

Effects of Infrared Laser Moxibustion on Cancer-Related Fatigue: A Randomized, Double-Blind, Placebo-Controlled Trial

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BACKGROUND: Fatigue is the most common symptom negatively affecting the quality of life of patients with cancer. The objective of the current study was to evaluate the preliminary efficacy and safety of 10.6- μm infrared laser moxibustion for cancer-related fatigue (CRF). **METHODS:** The authors conducted a randomized, placebo-controlled trial among 78 patients with cancer who were diagnosed with CRF. The group treated with infrared laser moxibustion received 10.6- μm of infrared laser moxibustion on the ST36 (bilateral), CV4, and CV6 acupoints. Each participant received a 20-minute treatment session 3 times per week for 4 weeks. The sham group received the same treatment duration on the same acupoints, but without infrared laser output. The outcome was change in fatigue as measured by the Chinese version of the Brief Fatigue Inventory between groups at week 4 with additional evaluation at week 8 for durability of treatment effects. A mixed effects model was used to evaluate the difference in treatment effect over time. **RESULTS:** Among those randomized, 61 patients (78%) completed the entire study. At the end of the intervention, the individuals in the group treated with the laser were found to have significantly less fatigue than those in the sham group (3.01 vs 4.40; $P = .002$). The improvement in fatigue persisted to week 8, favoring the group treated with laser moxibustion (3.03 vs 4.26; $P = .006$). Laser moxibustion was safe, with 3 cases of mild local erythema that resolved without medical intervention reported. **CONCLUSIONS:** Infrared laser moxibustion appeared to be safe and efficacious for improving CRF in a Chinese patient population. Larger studies in more racial/ethnically diverse populations are needed to confirm the benefit of this technique for fatigue in patients with cancer. *Cancer* 2016;122:3667-72. © 2016 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of *American Cancer Society*. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: acupuncture, cancer-related fatigue, clinical trial, laser, moxibustion.

INTRODUCTION

Cancer-related fatigue (CRF) is the most common and devastating symptom associated with tumor or cancer therapy. A systematic review of 40 CRF studies reported prevalence rates for this symptom ranging from 46% to 96% and determined that it persisted well beyond the end of treatment in at least 25% of patients.¹ Compared with fatigue in healthy individuals, CRF is more severe and distressing and cannot be alleviated through rest. CRF has been confirmed to be the most uncomfortable symptom for patients, with more devastating impacts on normal routine and quality of life than pain.²

Clinical treatments of CRF have been unsatisfactory, without recognized and effective drug treatments.³ Therefore, numerous nondrug and alternative treatments are of great interest among patients with cancer.^{4,5} In addition, there is growing evidence of the impact of complementary and integrative medicine on patients with CRF.⁶ Among various complementary and integrative medicine interventions, acupuncture has gained increasing attention as a tool for managing CRF. However, further rigorously designed randomized controlled trials (RCTs) adhering to acceptable standards of trial methodology are required to determine the effectiveness of acupuncture and its long-term effects on CRF.⁷

Moxibustion, a modality of traditional acupuncture, is a noninvasive procedure that involves burning moxa, the herb *Artemisia vulgaris*, on or above the skin at acupoints, warming them to alleviate symptoms.⁸ In traditional Chinese medicine, moxibustion is closely related to acupuncture and follows the same theoretical framework. Instead of stimulating acupuncture points using needles, moxibustion provides thermal stimulation of these points by burning the herb near them. Moxibustion

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has been practiced along with acupuncture in China for thousands of years to treat various disorders.^{9,10} Although empirically used for alleviating fatigue, to the best of our knowledge research concerning the effects of moxibustion for the treatment of CRF has only been reported in a few Chinese language articles to date. Because of the high risk of bias and low reporting quality of these studies, it has been difficult to determine whether moxibustion is an effective and safe treatment for patients with CRF.¹¹ Furthermore, shortcomings such as air pollution and potential burning of the skin are inherent in traditional moxibustion.

Infrared laser moxibustion represents a novel noninvasive and painless technology that provides self-regulation within treatment parameters. Recent research has indicated that the specific wavelengths of infrared radiation produced by moxibustion are as potent as generated thermal radiation.¹² Our previous study demonstrated that the peak wavelength of infrared radiation from conventional partitioned moxibustion was approximately 10 μm .^{13,14} The simulation of a specific wavelength of infrared radiation of conventional partitioned moxibustion on the human body was found to have significant efficacy in increasing the white blood cells of patients receiving both radiotherapy and chemotherapy.¹⁵ The 10.6- μm infrared laser applied in our research mimics the effects and avoids the shortcomings of traditional moxibustion treatment, such as smoke, unpleasant smell, and difficulty in controlling the dosage.

