Transcutaneous electrical acupoint stimulation (TEAS) relieved cancer-related fatigue in non-small cell lung cancer (NSCLC) patients after chemotherapy

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Background: To explore the effectiveness of transcutaneous electrical acupoint stimulation (TEAS) approach on cancer-related fatigue (CRF) in non-small cell lung cancer (NSCLC) chemotherapy patients.
Methods: A total of 162 participants who treated with gemcitabine combined with platinum-based drugs (GP chemotherapy) were randomly assigned to three groups: Control (Group A, n=56), Sham TEAS (Group B, n=49), and TEAS (Group C, n=57). The following acupoints were used in this study: Qihai (CV6), Keshu (UB17), and Zusanli (ST36). The Revised Piper Fatigue Scale (RPFS) were used to measure CRF on the day before chemotherapy (P1), days 8 (P2) and 28 (P3) separately. The Differences among three groups were analyzed.
Results: At the 28th day, the outcomes of the fatigue scores for Group C, Group B and Group A were 2.06±0.90, 2.80±1.34, 3.00±1.29 respectively. There were significantly different among three groups (F=9.784, P<0.01). At the 28th day, the outcomes of the affective fatigue (F=8.161, P<0.01), sensory fatigue (F=3.06, P=0.05) and cognitive fatigue (F=8.06, P<0.01) for Group C, Group B and Group A were significantly different among three groups.
Conclusions: Chemotherapy may increase the fatigue from P1 to P2 and P3 in NSCLC patients. And TEAS could help to relived CRF, especially at P3.

Keywords: Cancer-related fatigue (CRF); transcutaneous electrical acupoint stimulation (TEAS); lung cancer

Introduction

Lung cancer is the leading cause of cancer related mortality worldwide, which accounts for about 19.4% of all cancer-related deaths (1). In 2010 to 2012, the incidence of lung cancer was approximately 30 people per 10 million in Global (2). 80% to 85% of all lung cancer patients' diagnosis as non-small cell lung cancer (NSCLC).

Chemotherapy remains the primary treatment method for NSCLC patients, and gemcitabine combined with platinum-based drugs (GP regimen) is common used (3,4). Although GP regimen reduces the mortality of NSCLC patients significantly, majority patients could not endure the adverse reactions of chemotherapy. The fatigue is recognized as one of the most prevalent negative effects of the GP regimen (5,6). Up to 40% of cancer patients report fatigue at the time of diagnosis, and 80% of patients report fatigue at some point during chemotherapy (7). In 2014, National Comprehensive Cancer Network (NCCN) defined Cancer-related fatigue (CRF) as a distressing persistent tiredness

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with physical, emotional, and cognitive effects caused by cancer or chemotherapy (8). Fatigue is not only a prevalent adverse reaction, but a long-term problem. In the National Comprehensive Cancer Network (NCCN) guideline for Cancer-Ralted Fatigue (9), approximately one third of cancer patients who have completed their primary treatment for more than 6 years, still have certain levels of fatigue. As health professionals, however, the current fatigue after chemotherapy did not cause enough attention. It is hard to reduce the fatigue of cancer patients due to no standard guideline of fatigue intervention (10). Mitchell *et al.* (5) have suggested that exercise is an effective method to relieve cancerous fatigue, and scientific care interventions could improve the quality of life and treatment compliance of cancer patients with fatigue. However, Phillips *et al.* (6) demonstrated exercise is not associated with improved cancerous fatigue. Aerobic exercise caused by the cardiovascular system and skeletal muscle system adaptation is not permanent. After stop training for some time, the cardiovascular system function and skeletal muscle metabolism will gradually decline (11).

