Abstract

Objective: Idiopathic chronic fatigue (ICF), defined as medically unexplained chronic fatigue, is common these days. To date, there is no definite cure for ICF, and alternative therapies are being investigated. Oriental medicine music therapy (OMMT), a novel music therapy that occurs through an active behavioral process, has been applied to various chronic diseases, including ICF. In the present study, we aimed to evaluate the effect of OMMT on ICF.

Design: Randomized controlled trial of OMMT compared with the waitlist control (6 sessions each) during a 2-week period.

Participants: Thirty participants who had had ICF for at least 6 months before the experiments were recruited.

Outcome measures: We evaluated fatigue severity scale (FSS), visual analog scale (VAS) for overall fatigue, revised Chalder fatigue scale (RCFS), World Health Organization quality of life scale abbreviated version (WHOQOL-BREF), Buzhongyiqi-Tang questionnaire (BZTQ), and salivary cortisol level at baseline (week 0) and at the end of the study (week 2) in the two groups.

Results: FSS, VAS, and RCFS scores were significantly lower, and WHOQOL-BREF scores were significantly higher in the OMMT group than in the waitlist group (p = 0.006, p = 0.004, p = 0.002, and p = 0.002, respectively). In contrast, salivary cortisol level and BZTQ scores were not significantly different between the OMMT group and the waitlist group.

Conclusions: The present study suggests that OMMT may be an alternative treatment for ICF. Based on this result, further studies including possible mechanisms are needed.

Introduction

Chronic fatigue (CF) is a common condition with a prevalence of 4–30% worldwide.1,2 CF is defined as medically unexplained fatigue lasting over 6 months.3 It is divided into two types, based on its severity and accompanying symptoms: chronic fatigue syndrome (CFS) and idiopathic chronic fatigue (ICF). ICF is severe long-lasting fatigue not meeting the stringent criteria for CFS with less than four accompanying symptoms listed by the U.S. Centers for Disease Control and Prevention (CDC).3 In the clinic, ICF is more commonly encountered than CFS.1,5 Although various treatments, including cognitive behavioral therapy and antidepressants, have been used for CF, the response to these treatments has been unsatisfactory.6–8

Recently, severe chronic diseases have been reported to be improved by Oriental medicine music therapy (OMMT), which is different from conventional music therapies owing to its unique active behavioral process such as clapping, singing, and playing various instruments.9 Selection of music in OMMT depends on five elements theory (Wood, Fire, Earth, Metal, and Water in traditional oriental philosophy). Five elements is a conceptual scheme that explains a wide array of phenomena in nature, and interactions between internal organs and mechanisms of herbal medicine in traditional oriental medicine.10 OMMT has been used for
patients in various situations, including rehabilitation of patients with cerebral infarction, supportive care for patients with hematological malignancy, and treatment for patients with CF. To date, there has been one case report related to the effect of OMMT on ICF, which showed marked improvement of ICF after OMMT. However, there were no clinical trials about the effect of OMMT on ICF. This is the first clinical trial of OMMT for ICF using fatigue severity scale (FSS), revised Chalder fatigue scale (RCFS), World Health Organization quality of life scale abbreviated version (WHOQOL-BREF), and Buchongyiqi-Tang questionnaire (BZTQ).

Methods

Study design

The present study was a randomized, waitlist-controlled trial with 30 participants. All the participants first provided informed consent, and then were randomly allocated to either the OMMT group or the waitlist group. The entire study protocol was reviewed by the institutional review board of the Kyung Hee University Hospital at Gangdong, Seoul, Korea (KHNMC-OH-IRB 2012-0024).

Participants

The present study was conducted in an OMMT center of Kyung Hee University Hospital at Gangdong. Participants were voluntarily recruited through the bulletin boards of the hospital or short message service. Participants fulfilling the inclusion and exclusion criteria were enrolled (Table 1). This study has a pilot characteristic of OMMT as a new therapeutic strategy for ICF. Thus, a total of 30 patients were considered to be the minimal sample size for statistical significance of outcomes analysis.

