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Effect of therapeutic care for treating fatigue in patients with breast cancer receiving chemotherapy

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Abstract

Background: This study aimed to evaluate the effect of therapeutic care (TC) for fatigue in breast cancer patients receiving chemotherapy.

Methods: A total of 48 breast cancer patients receiving chemotherapy were randomly divided into the intervention group and the control group, with 24 patients in each group. The patients in the intervention group were treated with TC, while the participants in the control group received the sham intervention. The interventions in both groups were for 30 min/d, 3 days weekly for 12 weeks. The primary outcome of fatigue was measured by the multidimensional fatigue inventory (MFI). The secondary outcomes were measured by the Hospital Anxiety and Depression Scale (HADS) and Pittsburgh Sleep Quality Index (PSQI). All outcomes were assessed before and after 6 and 12 weeks of the intervention.

Results: The intervention with TC showed greater efficacy than sham TC in decreasing the MFI score after week 6 ($P < .05$) and week 12 ($P < .01$) of treatment. Significant differences were also found in the HADS and PSQI between the 2 groups after 12 weeks of treatment ($P < .01$).

Conclusion: This study demonstrated that TC might decrease fatigue and relieve the anxiety and depression of breast cancer patients receiving chemotherapy.

Abbreviations: CAT = complementary and alternative therapies, ECOG = Eastern Cooperative Oncology Group, HADS = Hospital Anxiety and Depression Scale, ITT = intention-to-treat, LI4 = Hegu, MFI = multidimensional fatigue inventory, PSQI = Pittsburgh Sleep Quality Index, QOL = quality of life, SP6 = Sanyinjiao, ST36 = Zusanli, TC = therapeutic care.

Keywords: breast cancer, chemotherapy, clinical trial, fatigue, therapeutic care

1. Introduction

Chemotherapy is one of the most common therapies for cancer.[1–7] However, most patients experienced a variety of side effects when they received chemotherapy, such as fatigue, diarrhea, anemia, infection, nausea, vomiting, and any other adverse events (AEs). Of those, fatigue is one of the most common side effects in patients receiving chemotherapy. It has been reported that about 50% to 75% patients had experienced fatigue when they received such treatment.[8] The others studies also reported that this number rises to 80% to 96% for cancer patients receiving chemotherapy and 60% to 93% for patients also undergoing radiation therapy.[9,10] Although the mechanism of chemotherapy-related fatigue is not well understood, rest and sleep alone cannot help to relieve the condition.[11] Additionally, if this condition cannot be treated effectively and timely, it can lead to anxiety, depression, and a very poor quality of life (QOL) for cancer patients.[12–16] Unfortunately, very few interventions are available to treat cancer-related fatigue.

It has been reported that complementary and alternative therapies (CAT) can be used to treat chemotherapy-related fatigue.[17] In addition to reducing fatigue, they can also enhance QOL and relieve depression and anxiety among cancer patients,[17] with the improvement of the median of brief fatigue inventory from 4.8 to 3.9 ($P < .001$), Hospital Anxiety and Depression Scale (HADS)-Anxiety from 8 to 7 ($P < .001$), HADS-Depression from 7 to 6 ($P < .001$), and global QOL improved from 50 to 67 ($P < .001$) after the treatment of 12 weeks. Therapeutic care (TC), especially acupressure, is one of the CAT interventions with the potential to reduce fatigue. In addition, 1 prior study reported a positive effect of acupressure in managing cancer treatment-related fatigue and achieved successful outcomes[18] with significant improvements of general fatigue ($P < .001$), physical fatigue ($P = .016$), activity ($P = .004$) and motivation ($P = .024$). Additionally, significant improvements of fatigue levels with 36% and 19% improvements in the acupuncture group, and acupressure group, when compared with 0.6% in the sham acupressure group. However, limited

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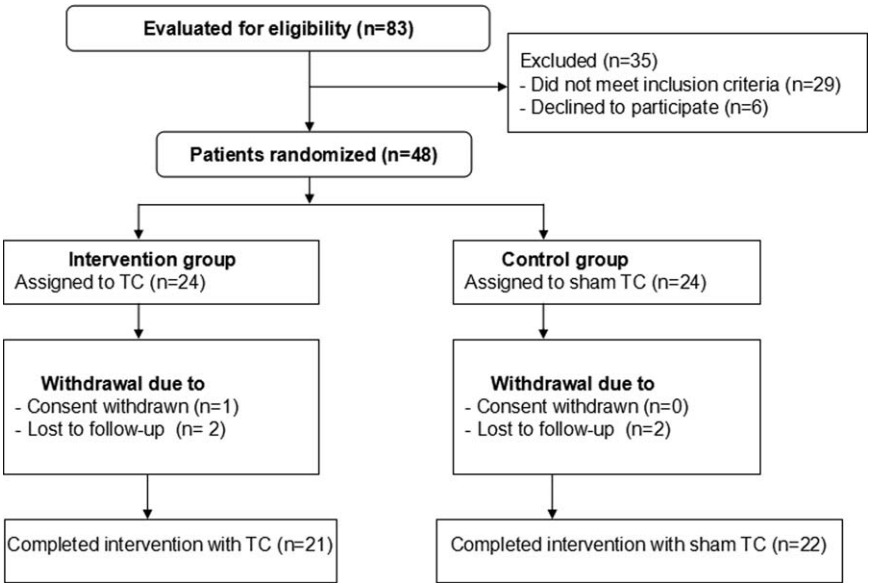

