



Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube

Use of transcutaneous electrical acupoint stimulation in pulmonary surgery for patients with tuberculosis

Xu Lu-lu^a, Zhao Wen-sheng^a, Li Lang-ping^b, Du Xin-dan^{a,*}

^a Department of Pain Medicine, Affiliated Hangzhou Chest Hospital, Zhejiang University School of Medicine, Hang Zhou 310003, China

^b Department of Anesthesiology, Ruijin Hospital /Luwan Branch, Shanghai Jiaotong University School of Medicine, Shanghai 200020, China

ARTICLE INFO

Keywords:

Transcutaneous electrical acupoint stimulation (TEAS)
Tuberculosis
One lung ventilation (OLV)
Inflammatory mediators
Lymphocyte subsets

ABSTRACT

Objective: This study aimed to analyze the effects of transcutaneous electrical acupoint stimulation (TEAS) on the immune function in patients with pulmonary tuberculosis (PT) and the inflammatory response following one-lung ventilation surgery by comparing the levels of inflammatory mediators, such as tumor necrosis factor alpha (TNF- α), interleukin 6 (IL-6), and interleukin 8 (IL-8); T lymphocyte subsets, including CD3⁺, CD4⁺, CD8⁺, and CD4⁺/CD8⁺ cells; and natural killer cells (NK cells).

Methods: We randomly divided 62 patients who underwent general anesthesia for thoracotomy into two groups: TEAS and sham TEAS. Patients in the TEAS group underwent bilateral acupoint electrical stimulation at the Hou.Xi, Zhi.Gou, Nei.Guan, and He.Gu acupoints from 30 min before anesthesia induction until the end of surgery. TEAS was continuously maintained throughout the procedure with a dilatational wave at 2/100 Hz. Those in the sham TEAS group underwent the same management but without stimulation, and the anesthesia induction and maintenance methods were the same in both groups. Venous blood was drawn to monitor inflammatory mediators and lymphocyte subsets before anesthesia induction and 5 days after the surgery.

Results: There was no statistical difference in the general conditions between the two groups ($P > 0.05$). Before anesthesia induction, the levels of inflammatory factors (IL-6, IL-8, and TNF- α), lymphocyte subsets (CD3⁺, CD4⁺, and CD4⁺/CD8⁺), and NK cells did not statistically differ between the two groups ($P > 0.05$). Compared to the sham TEAS group, the levels of IL-6, IL-8, TNF- α , and CD8⁺ were lower in the TEAS group, while those of CD3⁺, CD4⁺, CD4⁺/CD8⁺, and NK cells were higher; however, only the change in TNF- α was significant ($P < 0.05$).

Conclusion: TEAS at the Hou.Xi, Zhi.Gou, Nei.Guan, and He.Gu acupoints at 2 Hz/100 Hz can reduce the inflammatory response during one-lung ventilation but has no significant effect on the immune function in patients with tuberculosis.

1. Introduction

Tuberculosis (TB) is a chronic infection caused by *Mycobacterium tuberculosis*, which can affect many organs, among which the lung is the most common. China is one of the 22 countries in the world with a heavy burden of TB and ranks second in terms of the number of patients with multidrug-resistant TB (MDR-TB) [1,2]. Presently, most clinical responses to TB involve conservative treatment with drugs. More severe cases of TB, including MDR-TB, can cause atelectasis, cavity formation, bronchopleural fistula, and extensive cheese on one side of the lung or even lung destruction due to chronic inflammation. Such serious conditions can lead to a gradual loss of lung function on the affected side

with increased infectivity, requiring surgery. One-lung ventilation (OLV) is often used in patients with TB undergoing pulmonary surgery, and acute lung injury often occurs in the process as an inflammatory reaction accompanied by the rise of inflammatory mediators. Additionally, since patients with TB have low immunity and poor cardio-pulmonary compensatory function and endure lung surgery (long surgical time, large trauma, and multiple postoperative complications), perioperative management to reduce complications and improve prognosis has become the top priority (Figs. 1–3).

Transcutaneous electrical acupoint stimulation (TEAS) is a new therapy that combines the effect of acupoint therapy and that of transcutaneous electrical nerve stimulation [3]. Instead of

* Corresponding author.

