharmaceutical Co., Ltd.) and 0.5 mg atropine (cat. no. 1809131; Tianjin Jinyao Pharmaceutical Co., Ltd.). The patients were sent to the post-anesthetic care unit for further monitoring after extubation. The anesthesia time, operation time, volume of blood loss and urine were recorded.

Observation indexes. Visual analogue scale (VAS) scores (31) were recorded quantitatively to assess the postoperative pain intensity at the following time points post-surgery: 4 h (T_1), 12 h (T_2), 24 h (T_3) and 48 h (T_4). VAS scores ranged from 0-10, 0 indicated no pain and 10 indicated the worst pain. The use of the VAS score was detailed to each patient to ensure the accuracy of the assessment. Subjects were asked to make a mark on the VAS line to indicate the instant pain intensity.

The PCA pump bolus and the total consumption of opioids within 48 h post-surgery were recorded. In addition, the occurrence of postoperative adverse complications, including postoperative nausea and vomiting (PONV), pruritus, dizziness and headache, were observed up to 48 h after operation.

Blood sample collection. Peripheral venous blood (5 ml) was drawn from each participant at 30 min before the first treatment of TEAS (T_0), at T_1 , T_2 , T_3 and T_4 . The blood samples were collected using a heparinized anticoagulation tube for cytokine concentration analysis.

Cytokine assays. For cytokine measurements, the blood samples were centrifuged at 2,200 \times g for 10 min at 4°C. The supernatant was stored at -20°C until subsequent use. Plasma concentrations of IL-2 (cat. no. D2050), IL-4 (cat. no. D4050) and IFN- γ (cat. no. DIF50C) were detected using ELISA kits (all from R&D Systems, Inc.) The absorbance was measured at a wavelength of 450 nm using a Spectra Max 190 microplate reader (Molecular Devices, LLC). To determine the balance of Th1/Th2, the IL-2/IL-4 ratio was also calculated.

Statistical analysis. Statistical analyses were performed using the SPSS software, (version 19.0; IBM Corp.). Data were tested for

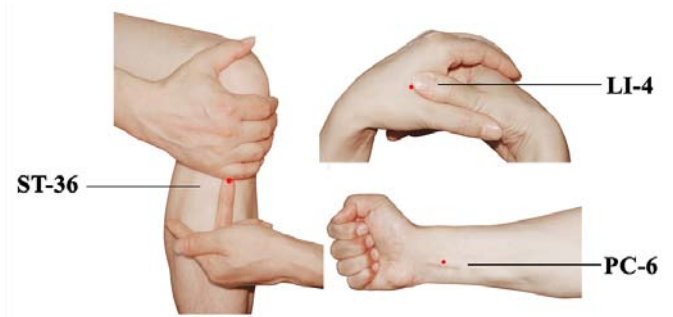


Figure 1. Location of acupoints for TEAS. TEAS, transcutaneous electrical acupoint stimulation.

normality using the Kolmogorov-Smirnov test. Continuous variables are presented as the mean \pm SD. Continuous variables were analyzed using the independent Student's t-test or Mann-Whitney U test. A mixed two-way ANOVA followed by Bonferroni correction were used to detect comparisons of cytokine concentrations between groups at the same time and within groups at the different time points. Categorical variables are presented as numbers or frequencies. Categorical variables were analyzed using the χ^2 test or Fisher's exact test, where appropriate. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Participant enrollment. Initially, 80 participants were recruited. Among them, 10 participants (12.50%) were excluded due to meeting the exclusion criteria and 5 participants (6.25%) were excluded for other reasons (Fig. 2). A total of one patient in the TEAS group and two patients in the sham TEAS group were excluded as they refused to receive TEAS after surgery. Similarly, two patients in the TEAS group had not completed all time point stimulations. Therefore, available data from 65 participants (81.25%) were included in the analysis.

Demographics and operation details. The demographic characteristics were comparable between the two groups. There were no significant differences between the two groups regarding the details of anesthesia and operation, in terms of duration, operation site, blood loss, infusion volume and urine volume (Table I).