Currently, Traditional Chinese Medicine (TCM) has been the focus of increasing research activity. In a phase II trial, after acupuncture Zusanli (ST36), Qihai (CV6), Guanyuan (CV4) twice a week, 31.1% patient undergoing chemotherapy improve fatigue level (12). Guo CH showed that stimulating CV4, CV6, ST36, Shenque (CV8), Keshu (UB17) with moxibustion is another TCM method to ameliorate fatigue in esophagus cancer patients (13). However, the interventions are still limited, and acupuncture is an invasive method. Patients experience pain. In additional, moxibustion is not adapted to lung cancer patients caused by producing smoking.

The aim of this research was to explore the effects of TEAS on CRF in NSCLC chemotherapy patients. TEAS is a therapeutic approach based on transcutaneous electrical nerve stimulation (TENS) (14). TEAS incorporates the use of an electrode into traditional Chinese acupuncture therapy to stimulate specific acupuncture points in order to relieve symptoms and rehabilitate (14). According to TCM channel and collateral theory, TEAS would be introduced to relieve fatigue at ST36, CV6, UB17. Combined effects of the three acupoints have not been studied yet, even the literature indicates no incompatibility between it.

Methods

Study design

This study was conducted with a prospective experimental design from July, 2014 to July, 2015.This research was a single-center, randomized trial last for 28 days. A research assistant collected the outcome surveys at baseline before the chemotherapy (P1), at day 8 (P2), and at day 28 of the program (P3). To recruit suitable patients, the investigators explained the purpose of the research and provided a confidentiality agreement to each participant. The research protocol for the retrospective analysis was approved by the ethics committee of the Shanghai Pulmonary Hospital, China (No. K14-170). The Clinical Trial Number of this research is NCT02663492.

Setting and subjects

All participants were recruited from the oncology ward of a specialist pulmonary hospital in Shanghai. Those patients were selected for inclusion in the study who (I) had been diagnosed with NSCLC; (II) were aged between 20 and 80 years; (III) were in the first cycle of-GP chemotherapy after diagnosis; (IV) had been prescribed the doses of GP regimen are Gemcitabine 1,000 mg/m^2 combine with Cisplatin 75 mg/m^2 or carboplatin AUC 5–7; (V) had no surgery within 3 months; (VI) were expected to survive more than 3 months based on a score ≥60 points on the Karnofsky Performance Status (KPS); and (VII) were able to understand and speak Mandarin. Patients who were pregnant, mentally ill, or unable to communicate were excluded.

According to the results of the pre-experiment, the calculated sample size formula was used to obtain at least 47 samples (including 20% of the sample wastage rate). The formula is $\frac{(u+v)^2\left(\sigma_1^2+\sigma_0^2\right)}{(\mu_1-\mu_0)^2}$. The power was 90% and α was 5%. To minimize the infection between the TEAS group, the sham TEAS group and the control group, the subjects were physically isolated from the wards until the longitudinal study was carried out.

The patients who met all the selection criteria were randomized to the study groups as follows: Control group (Group A), Sham TEAS group (intervention group, Group B), and TEAS group (Group C). To assign the patients to the study groups, the letters "A", "B", and "C" were each written on 3 pieces of paper for each ward in the hospital. Then, all of the papers were placed in a container, and the participants were instructed to choose one piece of paper randomly from the container before the study began, then replace the paper in the container. The participants were not told which treatment the letters corresponded to, and the nurses who assisted the participants were not involved in the investigation.

Table 1 Location of acupuncture sites for the TEAS program

Acupoints	Location
Qihai (CV6)	Lower abdomen, located at the anterior median line, 1.5 inches below the navel
Keshu (UB17)	Located at the thoracic vertebra spinous process of the back, 1.5 inches away from the midline
Zusanli (ST36)	Located on the lateral side of each lower leg, 3 inches under Dubi (S 35), in the line of Dubi and Jiexi (ST 41)

Intervention

All the participants received routine cancer care at the time of hospitalization in terms of disease observation, dietary care, and psychological care.

For the control group, participants received routine nursing care, in terms of strict observation of the changes in condition, dietary care, vein embolic protection, routine use of antiemetic and gastroprotective agents.