We conducted a 2-arm placebo-controlled RCT to evaluate the safety and efficacy of a 10.6- μm infrared laser moxibustion for CRF. The primary endpoint of the trial was the fatigue score at the end of the intervention as measured by the Chinese version of the Brief Fatigue Inventory (BFI-C). We also evaluated the durability of treatment effects at 4 weeks after the intervention.

MATERIALS AND METHODS

Study Participants

We conducted a 2-arm RCT from September 2011 to February 2014 at the Yueyang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine in Shanghai, China. Our research protocol was approved by the Institutional Review Board of Yueyang Hospital and registered in the Chinese Clinical Trial Registry (ChiCTR-TRC-12003870). All patients provided written informed consent before participating in the current study.

Patients were recruited from oncology clinics and their cancer diagnoses were confirmed by their own or study clinical oncologists. Participants were interviewed to ensure they met the National Comprehensive Cancer Net-

work's diagnostic criteria for CRF^{16,17} and that they had: 1) a period of ≥ 2 weeks within the preceding month with significant CRF or diminished energy each day or nearly every day along with additional CRF-related symptoms; 2) CRF resulting in significant distress or impairment of function; 3) clinical evidence suggesting that CRF was a consequence of cancer or cancer therapy; and 4) CRF that was not primarily a consequence of a concurrent psychiatric condition, such as major depression. Participants who met the above criteria, were aged 40 to 75 years, and were willing to sign the consent form were included. Participants were excluded if they had tumors or metastases within the irradiated acupoints, had an anticipated survival of <3 months, were bedridden, had received acupuncture within the past 6 months, had received a drug test within the past 6 months, were pregnant or lactating women, were diagnosed with severe mental illness, or had a systemic infection or infectious diseases.

Study Design

Participants were randomly assigned to real and sham laser moxibustion groups using computer-generated numbers sealed in opaque envelopes with an allocation ratio of 1 to 1. After random assignment to either real or sham laser moxibustion groups, participants received 20 minutes of treatment during each session 3 times per week for 4 weeks, for a total of 12 treatments. Participants were then evaluated at 4 weeks after the end of the intervention to evaluate the durability of the treatment effects.

Treatment Time and Method

Participants were treated in a private room at the appointed time and were instructed not to talk to each other. We used SX10-C1 laser moxibustion devices (Shanghai Wonderful Opto-Electrics Tech Co Ltd, Shanghai, China) for both groups. The laser probes were aligned with 4 points—the ST36 (bilateral), CV4, and CV6 acupoints—and irradiated each acupoint approximately 2 cm away from the skin surface for 20 minutes. The real and sham laser moxibustion instruments appeared to be identical. However, in the sham group, the laser source was cutting off when the instrument was turned on. Because the infrared laser is colorless, neither the operator nor the patients can see it. Each patient received the treatment session once every other day (3 times per week for a total of 4 weeks) for a total of 12 sessions. The laser operator was blinded with regard to whether the laser output was turned on.

Outcome Measures

Fatigue was measured using the BFI-C. The BFI-C was translated and revised based on the original English

version of the BFI.^{18,19} The scale had an excellent internal consistency of 0.96. The indicators of the scale assessment included the current level of fatigue; the fatigue level within the past 24 hours; and the impact of CRF on physical activities, emotions, ability to walk, ability to work, relationships with others, and enjoyment of life within the past 24 hours. The BFI-C uses 10-point numeric descriptions: scores of 1 to 3 represent mild levels of fatigue, scores of 4 to 6 represent moderate levels of fatigue, and scores of 7 to 10 represent severe levels of fatigue. Using the BFI score as the baseline value, patients underwent assessments before treatment, at 2 and 4 weeks after the beginning of the treatment, and at follow-up (4 weeks after termination of the treatment). The higher the reduction of the fatigue index, the better the treatment efficacy. The BFI-C at the end of treatment (4 weeks after the beginning of the treatment) was the primary endpoint of the trial.

Masking

In this trial, the principal investigator, study investigators, laser instrument operator, participants, outcome assessors, and statistician were all blinded to treatment assignments between the real and sham laser moxibustion groups. The individual who controlled the laser versus the sham treatment had no interactions with the participants. Throughout the study, blinded research staff monitored adverse events (AEs) at each visit using a standard AE case report form. Blinding between the 2 groups was evaluated by asking participants to guess to which group they were assigned at the end of the intervention.

