Effect of scar-producing moxibustion at the acupoints Zusanli (ST36) and Feishu (BL13) on neutrophil-to-lymphocyte ratio and quality of life in patients with non-small-cell lung cancer: A randomized, controlled trial

Zhang Mengxue, Guan Ling, Wang Lili, Li Ying

Abstract

OBJECTIVE: To evaluate the effect of heat stimulation via scar-producing moxibustion at the acupoints Zusanli (ST 36) and Feishu (BL 13) on the neutrophil-to-lymphocyte ratio (NLR) and quality of life in patients with non-small-cell lung cancer (NSCLC).

METHODS: Seventy patients with NSCLC were randomly assigned into two groups: group A received scar-producing moxibustion at the acupoints Zusanli (ST 36) and Feishu (BL 13) every day for 6 weeks, while group B received no intervention (control group). Outcome measures were the NLR and the scores from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). The NLR and the EORTC QLQ-C30 were assessed at baseline and at the end of 6 weeks.

RESULTS: Five participants dropped out, leaving a final total of 65 participants who completed the trial. Groups A and B had a similar mean NLR at baseline. After the treatment course, the NLR in group A was significantly lower than that in group B ($P < 0.001$). Compared with group B, the EORTC QLQ-C30 scores in group A were significantly greater in terms of global health status or quality of life ($P < 0.001$) and function ($P < 0.05$), and significantly lower in terms of symptoms ($P < 0.05$).

CONCLUSION: The present study suggests that performing scar-producing moxibustion by heat-stimulating the acupoints Zusanli (ST 36) and Feishu (BL 13) effectively decreases the NLR and improves the quality of life in patients with NSCLC.

INTRODUCTION

Lung cancer has become the most common cause of cancer-related death worldwide, with a 5-year survival rate of less than 17%. Lung cancer can be categorized into small-cell lung cancer and non-small-cell lung cancer (NSCLC), with the latter accounting for approximately 80% of all lung cancer cases. The primary treatment for early-stage lung cancer is lobectomy, while adjuvant chemotherapy or radiotherapy is performed in inoperable cases or after lobectomy.
ments in conventional cancer therapies, patients with NSCLC still have a poor 5-year survival rate, and their quality of life (QoL) usually dramatically declines because of the side effects of chemotherapy and radiotherapy. Scar-producing moxibustion is an ancient Chinese treatment method that is currently used to treat complicated and refractory diseases, including NSCLC. Numerous experimental studies and randomized clinical trials have shown that moxibustion can improve many aspects of immunity, such as by activating natural killer cells and cytokines (interleukin-1 and interleukin-2), and increasing the quantity of lymphocytes. It is well known that the immune system can affect many aspects of malignancy, including migration, invasion, and metastasis.

As a protective mechanism involving the immune system, inflammation is now considered the seventh hallmark of cancer. The systemic inflammatory response reflects the promotion of malignant tumors, and has prognostic value for survival in patients with various solid tumors. The neutrophil-to-lymphocyte ratio (NLR) is an easily derived marker of systemic inflammation, and it has been proved that higher NLR values are associated with poorer survival in patients with NSCLC.

Controlling the malignant inflammation in patients with NSCLC may improve their QoL. Suppression of such inflammation may be achieved via scar-producing moxibustion, which is a complementary treatment method that regulates the immune system. However, to date, few studies have investigated the association between scar-producing moxibustion and inflammatory markers affecting the QoL in patients with NSCLC. The present study aimed to evaluate the effect of scar-producing moxibustion on patients with NSCLC by assessing the NLR and the scores obtained using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

METHODS

Patients
In the present study, 70 patients were recruited from the Department of Thoracic Surgery, Cancer Center, Department of Traditional Chinese Medicine, and the Acupuncture-Moxibustion Center of the Chinese People’s Liberation Army (PLA) General Hospital from January 1, 2015 to March 1, 2015. The present study was approved by the Ethics Committee of the Chinese PLA General Hospital, and all included patients provided written informed consent. NSCLC was diagnosed according to the Non-Small Cell Lung Cancer Practice Guidelines revised by the National Comprehensive Cancer Network in 2014. Inclusion criteria were: (a) NSCLC diagnosed by specialists according to histopathologic examination findings; (b) completed lobectomy; (c) completed postoperative adjuvant chemotherapy or radiotherapy; (d) willing participation in the present study. Exclusion criteria were: (a) uncertain diagnosis; (b) inoperable cases; (c) currently undergoing chemotherapy or radiotherapy; (d) advanced disease, such as malignant pleural effusion and involvement or distant metastasis; (e) diabetes mellitus, dermatosis, or other diseases affecting the ability to heal; (f) undergoing repeat surgery or chemotherapy/radiotherapy during the study period; (g) participation in other clinical trials; (h) pregnancy or lactation.