Figure 1. Flow of patients through the trial.

evidence is still available to support the idea that TC can be effectively used to treat this condition.

In this study, we tested the hypothesis that TC can reduce cancer treatment-related fatigue in breast cancer patients receiving chemotherapy.

2. Methods

2.1. Design

This randomized controlled trial was approved by the Medical Ethical Committee of The Affiliated Hongqi Hospital of Mudanjiang Medical University and was also performed at such hospital. Forty-eight breast cancer patients receiving chemotherapy from January 2015 to December 2016 were included. All eligible participants were screened against the inclusion and exclusion criteria before selection. The patients were randomly divided into the intervention group or the control group in a 1:1 ratio.

2.2. Study population

All participants were recruited from The Affiliated Hongqi Hospital of Mudanjiang Medical University. The eligibility criteria for this study included patients aged from 18 to 70 years with an Eastern Cooperative Oncology Group (ECOG) performance score from 0 to 2. All participants had histologically proven breast cancer and were surgically treated with lumpectomy or mastectomy. Patients with active psychiatric illness, pregnancy, or refused to participate were excluded. Moreover, patients who take supplements, herbs, and medication-related fatigue were also excluded from this study. In addition, all patients had to provide informed consent, demonstrating that they understood they would receive active or sham treatment and would be unaware of group assignment. All patients were recruited and included prior to their first chemotherapy treatment.

2.3. Randomization and blinding

The software package SAS 8.3(SAS Institute Inc., Cary, NC) was used to perform a block randomization scheme. The randomization assignments were concealed in opaque sequentially numbered sealed envelopes prepared by the statistician. Forty-eight participants were assigned at a 1:1 ratio to the intervention group or control group according to the randomization assignments. The participants, researchers, outcome assessors, and data analysts were blinded to the treatment allocation.

All participants in both groups were told that they were testing the effects of 2 sets of acupoints by the same acupressure technique skills. All patients did not know which set of acupoints were applied by sham technique.

2.4. Intervention

All participants in the intervention group were administered TC with acupressure at bilateral Hegu (LI4, in the middle of the second metacarpal bone on the radial side), Zusanli (ST36, 3 cun below the lower border of the patella, 1 finger width lateral from the anterior border of the tibia), and Sanyinjiao (SP6, 3 cun directly above the tip of the medial malleoulus on the posterior border of the tibia), 30 min/d, each point 10 minutes, 3 days weekly for 12 weeks. All the selected points have been reported to relate with the energy in the human body and have been previously shown to relieve fatigue in cancer patients.[18] In the control group, all patients received sham TC at the first metacarpal head, patella, and inner ankle with the same scheme treatment session as the intervention group.[18] The 3 points in the control group within the range of locations without acupoints, have been reported to have no relationship with any ability to alleviate cancer-related fatigue.[19,20]

All 3 acupoints were stimulated through acupressure with thumbs of physicians. The acupressure of these 3 points should feel strong but not intolerably painful. Additionally, the acupressure skills in this study consisted of pointing, pressing, kneading, and pushing in both groups. Pointing technique is used for finding the acupoints. Pressing technique is used for releasing the qi flow by pressure. Kneading technique is used for stimulating the therapeutic effect by rotating the figures around the selected acupoints. Pushing technique is used for relaxing the local muscles and improving the blood circulation by pushing the thumb from the selected acupoints to the around area.

All acupressure interventions were performed by 2 practitioners, who were trained for acupressure technique skills by a 10 years qualified professional practitioner. The 2 practitioners were not allowed to know which groups they performed. All acupoints were selected by the other professional acupressure treatment expert, who did not involve the treatment assignments and also the acupressure interventions. The consistent of acupressure therapy was measured by the previous scale.[21] The accuracy of implementation was also confirmed by 2 professional experts.

2.5. Outcome measurements

The primary outcome was fatigue, which was measured by the multidimensional fatigue inventory (MFI).[22] This well-validated scale consists of 5 areas: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. Each subscale ranges from 0 to 20, with higher scores indicating a greater degree of fatigue.