Statistical Analysis

The sample size calculation was based on both reviewing the relevant literature^{20,21} and our pilot study comparing the BFI-C scores of the laser and sham groups at week 4. Per preliminary data, at week 4, the BFI-C scores in the group receiving laser moxibustion (7 patients) had improved by 31.03%, whereas the BFI-C scores in the sham group (5 patients) had improved by 5.88%. To detect this difference, we needed 30 participants ($\alpha = .05$; $1-\beta = .80$) for each group. We enrolled 39 patients for each group to allow for a possible 20% dropout rate.

The Student's *t* test, Wilcoxon and Chi-square test were performed to compare baseline group differences. Repeated measurements of longitudinal data were analyzed using the mixed linear model. All statistical tests were 2-sided. Statistical significance was set at the $<.05$ level.

RESULTS

We enrolled a total of 78 patients with CRF from the oncology department of Yueyang Hospital, which is affiliated with the Shanghai University of Traditional Chinese Medicine, into the trial from September 2011 to February 2014. These patients were randomly divided into the group receiving infrared laser moxibustion (39 patients) and the group receiving sham laser moxibustion (39 patients), with 17 patients (21.8%) dropping out before week 2. The remainder of the patients provided complete data at follow-up (Fig. 1).

Baseline Characteristics of the Patients

Table 1 shows the baseline data for the 78 participants. The mean age of the patients enrolled was 59.4 years (range, 40-75 years); 36 patients (46.2%) were male, whereas 42 patients (53.8%) were female. They were all of Han Chinese ethnicity. There were 50 patients (64.1%) undergoing active cancer treatment, whereas 28 patients (35.9%) were in the survivorship phase after curative cancer treatment. Other baseline characteristics were well balanced and not found to be significantly different between the 2 groups.

Changes in Fatigue Between the Groups

Figure 2 shows the fatigue scores at week 2, week 4, and week 8 between the laser moxibustion group (30 patients) and the sham group (31 patients). At baseline, the fatigue score was not significantly different between the 2 groups (4.67 ± 1.18 vs 5.03 ± 1.40 ; $P = .407$ [Cohen's *d*, 0.278]). By the middle of treatment (week 2), the fatigue score was statistically lower in the laser moxibustion group versus the sham group (3.80 ± 1.16 vs 4.70 ± 1.45 ; $P = .044$ [Cohen's *d*, 0.685]). At the end of treatment (week 4), the fatigue score was much lower in the laser moxibustion group compared with the sham group (3.01 ± 0.99 vs 4.40 ± 1.41 ; $P = .002$ [Cohen's *d*, 1.141]). At the follow-up (week 8), the fatigue score remained statistically much lower in the laser moxibustion group versus the sham group (3.03 ± 1.28 vs 4.26 ± 1.49 ; $P = .006$ [Cohen's *d*, 0.886]).

Assessment of AEs

No serious AEs were reported. In the laser moxibustion group, we observed localized erythema approximately 5 mm in diameter below the laser probe after treatment in 3 patients, which resolved within 3 days without any special instructions. No patient was found to have an infection. No AEs were reported for patients in the sham laser moxibustion group.