Randomization and allocation concealment

The random allocation table sequence was created by an independent statistician. In total, 30 participants were randomly allocated into the OMMT group or the waitlist group. The random allocation information was sealed in opaque envelopes and stored in a locked cabinet. Then, an independent clinical research coordinator revealed the contents of the envelopes to the participants at their second visit.

Intervention

OMMT was conducted for an hour per day, three times a week. Finally, 6 sessions of OMMT were provided to the participants in the OMMT group within 2 weeks. Each session comprised 6 steps: (1) Relaxing the body through abdominal respiration while listening to sound of Daegeum, a traditional Korean pipe, for 5 min. The melody of Daegeum represents metal, and helps one to feel calm and relaxed. (2) Clapping hands with high, low, and flat vocal sounds for 20 min, and imitating the sound of Janggu, a double-headed drum with a narrow waist, for 5 min. It helps one to relieve depression and stress. (3) Playing with wood blocks while listening to music representing wood, for 5 min. (4) Playing Janggu while listening to music representing earth, for 5 min. (5) Shaking maracas while listening to music representing water, and tapping of acupoints, for 5 min. The following acupoints were used: Neigu (PC6), Fengchi (GB20), Jianjing (GB21), Fengshifei (GB31), and Fenglong (ST40). It promotes circulation of qi and blood. (6) Singing a song during the last 20 min of the session, pronouncing “mo” and “mi,” which represent yin and yang.

Outcome measures

All variables were checked at baseline (week 0) and at the end of the study (week 2).

Fatigue severity scale

In this study, FSS was defined as the primary outcome. FSS is a useful questionnaire to measure the severity of fatigue experienced by the participants who suffer from unexplained exhaustion. It consists of nine items with a seven-point Likert scale. The average score of all items, ranging 1–7, is used as the final result. The higher score indicates more severe fatigue.

Visual analog scale for overall fatigue

VAS for overall fatigue is used to self-evaluate the severity of fatigue. When responding to a VAS item, participants are supposed to specify the level of their fatigue by indicating a position along a continuous line between two end-points. The higher VAS score indicates more severe fatigue.

Revised Chalder fatigue scale

RCFS is a representative questionnaire for patients who suffer from CFS. The abbreviated version of Chalder fatigue scale comprises 11 items, using a 4-point Likert scale. The total score, sum of 11 items, is the most preferred variable for accessing the severity of fatigue in the clinical field. However, two categorical scores, physical fatigue (items 1–7) and mental fatigue (items 8–11), are also frequently used as subscales. The total score ranges 0–33 and the higher score indicates more severe fatigue.
WHOQOL-BREF is a shortened version of the WHOQOL-100. It comprises 24 items, which measure the following four domains: physical health, medical treatment, psychological health, and environment (each ranging 4–20). Two additional items are analyzed separately: perception of overall QOL and general health (each ranging 1–5).

Buzhongyiqi-Tang questionnaire

BZTQ is a validated questionnaire that quantifies the severity of fatigue syndrome, also known as Lao Juan Shang (勞倦虛) in traditional Asian medicine. LJS is a condition characterized by exhaustion derived from physical, mental, or sexual overwork, and Buzhongyiqi-Tang (BZT) is a widely prescribed herbal medicine for LJS. BZTQ consists of 16 items, including 2 items related directly with fatigue and 14 items evaluating accessory symptoms such as pain and anorexia (Appendix 1).

Salivary cortisol

Salivary cortisol is known as one of the possible biological markers of fatigue. Participants were asked to refrain from meal as well as from washing or rinsing their mouth, because this might affect salivary cortisol values. Saliva was collected by using Salivette collection tubes (cotton swabs inside small plastic tubes, kept in a deep freezer at -80°C). The analysis of salivary cortisol was conducted at Seoul Clinical Laboratories (Seoul, Korea) using enzyme-linked immunosorbent assay. Saliva samples were taken at 9 PM and 9 AM over two consecutive days.