E-mail address: dxd37642991@sina.com (X.-d. Du).

<https://doi.org/10.1016/j.jctube.2022.100298>

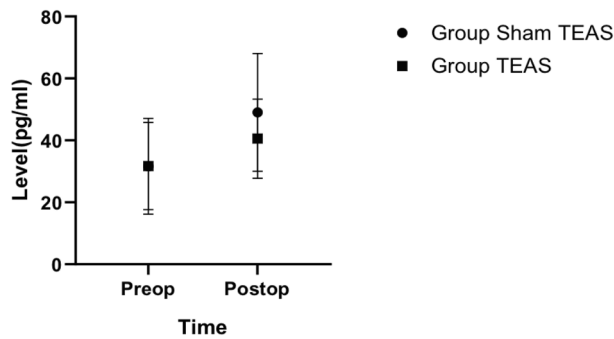


Fig. 1. The comparison of TNF- α .

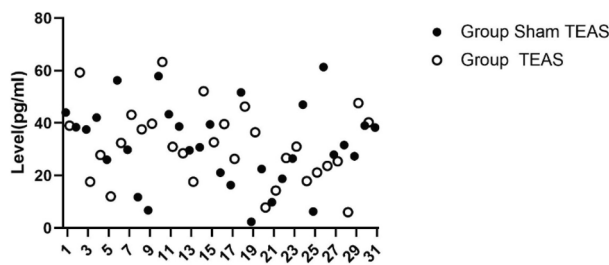


Fig. 2. The comparison of TNF- α pre-operation (n = 31).

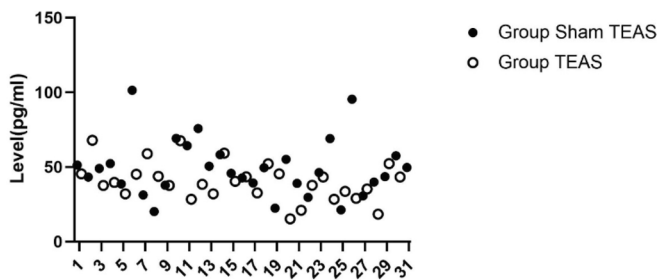


Fig. 3. The comparison of TNF- α post-operation (n = 31).

electroacupuncture stimulation, TEAS combined with general anesthesia makes up for the lack of acupuncture anesthesia and reduces the side effects of general anesthetic drugs. Numerous clinical trials have confirmed that acupuncture combined with anesthesia has the advantage of improving the postoperative immune function of patients. In this study, we sought to explore the effects of TEAS on the immune function of patients with pulmonary tuberculosis (PT) and to find the inflammatory response caused by lung surgery when operating patients with PT, thus providing new ideas and strategies for clinical practice.

2. Materials and methods

2.1. General information

The relevant ethics committee approved the trial. We selected sixty-two patients from the Department of Tuberculosis Surgery of Affiliated Hangzhou Chest Hospital, Zhejiang University School of Medicine. We enrolled participants with emphysema who underwent thoracotomy under general anesthesia from 2017 to 2018. All participants were provided a written informed consent form before randomization. Using a central randomization system for clinical research, we randomly assigned grade I and II American Society of Anesthesiologists criteria patients (ASA I: normal healthy patient, ASA II: patient with mild systemic disease, ASA III: patient with severe systemic disease, ASA IV:

patient with severe systemic disease that is a constant threat to life, ASA V: moribund patient who is not expected to survive without the operation, and ASA VI: declared brain-dead patient whose organs are being removed for donor purposes) into the TEAS (2 Hz/100 Hz TEAS) and sham TEAS groups. Each group had 31 patients among the 40 men and 22 females. The minimum age was 23 and the maximum was 58. We found no significant differences in age, gender, BMI index, preoperative vital signs and the duration of surgery, type of anesthesia, and one-lung ventilation in the two groups ($P > 0.05$), which were comparable (Table 1).