In the TEAS group, patients received TEAS. After training the intensity, frequency of TEAS program by a Traditional Chinese Medicine clinical experts. TEAS was applied to three acupoints: bilateral Zusanli (ST36), bilateral Keshu (UB17), and unilateral Qihai (CV6). These acupoints were located based on Chinese anatomical locations (*Table 1*). In this research, TEAS was applied on the 1st, 2nd, 3rd, 5th, 8th, 11th, 14th, and 28th days. TEAS was used the G6805-II (Shanghai Medical Equipment Technology Co. Ltd., Shanghai, China) with a dense-disperse frequency of 30/100 Hz and an intensity of 6–15 V. Each session performed 30 minutes. The optimal intensity was adjusted to remain a slight twitching of the regional muscle according to individual maximum tolerance. Participants should record each acupoint stimulation session, involving date of session, frequency, intensity. If there are complications, inform the doctors timely. After each session, participants made appointment for the next session. A total 57 patients of the TEAS group had no adverse reactions.

For the sham TEAS group, the procedure and duration of TEAS were same as those in the TEAS group, but the treatment was applied at nearby non-acupoint sites. The five sham points, located on each side of the belly button, the shin bone, and the scapula of the back, were selected. Those five sham points were either in similar dermatome regions as the five selected acupoints, or they were unknown with regard to their effects on fatigue (15). The sham TEAS

group was used to explore whether TEAS influenced the psychological status of the participants.

Measures and instruments

The instruments included the demographic status and the Revised Piper Fatigue Scale (RPFS).

The demographic status was assessed based on the participants' age, gender, financial status, family history, body mass index (BMI), body temperature, heart rate, respiratory rate, systolic pressure, diastolic pressure, cancer type, cancer staging and KPS.

The RPFS is a 22-item multidimensional self-report scale that assesses patient's overall fatigue status based on four dimensions, including behavioral fatigue, sensory fatigue, affective fatigue, and cognitive fatigue (16). Scores on the RPFS range from 0 to 10 for each item, and a higher score is associated with worse fatigue (17). The RPFS is classified into four categories as follows: a score of 0 represents no fatigue; a score of 1–3 indicates mild fatigue; a score of 4–6 represents moderate fatigue; and a score of 7–10 indicates severe fatigue (16). The total score on the RPFS is given as the mean score of all items, and the score for each dimension is also calculated. The RPFS has documented validity and reliability in many countries (18), and it has been translated into Chinese and applied to measure the fatigue status of cancer patients in various studies (17). The inter-rater reliability and consistency were shown to be 0.97 (19).

Data analysis

SPSS, version 19.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data in this study. Descriptive statistics were used, including the means, standard deviations, and percentages. Analysis of variance (ANOVA) and a *t*-test were applied to analyze the effectiveness of TEAS. Chi-squared test was used to evaluate the differences in the outcomes and the demographic data among the three groups in the case of categorical variables. Additionally, the ANOVA was performed to compare the differences in continuous variables. A P value less than 0.05 was considered statistically significant.

Results

Patients' demographic characteristics

Initially, 169 participants from Shanghai pulmonary hospital

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in China were randomized into three groups: Group A (n=58) was a control group, Group B (n=52) received sham TEAS, and Group C (n=59) received TEAS. During the study, 7 participants dropped out because they were too sick to continue the program or they could not tolerate chemotherapy. Finally, 162 participants completed the study (*Figure 1*).

The baseline characteristics of the participants are presented in *Tables 2* and *3*. There was no significant difference among three groups (P>0.05). The KPS did not differ significantly between the three groups (P=0.089), and all participants were expected to live more than six months [20]. There was no significant difference in the baseline characteristics between the dropouts and those who completed the study (P>0.05).

Effects of TEAS on CRF

Table 4 summarizes the results of the RPFS. At P1 and P2, there was no statistically significant difference between the three groups (P>0.05, *Table 4*). However, the outcomes showed statistically significant differences among the three groups at P3 (P<0.01, *Table 4*).