Randomization and blinding
A computerized randomization program (SPSS for Windows, version 21.0; IBM Corp, Armonk, NY, USA) was used to randomly assign the 70 patients to either group A to receive scar-producing moxibustion (n = 35 patients), or to group B to receive no intervention (n = 35 patients). The study was completed by a total of 33 patients in group A, and 32 patients in group B. All the outcome measures were assessed by an independent investigator who was blinded to the treatments.

Interventions
The bilateral Zusanli (ST 36) acupoints were located four transverse fingerlengths lateral to the ‘knee eyes’, and bilateral Feishu (BL 13) were located 1.5 transverse fingerlengths lateral to the spinous processes of the 12th thoracic vertebra. With the patient in supine position, 5 mg of delicate moxa was put on bilateral Zusanli (ST 36) and lit by an incense stick. After the first moxa cone was burnt out, another moxa cone was put on the acupoint and lit; this process was repeated nine times. The procedure was then repeated on bilateral Feishu (BL 13).

Group A received moxibustion treatment at all four acupoints once daily for 6 weeks. Group B received no treatment, and were just followed up every week for 6 weeks.

Outcome measures
The EORTC QLQ-C30 and NLR were used as outcome measures in this study. Both of these measures have been proven to be valid and reliable assessments in cancer patients.

The NLR is an indicator of systemic inflammatory response, and has prognostic value for survival in patients with NSCLC. A higher NLR is associated with more aggressive cancer with a poor prognosis.

The EORTC QLQ-C30 is a 30-item questionnaire used to assess health-related QoL, and includes five function scales (physical, role, emotional, cognitive, and social) and eight single-item symptom scales (fatigue, nausea and vomiting, pain, dyspnea, sleep difficulty, appetite loss, constipation, and diarrhea). All function and symptom scales are 4-point scales (e.g. a
score of 1 indicates that the symptom was not experienced at all, while a score of 4 indicates that the symptom was very frequently experienced) with a total score range of 0-100. QoL was assessed by a 7-point scale from "very poor" to "excellent". A high function scale score represents a high and healthy level of functioning, a high symptom scale score represents a high level of symptomatology, and a high general health status score represents a high QoL.

All participants underwent routine blood testing and completed the EORTC QLQ-C30 at the beginning of the study (at baseline), and again at the end of 6 weeks (endpoint). A follow-up survey was also completed by both group A and group B at the end of 6 weeks. No information was collected on participant-provider interactions or patient expectations.

**Statistical analysis**
The normality of the quantitative variables for each of the groups was confirmed using the Shapiro-Wilk test. Data that were normally distributed, including age, NLR, physical function, emotional function, level of fatigue, and general health status, were presented as the mean ± standard deviation. An independent-sample t-test was used to test the differences between the two groups in baseline scores and endpoint scores. Within each group, a paired-sample t-test was used for comparisons between baseline and endpoint values. The non-normally-distributed data, such as role function level and level of pain, were presented as the median (interquartile range); the Mann-Whitney U test was used for comparison of variables between the two groups, and the Wilcoxon test was used for comparisons within each group. All data analyses were carried out using SPSS for Windows, version 21.0 (Released 2012; IBM Corp., Armonk, NY, USA). Values of *P* < 0.05 were considered to indicate statistically significant differences.

**RESULTS**

**Patient characteristics**
Of the 70 patients, five dropped out during the course of the study; two from group A due to an unwillingness to continue the treatment, one from group B underwent chemotherapy again due to tumor progression, and two from group B could not be contacted. The dropout rates did not significantly differ between groups (*P* = 1.000, continuity correction test). Analyses were performed on the 65 patients who completed the study (Figure 1). Of these 65 patients, 42 were male and 23 were female. The median age was 55 years (range: 30-82 years). There were no significant differences between the two groups at baseline in terms of age, sex, pathological type, and TNM staging (Table 1).