2.2. Treatment method

During hospitalization, we monitored the electrocardiogram, heart rate, noninvasive blood pressure, pulse oximetry, and bispectral index (BIS). Additionally, Lactated Ringer's solution was infused through an open vein channel. To provide electrical stimulation, we used the HANS LH-202 electrical stimulator (Nanjing Ji Sheng Medical Technology Co, Ltd, Nanjing, China.). Patients in the TEAS group were placed on TEAS (with a frequency of 2 Hz/100 Hz [4], the intensity of the current ranged from 5 to 30 mA and the true stimulation being the maximum tolerable setting for a patient,) at bilateral Nei.Guan, He.Gu, Hou.Xi, and Zhi.Gou acupoints from thirty minutes before anesthesia induction until the end of the surgery. Patients in the sham TEAS group were given TEAS at the same acupoints but with no electrical stimulation. To achieve effective anesthesia, patients were placed on oxygen using a pressurized mask and were sequentially injected with intravenous midazolam 0.05 mg/kg, propofol 2–2.5 mg/kg, sufentanil 0.3–0.5 μ g/kg, and rocuronium bromide 0.8 mg/kg. Mechanical ventilation was then performed following tracheal intubation. The infusion rate of dexmedetomidine and the inhalation concentration of sevoflurane were adjusted during surgery, and cis-atracurium was intermittently added (0.04–0.045 mg/kg), maintaining the BIS between 45 and 55.

3. Efficacy observation

3.1. Observation indicators

Two monitoring time points were used to assess the effects of TEAS: preoperative (before induction of anesthesia) and postoperative (5 days after the surgery).

Venous blood was taken at preoperation and postoperation to measure the levels of tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and IL-8 in serum, T lymphocyte subsets (CD3⁺, CD4⁺, and CD8⁺), and natural killer cells (NK cells) using enzyme-linked immunosorbent assay

Table 1

Comparison of the general information between the two groups of patients (n = 31).

Index	sham TEAS	TEAS	F / t	P
Age (years)	49 (31-58)	37 (23-58)	-0.923	0.356
Gender (number)			0.282	0.596
Male	21 (67.74%)	19 (61.29%)		
Female	10 (32.26%)	12 (38.71%)		
BMI index	20.52 (18.2-21.8)	21.26 (19-23.12)	-1.211	0.226
Operation time (min)	162.48 \pm 56.73	162.74 \pm 46.97	-0.020	0.984
Anesthesia time (min)	235.77 \pm 51.78	234.71 \pm 57.4	0.077	0.939
OLV time (min)	120 (90-150)	120 (85-158)	-0.014	0.989
Preoperative MAP (mmHg)	87.35 \pm 10.24	90.58 \pm 7.63	-1.407	0.165
Preoperative heart rate (beats/min)	82.84 \pm 8.71	85.03 \pm 13.8	-0.748	0.458
Preoperative pulse oxygen saturation (%)	98 (98-99)	98 (98-99)	-1.066	0.286

Note: Compared to the sham TEAS group, $p > 0.05$

(ELISA). The preparation of all reagents, the working standards, and protocol were followed according to the manufacturer's instructions.

3.2. Statistical analysis

Statistical analysis was performed using the SPSS 22.0 software package. For data that were normally distributed, the mean \pm standard deviation was used to describe the data distribution, and independent sample *t* tests were used to compare the differences between groups. For non-normal data, the median and quartile were used, and the rank sum test was used to compare the differences between groups. All tests in this article were two-sided. The results were statistically significant ($P < 0.05$).

4. Results

4.1. Comparison of inflammatory factors

Table 2 shows the comparison of the levels of IL-6, IL-8, and TNF- α between the two groups of patients preoperation and postoperation. There was no statistical difference in the levels of inflammatory factors IL-6, IL-8, and TNF- α between the two groups in preoperation ($p > 0.05$). Although IL-6, IL-8, and TNF- α levels were lower in the TEAS group than in the sham TEAS group postoperation, only the difference in TNF- α was statistically significant ($p < 0.05$).

4.2. Comparison of lymphocyte subsets and NK cells

Table 3 shows the comparison of CD3⁺, CD4⁺, CD8⁺, CD4⁺/CD8⁺, and NK cells at different time points between the two groups of patients. We found no statistical difference in the levels of CD3⁺, CD4⁺, CD4⁺/CD8⁺, and NK cells between the two groups preoperation ($p > 0.05$). The CD3⁺, CD4⁺, CD4⁺/CD8⁺, and NK cells were higher and the CD8⁺ was lower in the TEAS group compared with the sham TEAS postoperation group, but the difference was not statistically significant ($p > 0.05$).