Effects of TEAS on the dimensions of the RPFS at P3

The outcome measures of the four dimensions of the RPFS at P3 are summarized in *Table 5*. Based on the results, all he dimension indicated statistically significant differences, with the exception of sensory fatigue (P=0.50). However, Group C (Mean =2.48) had a lower sensory fatigue score than Group A or Group B (Mean =3.20 and Mean =2.72, respectively, *Table 5*).

Discussion

According to the results, this study of the implementation of TEAS intervention to verify long-term use can relieve lung cancer chemotherapy in patients with CRF. This is associated with some previous literature. Studies have shown that percutaneous electrical stimulation of cancer patients with CRF has a certain mitigation effect [18]. Another study in the UK concluded that 36% of patients were significantly improved fatigue after 14 days of acupuncture [21].

Based on the findings, the fatigue level of most lung cancer patients increased slightly during chemotherapy. Lung cancer patients undergoing chemotherapy experience physical and psychological stress for a long period of time [22]. During process of treatments, the accumulation of chemotherapeutic drugs and products of cellular causes impairment to the body and brain cells, thereby affecting the patients' fatigue level through both physical and psychological mechanisms [23]. Jones *et al.* [24] discovered the longer the patient's chemotherapy, the heavier the level of fatigue.

This study demonstrates that the three major acupoints (ST36, CV6, UB17) used in this research positively influence fatigue level. In Chinese medicine, fatigue is considered to represent a series of physiological dysfunctions caused by spleen deficiency [25]. And ST 36 in the stomach meridian is commonly used to improve spleen-deficiency syndrome [26]. CV 6 adjusts the viscera Chi of the body to enhance the flow of Chi and soothe the organs so that body can rest [15,27]. UB 17 is usually targeted to relieve vomiting, hiccups, and backaches. Symptom control is an important strategy to alleviate patients' physical fatigue [28]. Meanwhile, the fatigue score of the sham TEAS group (Group B) is higher than the TEAS group (Group C) at day 28, which means participants experienced an improvement in their fatigue level through electrical stimulation of the three acupoints rather than psychological factors.

Based on the results in this research, the majority of the patients had a moderate fatigue status for sensory fatigue, affective fatigue and cognitive fatigue, but there was variability in the scores for the behavioral dimension. In other words, fatigue causes a varying degree of damage in lung cancer patients, in terms of daily activities, physical health, emotional status, and cognitive function. The sensory dimension showed less improvement than the other dimensions. Sun believed that the insufficient high-energy foods, such as protein, fat, and sugar, give rise to fatigue [29]. In addition, accumulation of chemotherapy metabolites in the body could increase the level of sensory fatigue. Finally, most lung cancer patients are at old age with the onset of disease at mean age of 76.9 years old. With aging, decreased physical function leads to intensification of the experience of fatigue [26].