Postoperative analgesia indexes. The postoperative VAS scores at T_2 and T_3 in the TEAS group were significantly lower compared with the sham TEAS group. There were no statistical differences at T_1 and T_4 between the groups (Fig. 3). Moreover, the total consumption of opioids in PCA pump and cumulative times of rescue analgesia during the 48-h postoperative period were significantly lower in the TEAS group compared with the sham TEAS group (Table II).

Compared with the sham TEAS group, the incidences of PONV and headache were significantly lower in the TEAS group. No significant differences between the two groups were detected regarding the incidence of pruritus and dizziness (Table II).

Immunological indexes. The baseline levels of IL-2, IL-4 and IFN- γ at T_0 were similar between the two groups. Compared

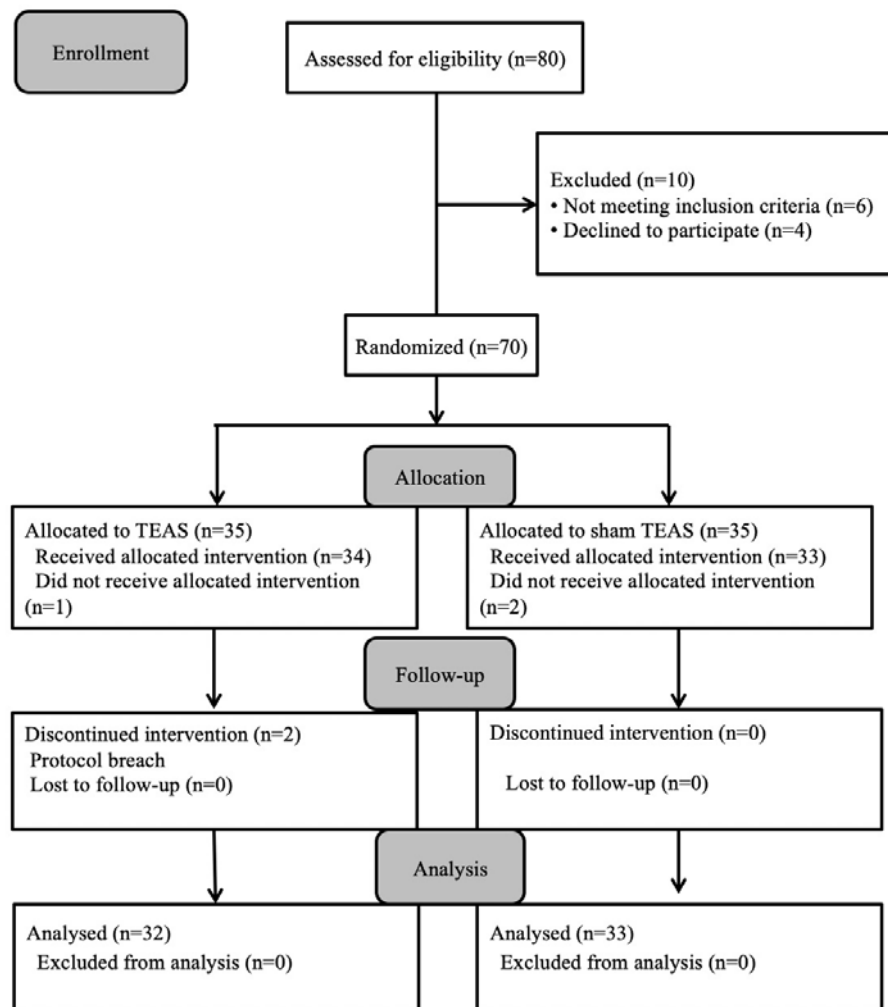


Figure 2. Flow chart showing participants randomized to receive TEAS or Sham TEAS. TEAS, transcutaneous electrical acupoint stimulation.