5. Discussion

Proinflammatory and anti-inflammatory factors occur in a balanced state in the body, and the production and expression of these two factors contribute to the occurrence and deterioration of the inflammatory response. When the body is infected and attacked by Mycobacterium tuberculosis, a strong inflammatory response follows, setting off numerous proinflammatory factors. Joshi L et al. [5] evaluated the levels of TNF- α , IL-10, and IL-6 cytokines among patients with TB, their household contacts, and healthy people using ELISA and found higher serum levels of IL-6, IL-10, and TNF- α in patients with TB than in controls. Additionally, studies have shown that even in the absence of surgery, inflammatory cytokines increased significantly in the bronchoalveolar lavage fluid of collapsed lung after one-lung ventilation. Surgical procedures can lead to diffuse alveolar damage, including

Table 2
Comparison of IL-6, IL-8, and TNF- α preoperation and postoperation in the two groups (n = 31).

Point time	Index (pg/ml)	Sham TEAS	TEAS	t/Z	P
Preop	TNF- α	31.64 \pm 15.48	31.69 \pm 14.06	-0.014	0.989
	IL-6	25.66 \pm 9.22	25.71 \pm 10.04	-0.022	0.983
	IL-8	18.77 (13.31–23.72)	18.77 (16.03–24.69)	-0.415	0.678
Postop	TNF- α	49.06 \pm 19.00	40.54 \pm 12.77	2.070	0.043*
	IL-6	40.89 \pm 9.44	36.35 \pm 9.55	1.881	0.065
	IL-8	30.65 (25.63–38.26)	29.05 (23.31–33.56)	-1.309	0.190

Note: Compared to the sham TEAS group, * $p < 0.05$

Table 3

T lymphocyte subsets and NK cell levels preoperation and postoperation in the two groups (n = 31).

time	index	Sham TEAS	TEAS	t/Z	P
preop	CD3 ⁺ (%)	69.38 \pm 7.92	69.21 \pm 7.68	0.085	0.932
	CD4 ⁺ (%)	38.31 \pm 8.52	38.18 \pm 7.57	0.064	0.949
	CD8 ⁺ (%)	24.92 \pm 6.6	24.93 \pm 6.83	-0.004	0.997
	CD4 ⁺ / CD8 ⁺	1.45(1.18–2.1)	1.5(1.15–2.03)	-0.211	0.833
	NK cells (%)	9.87(7.53–16.7)	10.39 (8.47–14.35)	-0.176	0.860
postop	CD3 ⁺ (%)	57.89 \pm 6.7	61.01 \pm 7	-1.795	0.078
	CD4 ⁺ (%)	27.49 (24.23–30.28)	30.38 (25.48–33.57)	-1.795	0.073
	CD8 ⁺ (%)	32.07 \pm 6.43	29.71 \pm 6.72	1.412	0.163
	CD4 ⁺ / CD8 ⁺	0.9(0.7–1.05)	1.03(0.78–1.19)	-1.852	0.064
	NK cells (%)	7.23 (5.27–10.42)	7.46 (6.35–13.27)	-1.408	0.159

Note: Compared to the sham TEAS group, $p > 0.05$

neutrophil infiltration, atelectasis, interstitial edema, or microbleeding [6]. These can also induce the expression of inflammatory factors, proinflammatory factors, TNF- α , and IL-1 β in collapsed lungs after retraction [7].