**NLR**
The NLRs in both groups at baseline and at the endpoint were normally distributed (PA = 0.278, PB = 0.402) and showed homogeneity of variance (*P* > 0.5). There was a significant difference between groups A and B in the NLR at the endpoint (*t* = −7.056, *P* < 0.001), whereas the NLR did not significantly differ between groups at baseline (*t* = −0.038, *P* = 0.970; Table 2). The mean NLR in group A at baseline (4.9 ± 1.6) was significantly decreased to 2.5 ± 0.8 at the end of treatment (*t* = 13.214, *P* < 0.001). In contrast, the NLR in group B did not significantly differ from baseline to the endpoint (*t* = −1.488, *P* = 0.147; Figure 2).

**European organization for research and treatment of cancer quality of life questionnaire scores**
The results were calculated for the following subscales of the EORTC QLQ-C30: physical function, emotional function, cognitive and social function, single-item symptom scales, and global health status/QoL. All the scores at baseline were similar in both groups, except for the scores for nausea and vomiting, constipation, and diarrhea, and have not been discussed here.

Table 3 summarizes the QoL scores and function scale scores. There was only mild or no improvement in the subscales of role function (*Z* = −1.221, *P* = 0.222) and social function (*Z* = −1.414, *P* = 0.157). The general health status/QoL subscale significantly differed between groups A and B (*t* = 8.825, *P* < 0.001). The mean raw QoL score in group A significantly increased from 41.2 ± 11.6 at baseline to 67.2 ± 12.5 at the endpoint (*t* = −14.414, *P* < 0.001), while there was no significant difference between the baseline and endpoint QoL scores in group B (*t* = −0.291, *P* = 0.773). Compared with group B, group A had significantly superior scores at the endpoint for physical function (*t* = 4.561, *P* < 0.001), emotion function (*t* = 5.726, *P* < 0.001), and cognitive function (*Z* = −4.290, *P* < 0.001; Table 3). In group A, there was a significant increase from baseline to the endpoint in the mean scores for physical function (*t* = −12.161, *P* < 0.001), emotional function (*t* = −9.540, *P* < 0.001), and cognitive function (*Z* = −4.465, *P* = 0.000); there were no significant differences between the baseline and endpoint scores in group B (Table 3).

Table 4 summarizes the symptom scale scores. The only symptom scale score for which the data were normally distributed was the fatigue score, which significantly differed between groups (*t* = −8.199, *P* < 0.001) as well as between baseline and endpoint in group A (*t* = 12.567, *P* < 0.001). The other symptom scales analyzed by non-parametric testing all significantly differed between the two groups, with group A reporting significantly less fatigue (*t* = −8.199, *P* < 0.001), pain (*Z* = −2.110, *P* = 0.035), dyspnea (*Z* = −2.115, *P* = 0.034), sleep difficulty (*Z* = −2.788, *P* = 0.005), and appetite loss (*Z* = −7.142, *P* < 0.001) than group B. Group A showed significant decreases from baseline to endpoint in fatigue (*t* = 12.567, *P* < 0.001), pain (*Z* = −2.536, *P* = 0.011), dyspnea (*Z* = −2.299, *P* = 0.021), sleep difficulty (*Z* = −2.358, *P* = 0.018), and
appetite loss ($Z = -5.112, P < 0.001$), but there were no differences from baseline to endpoint in group B (Figures 2, 3).

No substantial adverse effects were reported during the study period. Only one participant reported an adverse event, which was aggravation of hotness and sore throat after the third treatment. These symptoms subsided without intervention within 24 h and did not recur.