with baseline levels at T_0 , serum levels of IL-2, IFN- γ and the ratio of IL-2/IL-4 were significantly decreased at T_1 - T_4 in the sham TEAS group, whereas the serum levels of IL-4 were significantly increased at all postoperative time points. Similarly, in the TEAS group, significantly lower serum levels of IL-2 and IFN- γ , a decreased IL-2/IL-4 ratio, and higher levels of IL-4 were observed at T_1 , T_2 and T_3 compared with T_0 . However, postoperative serum levels of IL-2 and IL-4, and the IL-2/IL-4 ratio at T_4 were similar to those at T_0 in the TEAS group, and the serum levels of IFN- γ were still decreased at T_4 .

In the TEAS group, the serum levels of IL-2 at T_2 - T_4 and IFN- γ at T_3 and T_4 were higher compared with the sham TEAS group. By contrast, the serum levels of IL-4 were lower at T_2 - T_4 . Moreover, the IL-2/IL-4 ratio in the TEAS group was significantly higher compared with the sham TEAS group at T_2 - T_4 (Fig. 4).

Discussion

Increasing evidence suggested that surgical trauma-induced stress or general anesthesia could lead to immunosuppression (3-5,32). A recent prospective and randomized pilot analysis investigated the effect of anesthetic technique on immunocyte infiltration in breast cancer (33). The analysis

indicated that balancing general anesthesia with opioid analgesia could attenuate perioperative immunity. A previous study also indicated that regional anesthesia and avoidance of opioids could reduce perioperative residual disease (34), which was consistent with another study (35).

Postoperative pain could lead to the release of inflammatory factors and result in immune disorder (9). Therefore, minimizing the immunosuppressive regimen has been beneficial for patients with cancer (34-36). Opioids are recommended to relieve postoperative or cancer-related pain (10,37). However, intractable opioid-induced adverse reactions, especially immunosuppression, could be easily overlooked (38). Although weak opioids (for example, tramadol) and non-steroidal anti-inflammatory drugs cannot inhibit immune function (39,40), they are rarely used alone for postoperative pain control, given their weak analgesic effects and side effects. In the present study, TEAS in combination with low-dose opioids was selected for analgesia. The results suggested that patients in the TEAS group displayed significantly lower VAS scores at 12 and 24 h post-operation, as well as reduced consumption of PCA within 48 h post-surgery, indicating that TEAS displayed potent analgesic effects, which was consistent with a previous study (27). Therefore, TEAS might be associated with effective postoperative pain relief

Table I. Clinical characteristics of patients between two groups.

Variable	TEAS	Sham TEAS	P-value
Average age (years)	45.6±9.8	46.9±8.6	0.572
BMI (kg/m ²)	23.4±4.2	22.6±3.3	0.396
ASA physical status			0.426
I	26	24	
II	6	9	
Operation site			0.444
Left	18	16	
Right	14	17	
Anesthesia duration (min)	131.6±21.2	128.6±25.6	0.609
Operation duration (min)	98.8±16.8	96.1±20.2	0.561
Blood loss volume (ml)	109.5±28.6	105.6±25.7	0.565
Infusion volume (ml)	895.2±120.5	910.7±143.6	0.636
Urine volume (ml)	170.3±25.4	158.6±30.1	0.095

Values are presented as the mean ± standard deviation or count. ASA, American Society of Anesthesiologists; TEAS, transcutaneous electrical acupoint stimulation.

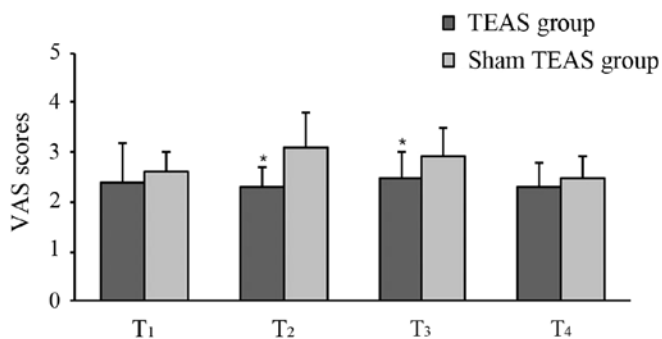


Figure 3. Comparison of VAS scores between two groups. Values are presented as the mean ± standard deviation. *P<0.05 vs. Sham TEAS group. VAS, Visual Analog Scale; TEAS, transcutaneous electrical acupoint stimulation.