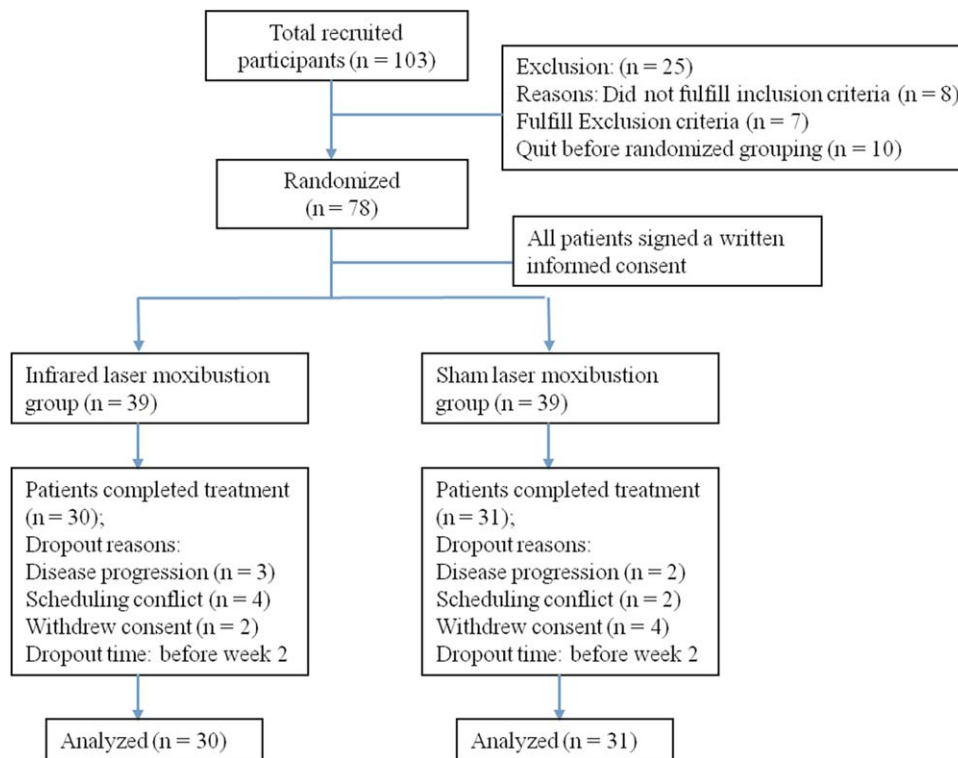


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram illustrating screening; randomization; and completion evaluations at week 2, week 4, and week 8.

TABLE 1. Baseline Characteristics of the Participants

Characteristic	Treatment Group n=39	Sham Group n=39	P
Age, y	59.1 ± 7.1	59.7 ± 7.8	.704
Length of cancer diagnosis, mo	18.0, 32.0 (1.0-104.0)	16.0, 26.0 (2.0-130.0)	.749
Sex, no. (%)			
Male	19 (48.7%)	17 (43.6%)	.821
Female	20 (51.3%)	22 (56.4%)	
Cancer treatment received, no. (%)			
Surgery	2 (5.1%)	1 (2.6%)	.237
Chemotherapy	8 (20.5%)	3 (7.7%)	
Surgery and chemotherapy	22 (56.4%)	31 (79.5%)	
Chemotherapy and radiotherapy	1 (2.6%)	1 (2.6%)	
Surgery, chemotherapy, and radiotherapy	6 (15.4%)	3 (7.7%)	
Current treatment, no. (%)			
Undergoing cancer treatment	23 (59.0%)	27 (69.2%)	.479
After cancer treatment	16 (41.0%)	12 (30.8%)	
Clinical stage of disease (TNM), no. (%)			
I	1 (2.6%)	1 (2.6%)	.801
II	8 (20.5%)	9 (23.1%)	
III	7 (17.9%)	7 (17.9%)	
IV	23 (59.0%)	22 (56.4%)	
Cancer type, no. (%)			
Lung	9 (23.1%)	8 (20.5%)	.544
Breast	10 (25.6%)	6 (15.4%)	
Colorectal	6 (15.4%)	8 (20.5%)	
Gastric/liver/esophageal	9 (23.1%)	6 (15.4%)	
Ovarian/endometrial/cervical	4 (10.3%)	8 (20.5%)	
Others (thymic/pharyngeal/bladder)	1 (2.6%)	3 (7.7%)	

Data were presented as the mean (standard deviation); number (%); or median, quartile (minimum-maximum). Race was reported by the participants.

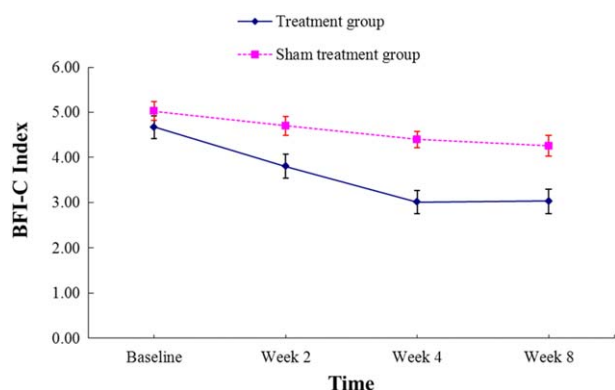


Figure 2. Comparing fatigue scores of the infrared laser moxibustion (treatment) (30 patients) and sham treatment (31 patients) groups at baseline, week 2, week 4, and week 8 (shown as the mean \pm the standard error). BFI-C indicates Chinese version of the Brief Fatigue Inventory.

Assessment of Masking

At the end of the intervention period, the majority of the participants believed that they received real laser moxibustion (87% of the infrared laser group and 81% of the sham group; $P = .77$).

DISCUSSION

CRF is the most common and distressful symptom experienced by patients and, to the best of our knowledge, few effective interventions exist. Herein, we conducted a randomized, placebo-controlled, double-blind clinical trial and found that 4 weeks of treatment with 10.6- μ m infrared laser moxibustion improved CRF significantly compared with a sham treatment group. Furthermore, the therapeutic effect persisted at least 4 weeks after the end of the intervention. Both the laser moxibustion and sham treatments were safe, without significant AEs reported. The findings of the current study suggest that 10.6- μ m infrared laser moxibustion holds therapeutic potential as a potentially safe and effective nonpharmacological intervention for CRF.