This research has a few limitations. First, all the patients were in the first cycle of GP chemotherapy treatment after diagnosis. However, CRF might be increased during later cycles of chemotherapy [7]. Thus, subsequent studies should recruit participants in other lines of chemotherapy to explore the effects of TEAS on CRF. Secondly, the daily activities of the participants may have affected their fatigue level [30]. In this research, the level of physical activity of the participants was variable and might have influenced
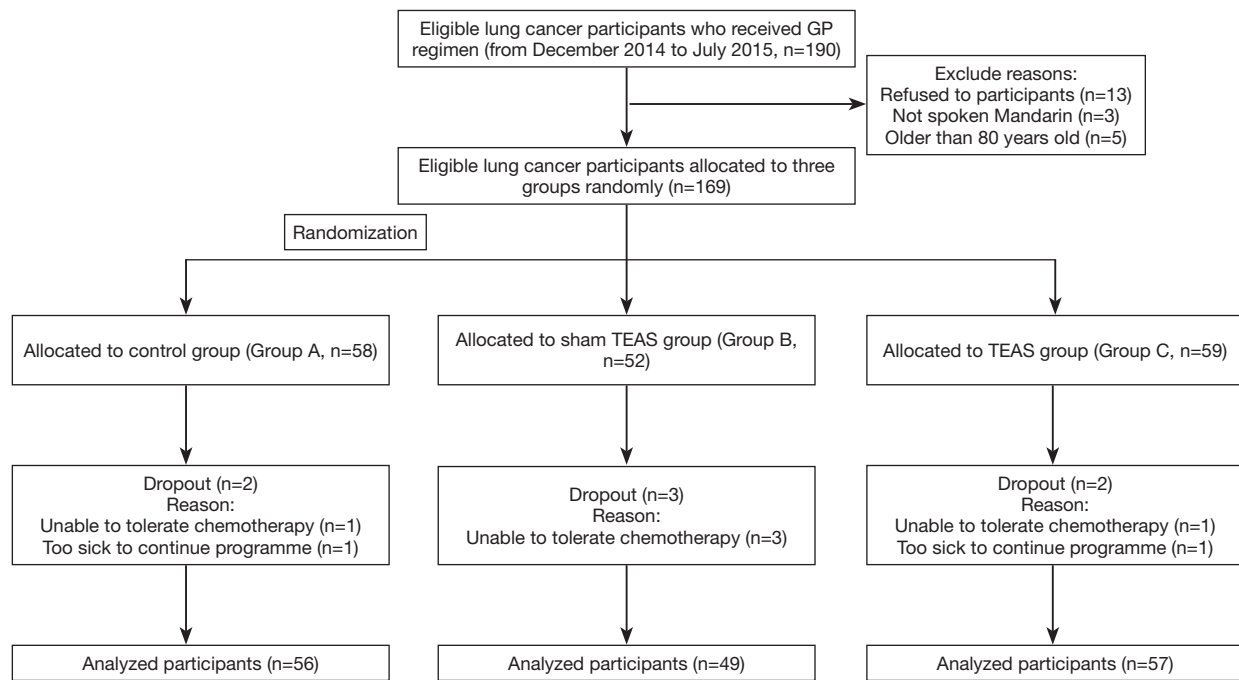
Figure 1 Flow chart of allocation and dropouts of participants.

Table 2 Demographic values for categorical variables by group

Categorical variables	Group A (n=56), n (%)	Group B (n=49), n (%)	Group C (n=57), n (%)	Chi-squared test	P
Gender				2.54	0.97
Male	46 (82.1)	34 (69.4)	42 (73.7)		
Female	10 (17.9)	15 (30.6)	15 (26.3)		
Financial status				0.46	0.53
Pension	32 (57.1)	26 (53.1)	29 (50.9)		
Non-pension	24 (42.9)	23 (46.9)	28 (49.1)		
Family history				0.40	0.98
Yes	1 (1.8)	1 (2.0)	2 (3.5)		
No	55 (98.2)	48 (98.0)	55 (96.55)		
Cancer type				0.70	0.91
Adenocarcinoma	30 (53.6)	24 (49.0)	29 (50.9)		
Squamous carcinoma	18 (32.1)	15 (30.6)	18 (31.6)		
Others	8 (14.3)	10 (20.4)	10 (17.5)		
Cancer staging				0.28	0.83
I–III	52 (92.9)	46 (93.9)	52 (91.2)		
IV	4 (7.1)	3 (6.1)	5 (8.8)		

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Table 3 Baseline values for continuous variables by group