and lower analgesic consumption. In addition, the incidences of nausea, vomiting and headache were lower in the TEAS group, which suggested that TEAS could attenuate the incidence of adverse effects. TEAS displayed an analgesic role via certain intensity stimulation on specific acupoints, which was characterized by low stimulation, strong operability and few side effects. In a previous trial, the therapeutic advantage of pretreatment with TEAS at Jia ji EX-B2 was assessed, and the results indicated reduced post-procedural discomfort and abdominal pain following colonoscopy (41). A meta-analysis including a total of 1,350 participants demonstrated that the use of TENS could significantly reduce the consumption of postoperative analgesics (42), whereas TEAS combined the effect of TENS and acupuncture. In addition, Liang *et al* (43) reported that TEAS was an effective adjunct to opioid therapy for moderate and severe cancer-related pain, and could reduce side effects and improve immune function. Therefore, the utilization of TEAS may have a direct clinical application value, especially for patients with cancer. In a previous study, the PC6 acupoint stimulation effectively prevented and relieved

nausea and vomiting that was associated with surgery (44). In addition, two previously published randomized controlled trials reported that acupuncture at PC6 was associated with the relief of postoperative nausea and vomiting (45,46). ST36 and LI-4 are the most common acupoints for analgesia, and stimulation at LI-4 is especially effective for head and neck pain (47). A previous study indicated that acupuncture at LI-4 was as effective as analgesics in relieving headaches with fewer side effects, which was suggested as an alternative to the non-pharmacological analgesia method (48). In an animal experiment, electroacupuncture (EA) at LI-4 and ST-36 significantly enhanced the immune function of rats with gastric carcinoma after operation (49). Moreover, EA at acupoint ST36 alone in mice may ameliorate inflammation and modulate immune function in collagen-induced arthritis (50). EA at acupoint ST36 has been revealed to be beneficial for preserving immune function and improving postoperative recovery (17,29). Consequently, PC-6, LI-4 and ST-36 acupoints were investigated in the present study.

Although TEAS is widely used in daily clinical practice, the specific analgesic mechanism is not fully understood. TEAS serves as an alternative to acupuncture, which provides stimulation by needles on the surface of target acupoints. TEAS can also generate an action potential to activate nerve fibers (51,52) as signals are transmitted to the central nervous system to induce corresponding analgesic effects by modulating the release of neurotransmitters, such as endorphins and enkephalins, and blocking pain signaling pathways (53). EA has also been reported to slowly increase pain thresholds, producing analgesia via counter-regulation of glial activation (54,55). Furthermore, a neuromodulator with antinociceptive properties, adenosine, has been implicated in mediating the analgesia effect of EA, which could be prolonged by manipulation of adenosine metabolism (56).

The present study demonstrated that immune function in both groups was suppressed after surgery, which was associated

Table II. Effective press, consumption of opioids and incidence of adverse events.

Variable	TEAS	Sham TEAS	P-value
Number of effective press	6.2±3.7 ^a	12.3±4.6	<0.001
Consumption of opioids (ml)	102.8±7.4 ^a	120.6±9.2	<0.001
Dizziness	7	9	0.614
Pruritis	2	4	0.672
Headache	2 ^a	9	0.044
PONV	4 ^a	12	0.042

Values are presented as the mean ± standard deviation or count. ^aP<0.05 vs. Sham TEAS group. VAS, Visual Analog Scale; PCA, patient-controlled analgesia; PONV, postoperative nausea and vomiting.