Although moxibustion and acupuncture are considered to be in the same categories of interventions from the perspective of traditional Chinese medicine, to the best of our knowledge only a few clinical trials to date have investigated acupuncture treatment for CRF.⁷ In general, these trials demonstrated that real acupuncture produced a clinically meaningful reduction in the fatigue score and was superior to usual care or waitlist controls,²²⁻²⁵ but the efficacy against sham controls was uncertain. To our knowledge, the current study is the first RCT of laser moxibustion for CRF in which the therapeutic effect from the laser intervention appears to be consistent with previous findings in acupuncture trials; it also was better than

our sham intervention. The laser moxibustion group had a mean level of fatigue that was within the mild range at 4 weeks (3.01), whereas the level of fatigue for the sham group was within the moderate range (4.40). The National Comprehensive Cancer Network guidelines recommend supportive education and ongoing reevaluation for mild fatigue (score of 0-3). Moderate (score of 4-6) to severe (score of 7-10) fatigue calls for further evaluation and management by a clinician. The results of the current study suggest that laser moxibustion produces clinically significant differences and is an efficacious intervention that may be particularly appealing to patients who do not like the needle penetration associated with acupuncture.²⁶

Because of the placebo effects observed in prior acupuncture/moxibustion research, masking remains a major challenge in acupuncture/moxibustion-related clinical research. The design of the current study overcame some of the challenges in existing research. The sham laser moxibustion group was identical in appearance and weight to the laser moxibustion group without actual laser output. Operators knew the grouping number of the patients, but were blinded to the type of laser moxibustion each group received (whether their moxibustion device delivered laser output or not). Patients had never received laser moxibustion before and were blinded to their grouping. A nearly identical number of participants guessed that they had received the real laser intervention, which suggests that our blinding procedure was successful. Therefore, the findings of the current study are unlikely to be influenced by the bias introduced by knowing that an individual is randomized to an active group.

Currently, the pathophysiological mechanism of CRF is believed to be multifactorial.^{27,28} Researchers have hypothesized that dysregulated inflammation and its toxic downstream effects constitute a significant biological basis for CRF.²⁹ Limited research has suggested that thermostimulation achieved by moxibustion may have immune modulatory effects.³⁰ Given the promising clinical effects observed in the current study, more research is needed to elucidate the underlying mechanism of laser moxibustion for patients with CRF.

The current study has several limitations. First, it was a phase 2 study with a limited sample size and short follow-up period. Second, the dropout rate in the current study was 20%, mostly due to worsening of patients' clinical conditions during active cancer treatment; however, the dropout rate was balanced between the 2 groups. Third, the lack of a longer follow-up period made it impossible to assess the long-term effects of this treatment. Fourth, the lack of a usual-care group did not allow us to

estimate the overall effect of laser moxibustion for CRF. Last, the study population was of Han Chinese ethnicity and from one institution, and therefore replication of these preliminary findings in other populations will increase the generalizability of the results.

Infrared laser moxibustion demonstrated preliminary safety and efficacy in improving CRF in a Chinese patient population. Larger studies with long-term follow-up in more racially/ethnically diverse populations are needed to confirm the benefit of this noninvasive technique for the treatment of fatigue in patients with cancer. Future research also needs to elucidate the mechanisms underlying the clinical effects of infrared laser moxibustion for CRF.

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CONFLICT OF INTEREST DISCLOSURES

Ke Cheng, Jianzi Wei, and Xueyong Shen have had a patent issued for a type of laser therapy apparatus simulating the infrared radiation spectrum of traditional Chinese moxibustion (China Invention Patent ZL 200910056991.4; issued December 1, 2010).

AUTHOR CONTRIBUTIONS

Huijuan Mao: Study design, quality control of data and algorithms, data analysis and interpretation, article preparation, article editing, and article review. **Jun J. Mao:** Data analysis and interpretation, article editing and article review. **Menghu Guo:** Data acquisition and article preparation. **Ke Cheng:** Statistical analysis and article preparation. **Jianzi Wei:** Data acquisition and article preparation. **Xubo Shen:** Article preparation. **Xueyong Shen:** Study design and article concepts, study design, data analysis and interpretation, article editing, and article review. **Huijuan Mao** and **Xueyong Shen** are responsible for the overall content of the article.

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