The secondary outcomes included anxiety, depression, and sleep quality. The HADS was used to evaluate anxiety and depression,[23,24] and the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality.[25]

2.6. Statistical analysis

The sample size was estimated based on the given outcome measurement of fatigue, with a significant difference with a standard deviation of 0.8, $\alpha = 0.05$ (2-sided) and $\beta = 0.20$. Assuming a 20% dropout rate, at least 48 patients with 24 in each group were required to be recruited to this study. All outcome data were analyzed by an intention-to-treat (ITT) approach. *t* tests or chi-squared tests were used to analyze the data with relative risks and 95% confidence intervals.

3. Results

A total of 83 participants were initially considered for this study (Fig. 1). Of these 83, 35 patients were excluded because of failure to meet the inclusion criteria or refusal to enroll in the study. Thus, 48 subjects were randomized into the study, 24 per group. Finally, 43 patients completed the treatment, and 5 subjects withdrew from the study, mainly because of withdrawal of consent or being lost to follow-up (Fig. 1).

The characteristics of all included patients are presented in Table 1. No significant differences in terms of age, race, education background, marital status, occupation, ECOG performance status, previous chemotherapy treatment, hemoglobin, or albumin existed between the 2 groups at baseline (Table 1).

In this study, the mean change from the baseline by intervention and the difference between the intervention and control groups were analyzed to evaluate the effects of TC. The results for the effect endpoints at week 6 and week 12 are summarized in Table 2. TC alleviated the primary outcome of fatigue as compared with sham TC at week 6 and week 12 ($P < .01$, Table 2). At the end of week 6 of the intervention, no significant differences in HADS and PSQI were found between the 2 groups ($P > .05$). However, the intervention group exhibited significant improvements in HADS and PSQI compared with the control group at week 12 ($P < .01$, Table 2).

In this study, no any kinds of adverse events, related to the acupressure were found in both groups, such as headache, dizziness, and some skin reactions.

Table 1

Patients characteristics at baseline.

Variable	Intervention group (n = 24)	Control group (n = 24)	*P*
Age, y	51.8 (9.6)	52.4 (9.3)	.83
Race (Han ethnicity)	24 (100.0)	24 (100.0)	1.00
Education background			
Primary school and below	5 (20.8)	4 (16.7)	.71
Secondary school	11 (45.8)	13 (54.2)	.56
College and above	8 (33.3)	7 (29.2)	.76
Marital status			
Single	4 (16.7)	6 (25.0)	.48
Married	17 (70.8)	14 (58.3)	.37
Divorced/widowed	3 (12.5)	4 (16.7)	.68
Occupation			
Employed	10 (41.6)	9 (37.5)	.77
Unemployed	7 (29.2)	9 (37.5)	.55
Retired	7 (29.2)	6 (25.0)	.75
ECOG performance status			
0	3 (12.5)	4 (16.7)	.37
1	16 (66.4)	14 (58.3)	.55
2	5 (20.8)	6 (25.0)	.73
MFI scale			
MFI-general fatigue	17.1 (2.9)	16.9 (3.2)	.82
MFI-physical fatigue	16.7 (2.6)	16.4 (2.7)	.69
MFI-activity	15.3 (3.2)	14.9 (3.5)	.68
MFI-motivation	13.1 (4.0)	13.4 (3.8)	.79
MFI-mental fatigue	14.4 (3.3)	14.7 (3.6)	.76
HADS-anxiety	7.0 (3.0)	6.8 (3.2)	.82
HADS-depression	7.4 (3.6)	7.3 (3.5)	.92
PSQI	9.2 (4.5)	9.0 (4.4)	.88
Chemotherapy			
Gemcitabine	4 (16.7)	5 (20.8)	.71
Platinum	5 (20.8)	6 (25.0)	.73
Paclitaxel	7 (29.2)	7 (29.2)	1.00
Doxorubicin	5 (20.8)	4 (16.7)	.71
Other	3 (12.5)	2 (8.3)	.64
Hemoglobin, g/dL	12.6 (1.5)	12.8 (1.6)	.66
Albumin, g/dL	4.0 (0.3)	4.1 (0.3)	.25

Note: Data are present as mean ± standard deviation or number (%); ECOG = Eastern Cooperative Oncology Group; MFI = multidimensional fatigue inventory; HADS = Hospital Anxiety and Depression Scale; PSQI = Pittsburgh Sleep Quality Index.

4. Discussion

CAT is a nursing care intervention and does not require a doctor's prescription. TC is one of the most important types of CAT that effectively relieves a variety of symptoms.[26] It has been reported that it can reduce stress, anxiety,[27] and pain,[28] as well as other symptoms.[27] In the present study, we explored the effect of TC for relieving chemotherapy-induced fatigue in breast cancer patients receiving chemotherapy.