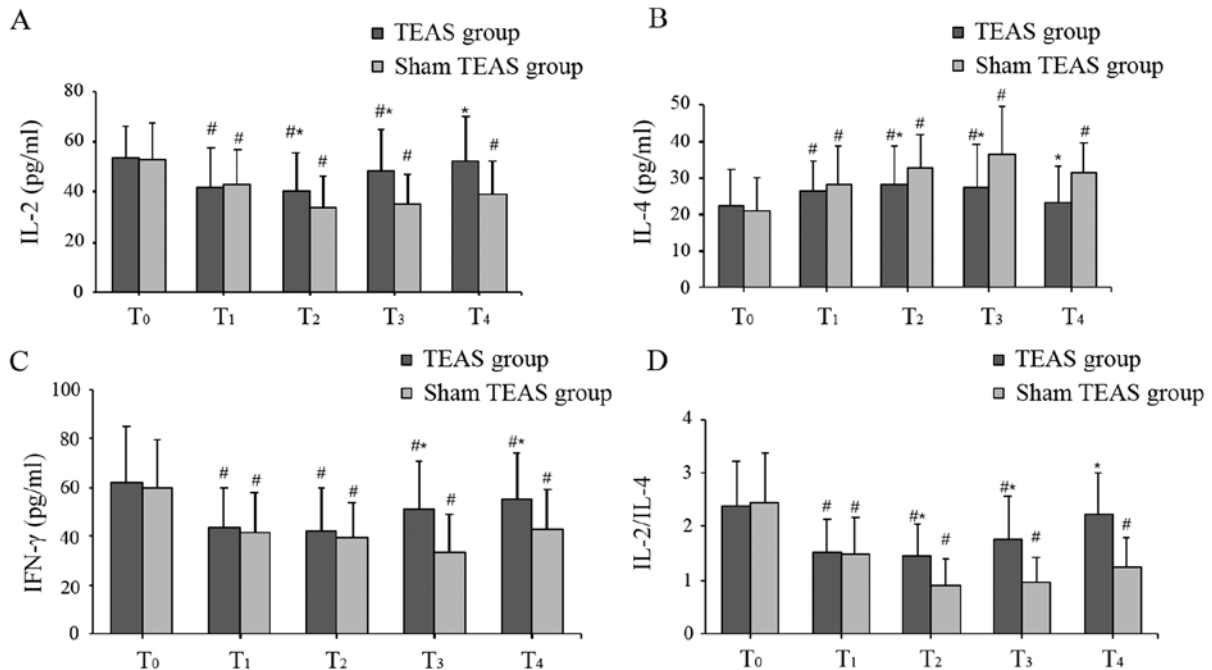


Figure 4. Serum levels of (A) IL-2, (B) IL-4, (C) IFN- γ and (D) IL-2/IL-4 ratio between two groups. Values are presented as the mean ± standard deviation. [#]P<0.05 vs. sham TEAS group; ^{*}P<0.05 vs. T0. TEAS, transcutaneous electrical acupoint stimulation.

with downregulated serum levels of IL-2 and IFN- γ , and increased serum levels of IL-4. In the TEAS group, the levels of IL-2 and IL-4 were restored to the preoperative level at 48 h post-surgery. However, the levels of IL-2 and IL-4 in the sham TEAS group did not restore to the baseline level until 48 h post-surgery. Moreover, the serum levels of IL-2 at T₂, T₃ and T₄, and IFN- γ at T₃ and T₄ in the sham TEAS group were lower compared with the TEAS group. By contrast, the serum levels of IL-4 were higher in the sham TEAS group at T₂, T₃ and T₄. TEAS returned the aforementioned cellular immune factors to the preoperative control value at a faster rate, exerting a modulatory effect on the immune system. A previous animal study indicated that EA at the ST36 acupoint significantly enhanced the levels of IFN- γ and IL-2 (57). Similarly, surgical trauma has contributed to postoperative immunosuppression, which is associated with decreased expression levels of IL-2 and IFN- γ , and increased expression of IL-4 in a surgical traumatized rat model (58). In the present study, TEAS treatment increased the serum levels of IL-2, IFN- γ , and decreased IL-4