**DISCUSSION**

The present study revealed a significant decrease in NLR in the intervention group compared with the control group. NLR is a marker of systemic inflammation, as represented by the balance between neutrophils and lymphocytes. Lymphocytes play an important role in the anti-tumor process, while neutrophils are key effector cells in innate immunity that activate inflammation and undergo apoptosis during the adaptive immunity process. If the neutrophils are higher for a long time, the microenvironment will grow up chronic inflammation which can promote cancer. Along with the adaptive immunity activeing, neutrophils also prevent necrotic cell lysates, cytotoxic protein, and reactive oxygen species from releasing their contents, and promote the cessation of inflammation with the help of macrophages. It is also helpful for anti-tumor. A lower NLR means that there are decreased numbers of neutrophils and increased numbers of lymphocytes, which indicates that adaptive immunity has taken effect and neutrophils have begun to undergo programmed cell death. The inflammatory manifestations are then relieved, and the QoL is improved.
In conclusion, the present results suggest that scar-producing moxibustion at the acupoints Zusanli (ST 36) and Feishu (BL 13) is effective in decreasing the NLR and improving the QoL in patients with NSCLC. The EORTC QLQ-C30 scores obtained in the present study indicated that the moxibustion intervention caused positive changes with respect to physical function, emotional function, cognitive function, general health status, and symptom scales. This indicates that scar-inducing moxibustion can regulate the immunity of patients with NSCLC by decreasing systemic inflammation and improving postoperative QoL. The present results are consistent with previous studies on the outcomes of moxibustion, and should extend the anti-tumor application of moxibustion.

The limitations of the present study were the relatively short observation period and small sample size. Larger-scale, long-term studies are required to confirm the present findings.

In conclusion, the present results suggest that scar-producing moxibustion at the acupoints Zusanli (ST 36) and Feishu (BL 13) is effective in decreasing the NLR and improving the QoL in patients with NSCLC.

**REFERENCES**


| Table 3 European organization for research and treatment of cancer quality of life questionnaire scores for quality of life and function |
|---|---|---|---|---|
| Item | Variable | Group A (n = 33) | Group B (n = 32) | t/Z value | P value |
| QoL | Baseline | 41±12 | 40±11 | 0.373 | 0.711 |
| | End of treatment | 67±12 | 41±12 | 8.825 | <0.001 |
| PF | Baseline | 51±15 | 53±15 | -0.482 | 0.631 |
| | End of treatment | 71±15 | 53±17 | 4.561 | <0.001 |
| RF | Baseline | 50 (33) | 50 (33) | -1.098 | 0.272 |
| | End of treatment | 50 (33) | 50 (33) | -1.221 | 0.222 |
| EF | Baseline | 53±18 | 48±17 | 1.180 | 0.243 |
| | End of treatment | 70±18 | 48±14 | 5.726 | <0.001 |
| CF | Baseline | 33 (25) | 33 (29) | -0.660 | 0.509 |
| | End of treatment | 50 (25) | 33 (17) | -4.290 | <0.001 |
| SF | Baseline | 50 (33) | 50 (29) | -1.365 | 0.172 |
| | End of treatment | 50 (33) | 50 (29) | -1.414 | 0.157 |

Notes: group A: scar-producing moxibustion group; group B: control group. Group A received moxibustion treatment at bilateral Zusanli (ST 36) and bilateral Feishu (BL 13) once daily for 6 weeks. Group B received no treatment. Data are expressed as the mean ± standard deviation, or the median (interquartile range). QoL: quality of life, PF: physical function, RF: role function, EF: emotional function, CF: cognitive function, SF: social function.

| Table 4 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire single-item symptom scale scores |
|---|---|---|---|---|
| Item | Variable | Group A (n = 33) | Group B (n = 32) | t/Z value | P value |
| FA | Baseline | 68±15 | 67±16 | 0.428 | 0.670 |
| | End of treatment | 35±16 | 67±15 | -8.199 | <0.001 |
| PA | Baseline | 17 (33) | 17 (50) | -0.967 | 0.333 |
| | End of treatment | 17 (17) | 17 (50) | -2.110 | 0.035 |
| DY | Baseline | 67 (33) | 100 (33) | -0.956 | 0.339 |
| | End of treatment | 67 (50) | 67 (33) | -2.115 | 0.034 |
| SL | Baseline | 100 (33) | 100 (25) | -1.231 | 0.218 |
| | End of treatment | 67 (33) | 100 (25) | -2.788 | 0.005 |
| AP | Baseline | 100 (33) | 100 (33) | -0.416 | 0.677 |
| | End of treatment | 0 (33) | 100 (33) | -7.142 | <0.001 |

Notes: group A received moxibustion treatment at bilateral Zusanli (ST 36) and bilateral Feishu (BL 13) once daily for 6 weeks. Group B received no treatment. Data are expressed as the mean ± standard deviation, or the median (interquartile range). Group A underwent 6 weeks of scar-producing moxibustion, while group B had no intervention. FA: fatigue; PA: pain; DY: dyspnea; SL: sleep difficulty; AP: appetite loss.