Continuous variables	Group A (n=56), mean ± SD	Group B (n=49), mean ± SD	Group C (n=57), mean ± SD	F-test	P
Age	58.27±10.57	54.44±10.48	58.06±8.42	2.660	0.062
BMI	22.97±2.55	22.18±3.43	23.23±2.56	2.638	0.071
Body temperature	36.06±0.30	36.77±0.22	36.57±0.29	0.198	0.922
Heart rate	81.77±5.35	82.45±2.66	82.58±7.17	0.324	0.727
Respiratory rate	21.00±11.90	19.27±0.81	20.96±6.55	0.613	0.572
Systolic pressure	125.46±15.42	119.75±14.00	121.62±14.83	2.006	0.205
Diastolic pressure	78.83±6.38	75.69±9.04	75.83±9.73	2.312	0.098
KPS	85.02±4.98	83.31±4.77	83.31±4.77	2.328	0.103

Table 4 Results of RPFS among the groups at P1, P2 and P3

Groups	P1, mean ± SD	P2, mean ± SD	P3, mean ± SD
Group A, n=56	1.49±1.58	2.68±1.36	3.00±1.29
Group B, n=49	1.91±1.37	2.59±1.18	2.80±1.34
Group C, n=57	1.68±1.57	2.85±1.62	2.06±0.90
Total, n=162	1.69±1.52	1.69±1.52	2.61±1.25
F-test	1.091	0.488	9.784
P	0.338	0.615	<0.01
Multiple comparison: P			
Group A vs. Group B	0.142*	0.724*	0.821**
Group A vs. Group C	0.490*	0.526*	<0.01**
Group B vs. Group C	0.419*	0.334*	0.005**

*, refers to LSD-test; **, refers to Tamhane-test. P1, before chemotherapy; P2, day 8 after chemotherapy; P3, day 28 after chemotherapy.

Table 5 Results for the four dimensions of the RPFS among the groups at P3

Outcome measures (P3)	Behavioral fatigue, mean ± SD	Affective fatigue**, mean ± SD	Sensory fatigue, mean ± SD	Cognitive fatigue, mean ± SD
Group A, n=56	2.497±1.105	3.039±1.524	3.20±1.79	3.31±2.12
Group B, n=49	2.36±1.25	3.216±1.731	2.72±1.63	2.96±2.24
Group C, n=57	1.80±0.89	2.143±1.198	2.48±1.30	1.91±1.37
F-test	6.471	8.161	3.060	8.060
P	0.002	<0.01	0.050	<0.01
Multiple comparison: P				
Group A vs. Group B	0.919**	0.927**	0.122*	0.795**
Group A vs. Group C	0.001**	0.002**	0.016*	<0.01**
Group B vs. Group C	0.031**	0.001**	0.428*	0.016**

*, refers to LSD-test; **, refers to Tamhane-test. RPFS, Revised Piper Fatigue Scale; P3, day 28 after chemotherapy.

the results. Further studies are needed to address the effects of exercise on the effectiveness of TEAS. Third, only three times data collection during 28 days might increase memorizing bias, which could affect the results. For the further research, data collection would be more frequently in order to avoid memorizing bias, Additionally, this study only included lung cancer patients undergoing chemotherapy, and the findings cannot be generalized to cancer patients who receive other forms of treatment, such as radiotherapy, surgery, or targeted therapy. Future studies should consider different cancer diagnoses and treatments to increase generalizability. Finally, appropriate frequency and duration of TEAS for each participant could be analyzed more precisely in future studies.

Conclusions

In conclusion, the results of this research support the hypothesis that CRF in patients with lung cancer undergoing GP chemotherapy could be relieved by TEAS. It is feasible to provide TEAS and to implement the program in chemotherapy patients. This study demonstrates the effectiveness of the TEAS, although additional studies are needed to determine the appliance of the TEAS in other chemotherapy regimens and other lines of chemotherapy to alleviate CRF in Chinese patients. Future studies should aim to improve the generalizability of the sample, develop an intervention that is easier to implement, and utilize stronger study designs.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Ethical approval was given by the ethics committee of the Shanghai Pulmonary Hospital, China (No. K14-170). Individual consent was not required as this was a secondary data study using a pseudo-anonymised database extract.

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