We found that there are different inflammatory factors detected in different experiments, and in this experiment, we found changes in IL-6, IL-8, and TNF- α levels. According to Lai WY et al. [8] TNF- α is a cytokine that contributes to the early stage of local and systemic inflammation. It can activate tissue resident neutrophils and macrophages to secrete TNF- α and other proinflammatory cytokines, such as IL-6 and IL-8, which in turn recruit polymorphonuclear leukocytes (PMNs) into the damaged tissues and aggravate the cascade of cell death signaling. IL-6 is produced by activated monocyte macrophages, endothelial cells, and T lymphocytes, which can promote monocytes and T lymphocytes to secrete pro-inflammatory factors, such as interferon (IFN)- γ and TNF- α , and aggravate the inflammatory response. Therefore, the detection of IL-6 in blood is helpful to estimate the inflammatory status of lung tissue [9]. IL-8 is mainly produced by monocyte macrophages and neutrophils, but also a neutrophil activator, which promotes the expression of pro-inflammatory factors, including TNF- α , IL-17, and IL-1 β that intensifies the inflammatory response. IL-8 also promotes cell apoptosis, inhibits cell activity, and eventually causes acute lung injury by inhibiting SP-A and SP-B protein levels. It is, therefore, an important determinant of lung injury [10]. In this experiment, the inflammatory factors (IL-6, IL-8, and TNF- α) did not statistically differ between the two groups' preoperation. However, their postoperation levels in the two groups were higher that are consistent with related research [11], which were more significant in the control group. There was no significant difference in the levels of IL-6 and IL-8 between the two groups, only the difference in TNF- α was statistically significant. We believe that TEAS could inhibit the inflammatory damage caused by PT surgery to a certain extent by reducing the release of TNF- α , thereby weakening the cascade amplification effect of inflammatory damage initiated by TNF- α and preventing further damage to the lung tissue.

T lymphocytes play important roles in the occurrence and development of TB. Changes in the number or proportion of T cell sub-populations, especially the CD4⁺ and CD8⁺ T cells, will directly affect the form of *Mycobacterium tuberculosis* in vivo, thereby affecting the progress of the disease. Green et al. [12] confirmed that the decline in CD4⁺ T cells positively correlated with the severity of the disease and the bacterial growth index, and the host cell death index increased with their depletion during chronic infection. CD8⁺ T cells exhibit cytolytic functions to kill *M. tuberculosis*-infected cells via granule-mediated function (perforin, granzymes, and granulysin) or Fas–Fas ligand interaction to induce apoptosis [13]. This entails that the more severe the disease is, the higher the level of CD8⁺ cells. Bold et al. [14] pointed out

that CD8⁺ T cells depended on CD4⁺ T cells, the CD4/CD8 ratio in patients with TB was significantly lower than that in healthy people, and the decline in this ratio positively related to the severity of the disease.

Presently, most experimental results [15,16] suggest that TEAS can reduce postoperative immunosuppression and have a positive regulatory effect on immune function, especially cellular immune function, but the time points of each experiment are different. In this study, there was a significant decline in the levels of CD3⁺, CD4⁺, CD4⁺/CD8⁺, and NK cells between the two groups preoperatively and a significant rise in CD8⁺ level. It can be seen that the immune function of patients with PT is suppressed to a certain extent by surgery and anesthesia, and TEAS has a certain effect on the immune function on the fifth day after surgery, which is not significant. As evidenced by the above clinical studies, lymphocyte subsets and NK cells changed over time. In this experiment, few time points were selected due to the limited funds and time; thus, we could not rule out the significant difference immediately following the surgery to the fifth day postoperation. The advantage of TEAS in improving postoperative immune function is still affected by many factors in the clinic, such as the stability of the effect, the time limit of the evaluation index, and the combination of acupoints. Moreover, the effects of acupuncture anesthesia vary for people of different constitutions. Generally, the sample size of this study was relatively small, and this was a single center design making the selection bias, which may lead to differences in measurement indicators. Therefore, further research is needed to explore the effect of TEAS on immune function of patients undergoing TB surgery.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

All authors thank for ZHANG Tie-shan and ZHAO Wen-sheng (The Department of Anesthesiology and Pain Medicine, Affiliated Hangzhou Chest Hospital, Zhejiang University School of Medicine, China) for patient recruitment and data collection. The authors thank Nelson Brandon J (Department of Biomedical Engineering and Physiology, Mayo Clinic, Rochester, MN) for English proofreading.