The results of the present study are partly consistent with the previous study,[18] which specifically focused on the acupressure therapy for the treatment of fatigue in breast cancer patients receiving chemotherapy. It was designed as a 3-group randomized controlled trial with total of 47 patients comparing acupuncture therapy and acupressure therapy with sham acupressure treatment control.[18] It consisted of 2-week treatment, and 2-week follow-up after the treatment. The acupuncture group and acupressure group reported significantly greater reductions in fatigue compared with the control group with general fatigue ($P < .001$), physical fatigue ($P = .016$), activity ($P = .004$), and motivation ($P = .024$). In addition, there were also more significant differences of fatigue levels with 36%

Table 2

Primary and secondary outcome measurements at the end of 6-week, and 12-week treatment (change from baseline).

Outcomes	Week 6				Week 12			
	Intervention group (n = 24)	Control group (n = 24)	Difference	*P*	Intervention group (n = 24)	Control group (n = 24)	Difference	*P*
Fatigue								
General fatigue	−2.9 (−3.6, −2.1)	−0.9 (−1.3, −0.1)	−2.0 (−2.8, −1.7)	<.01	−4.5 (−6.1, −3.1)	−1.4 (−2.2, −0.7)	−3.1 (−3.9, −2.3)	<.01
Physical fatigue	−2.1 (−2.7, −1.3)	−0.4 (−0.8, 0.1)	−1.8 (−2.6, −1.5)	<.01	−4.3 (−6.4, −3.5)	−1.1 (−1.5, −0.8)	−3.2 (−4.0, −2.6)	<.01
Activity	−3.0 (−3.8, −1.9)	−1.3 (−1.8,−0.5)	−1.7 (−2.2, −0.9)	<.01	−5.0 (−6.9, −3.8)	−2.2 (−3.0,−1.5)	−2.8 (−3.7, −2.2)	<.01
Motivation	−1.9 (−2.4, −1.0)	−0.6 (−0.9, −0.1)	−1.4 (−1.8, −0.7)	<.05	−4.1 (−5.7, −2.8)	−1.2 (−1.9, −0.7)	−2.9 (−3.8, −2.0)	<.01
Mental fatigue	−2.0 (−2.7,−1.2)	−0.7 (−1.0, −0.3)	−1.3 (−1.7,−0.9)	<.05	−4.4 (−5.8,−3.3)	−1.3 (−1.8, −0.6)	−3.0 (−4.0,−2.1)	<.01
HADS-anxiety	−1.8 (−2.7,−1.2)	−1.4 (−2.0, −0.8)	−0.4 (−0.7,−0.2)	.18	−3.1 (−4.0,−2.2)	−1.6 (−2.4, −1.2)	−1.5 (−2.1,−0.9)	<.01
HADS-depression	−1.1 (−1.5,−0.7)	−0.8 (−1.2, −0.3)	−0.3 (−0.5, −0.2)	.11	−3.3 (−4.1,−2.1)	−1.5 (−1.7, −0.6)	−1.8 (−2.6, −1.2)	<.01
PSQI	−1.7 (−2.3, −1.1)	−1.3 (−1.6,−0.9)	−0.4 (−0.6, −0.3)	.16	−3.5 (−4.3, −3.0)	−1.9 (−2.6,−1.5)	−1.6 (−2.2, −1.0)	<.01

Note: Data are present as mean ± standard deviation; HADS = Hospital Anxiety and Depression Scale; PSQI = Pitts-burgh Sleep Quality Index.

and 19% improvements in the acupuncture and acupressure group respectively, when compared with 0.6% in the sham acupressure group. In this study, we treated all patients for 12 weeks and measured the outcomes at the end of 6-week and 12-week treatment, respectively. At the end of 6-week and 12-week treatment, the significant improvements of fatigue in the intervention group were found, compared with the sham acupressure in the control group. However, only at the end of 12-week treatment, anxiety and depression, measured by HADS-Anxiety, and HADS-Depression; and sleep quality, measured by PSQI exhibited more significant enhancements in the intervention group, compared with those in the control group.

Although a positive effect of TC for relieving cancer treatment-related fatigue was achieved, this study still suffered from several limitations. First, the sample size was pretty small, which may affect the detection of differences between the groups. In addition, the effect of the intervention may have been affected by the patient–provider relationship. Third, the cancer treatment-related fatigue relief was evaluated using the MFI scale, which is a relatively subjective tool and may be affected by multiple unknown factors. Finally, this study was conducted at only 1 center of The Affiliated Hongqi Hospital of Mudanjiang Medical University, and all of the participants were Han Chinese, which might have influenced the generalizability of our findings to patients in other hospitals and other ethnicities.

We demonstrated that the administration of TC to breast cancer patients receiving chemotherapy induced a significant reduction in cancer treatment-related fatigue and relieved anxiety, depression, and poor sleep quality. Future studies with larger sample sizes are necessary to verify this result.

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