secretion, suggesting that TEAS could attenuate the postoperative immune dysfunction of patients with breast cancer via altering the expression of Th1/Th2 cell-associated cytokines. The results were consistent with a previous study (59). Moreover, Li *et al.* (60) demonstrated that EA combined with anesthesia was able to reduce perioperative immunosuppression compared with general anesthesia alone. Under normal conditions, Th1 and Th2 cells are in a relatively balanced state. Since the shift from Th1 to Th2 is associated with immunosuppression and cancer development, the balance between Th1 and Th2 cells is of importance in patients with cancer (61). The ratio of IL-2/IL-4 is typically used to represent the Th1/Th2 cell ratio (32,62). In the present study, the balance between Th1/Th2 was measured to investigate the impact of EA on immune function. The results suggested that the IL-2/IL-4 ratio was significantly altered secondary to mastectomy, whereas TEAS partially restored the imbalance of Th1/Th2.

Although the exact mechanisms underlying EA stimulation-mediated promotion of the functions of the immune

system are not completely understood, previous studies have indicated that certain signaling pathways could be associated with the signaling mechanisms (57,58,63). EA administration could regulate the production of Th1 and Th2 cytokines, and the expression of mRNA splenic T cells (58). Additionally, the immunomodulatory effects of EA are likely connected with the MAPK signaling pathway, which serves an important role in the regulation of T cell activation and cytokine production (58). EA applied to the ST36 acupoint enhanced the level of immune cytokines and cluster of differentiation 4 in spleen cells via transient receptor potential vanilloid (TRPV) channels (57). The aforementioned study also suggested that the activation of TRPV channels was related to Ca^{2+} influx in spleen cells. Moreover, by acupuncture application, an increase in neurotransmitter levels, such as β -endorphin, serotonin, met-enkephalin and leu-enkephalin have been detected in the central nervous system and plasma, which have been revealed to exhibit immunomodulator effects on the immune system (63,64). However, pain relief could also have the potential to benefit immune function by reducing postoperative stress and inhibiting excessive release of inflammatory cytokines (9,36).

The present study had a number of limitations. Firstly, the present study was a single center study with a strictly defined participant population; therefore, the findings might not be applicable to other centers despite high homogeneity of both groups. Secondly, although the sham group was treated in the same manner as the TEAS group, other than the stimulation, blinding of TEAS treatment was not possible as patients eventually knew whether they were receiving electrical stimulation. Thirdly, it was not possible for the operators to be blinded to the grouping because the effectiveness of TEAS was determined via the sensation of *de qi*. In addition, the present study did not detect the influences on long-term sequelae, such as tumor metastasis, recurrence and mortality, which could be associated with perioperative immunosuppression. Moreover, the relatively small sample size of the present study may have partially affected the outcomes. Therefore, further studies with larger sample sizes and multi-indicators are required to evaluate the potential advantages of TEAS.

To conclude, the present study indicated that TEAS maintained cellular immune function, alleviated postoperative pain and reduced the occurrence of opioid-related side effects, providing a novel insight for selection of postoperative analgesia. The results of the present study may have implications for postoperative pain management in patients with cancer regarding immune function and postoperative recovery.

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Availability of data and materials

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

Authors' contributions

LA and JS drafted the manuscript. JS and JG were in charge of patient recruitment. LA collected individual data. SZ and YB performed statistical analyses. JG and YB contributed to study conception. JG reviewed the manuscript and the approved final submission. All authors read and approved the final manuscript.

Ethical approval and consent to participate

The present study was approved by the Ethics Committee of Human Research of Tangshan People's Hospital (approval no. RMY-YWLL-2017-1110; Tangshan, China). The trial was also registered prior to participant enrollment at www.chictr.org.cn (clinical trial no. ChiCTR1800017768). Written informed consent was obtained from each patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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