Authors' Contributions

Xu Lu-lu drafted the manuscript and performed statistical analyses. Du Xin-dan reviewed the manuscript and approved final submission.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

- [1] World Health Organization. Global Tuberculosis Report 2015[M]. http://www.who.int/tb/publications/global_report/en/.
- [2] Technical Guidance Group of the Fifth National TB Epidemiological Survey, The Office of the Fifth National TB Epidemiological Survey The fifth national tuberculosis epidemiological survey in 2010[J] Chin J Antituberc. 2012;34(8): 485–508.
- [3] Wang JQ, Mao L, Han J-S. Comparison of the antinociceptive effects induced by electroacupuncture and transcutaneous electrical nerve stimulation in the rat. *Int J Neurosci* 1992;65(1-4):117–29.
- [4] Huang S, Peng WenPing, Tian X, Liang H, Jia Z, Lo T, et al. Effects of transcutaneous electrical acupoint stimulation at different frequencies on perioperative anesthetic dosage, recovery, complications, and prognosis in video-assisted thoracic surgical lobectomy: a randomized, double-blinded, placebo-controlled trial. *J Anesth* 2017;31(1):58–65.
- [5] Joshi L, Ponnana M, Sivangala R, Chelluri LK, Nallari P, Penmetsa S, et al. Evaluation of TNF- α , IL-10 and IL-6 cytokine production and their correlation with genotype variants amongst tuberculosis patients and their household contacts. *PLoS ONE* 2015;10(9):e0137727.
- [6] Kozian A, Schilling T, Röcken C, Breiting C, Hachenberg T, Hedenstierna G. Increased alveolar damage after mechanical ventilation in a porcine model of thoracic surgery. *J Cardiothorac Vasc Anesth* 2010;24(4):617–23.
- [7] Funakoshi T, Ishibe Y, Okazaki N, Miura K, Liu R, Nagai S, et al. Effect of re-expansion after short-period lung collapse on pulmonary capillary permeability and pro-inflammatory cytokine gene expression in isolated rabbit lungs. *Br J Anaesth* 2004;92(4):558–63.
- [8] Lai W-Y, Wang J-W, Huang B-T, Lin E-Y, Yang P-C. A Novel TNF- α -Targeting Aptamer for TNF- α -mediated acute lung injury and acute liver failure. *Theranostics* 2019;9(6):1741–51.
- [9] Arpin D, Perol D, Blay J-Y, Falchero L, Claude L, Vuillermoz-Blas S, et al. Early variations of circulating interleukin-6 and interleukin-10 levels during thoracic radiotherapy are predictive for radiation pneumonitis. *J Clin Oncol* 2005;23(34): 8748–56.
- [10] Yang Y, Li Q, Tan F, Zhang J, Zhu W. Mechanism of IL-8-induced acute lung injury through pulmonary surfactant proteins A and B. *Exp Ther Med* 2020;19(1):287–93.
- [11] Jiang JH, Yang EJ, Baek MG, Kim SH, Lee SM, Choi SM, et al. Anti-inflammatory effects of electroacupuncture in the respiratory system of a symptomatic amyotrophic lateral sclerosis animal model. *Neurodegener Dis* 2011;8(6):504–14.
- [12] Green AM, DiFazio R, Flynn JL. IFN- γ from CD4 T cells is essential for host survival and enhances CD8 T cell function during mycobacterium tuberculosis infection. *J Immunol* 2013;190(1):270–7.
- [13] Lin PL, Flynn JL. CD8 T cells and Mycobacterium tuberculosis infection. *Semin Immunopathol.* 2015;37(3):239–49.
- [14] Bold TD, Ernst JD. CD4⁺ T cell-dependent IFN- γ production by CD8⁺ effector T cells in Mycobacterium tuberculosis infection. *J Immunol* 2012;189(5):2530–6.
- [15] Tu Q, Yang Z, Gan J, Zhang J, Que B, Song Q, et al. Transcutaneous electrical acupoint stimulation improves immunological function during the perioperative period in patients with non-small cell lung cancer undergoing video-assisted thoracic surgical lobectomy. *Technol Cancer Res Treat* 2018;17: 1533033818806477.
- [16] Fan WC, Ma W, Zhao C, Tong QY, Shen WD. Influence of acupuncture-drug compound anesthesia with different frequency electroacupuncture on immune function in patients undergoing pneumonectomy. *Zhongguo Zhen Jiu* 2012;32(8): 715–9.