Data analysis

The demographic and individual variables and study outcomes were described by way of frequencies (percentages) and mean values. Two-sample t-test was used to determine significant differences between groups at baseline and at the end of the study. Fisher’s exact test was used to compare categorical values at baseline. Pearson’s correlation coefficient was used for correlation analysis. Analyses were performed using PASW statistics 18.0 (SPSS Inc., Chicago, IL) and a p-value of < 0.05 was considered statistically significant.

Results

Participants

Thirty-four participants with CF visited our clinics for the screening test. As a result of the screening test, four of them failed to be enrolled in the study due to their underlying diseases. All enrolled participants completed the treatment sessions or waiting period without any dropouts (Fig. 1). There were no differences in baseline characteristics between the two groups (Table 2).

Fatigue severity scale

As a primary outcome, FSS scores of the OMMT group were significantly lower than those of the waitlist group at week 2: 3.2 ± 1.4 versus 4.5 ± 0.9 (p = 0.005; Fig. 2).

Visual analog scale for overall fatigue

VAS scores of the OMMT group were significantly lower than those of the waitlist group at week 2: 41.5 ± 23.2 versus 63.3 ± 13.8 (p = 0.004; Fig. 2).

Revised Chalder fatigue scale

Total RCFS scores of the OMMT group were significantly lower than those of the waitlist group at week 2: 8.7 ± 5.1 versus 15.5 ± 5.9 (p = 0.002; Fig. 2). Similarly, scores of the OMMT group were significantly lower than those of the waitlist group for physical domain: 5.6 ± 3.8 versus 10.3 ± 3.5 (p = 0.001), and for psychological domain: 3.1 ± 1.6 versus 5.2 ± 3.1 (p = 0.031).

World Health Organization quality of life scale abbreviated version

Scores of the OMMT group were significantly higher than those of the waitlist group at week 2 for overall QOL:

![Flowchart for the study](image)

FIG. 1. Flowchart for the study. OMMT, Oriental medicine music therapy.
Table 2. Sample Characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OMMT (n = 15)</th>
<th>Control (n = 15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographic features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>1:14</td>
<td>2:13</td>
<td>1.00</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.7 ± 9.8</td>
<td>47.1 ± 14.5</td>
<td>0.34</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.3 ± 3.7</td>
<td>21.5 ± 2.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Less than high school education, n (%)</td>
<td>1 (6.7)</td>
<td>5 (33.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Duration of fatigue (years)</td>
<td>7.6 ± 9.1</td>
<td>10.4 ± 10.2</td>
<td>0.42</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Alcohol intake, n (%)</td>
<td>2 (13.3)</td>
<td>5 (33.3)</td>
<td>0.39</td>
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<tr>
<td>BDI</td>
<td>10.5 ± 6.0</td>
<td>12.1 ± 7.7</td>
<td>0.55</td>
</tr>
<tr>
<td>PSQI</td>
<td>6.9 ± 2.7</td>
<td>7.7 ± 3.5</td>
<td>0.45</td>
</tr>
<tr>
<td>Outcome measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSS</td>
<td>4.6 ± 0.8</td>
<td>4.9 ± 0.9</td>
<td>0.44</td>
</tr>
<tr>
<td>VAS</td>
<td>65.4 ± 18.0</td>
<td>70.0 ± 14.0</td>
<td>0.44</td>
</tr>
<tr>
<td>RCFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>19.1 ± 4.4</td>
<td>17.4 ± 5.9</td>
<td>0.37</td>
</tr>
<tr>
<td>Physical domain</td>
<td>12.6 ± 3.5</td>
<td>10.27 ± 3.6</td>
<td>0.08</td>
</tr>
<tr>
<td>Psychological domain</td>
<td>6.5 ± 1.6</td>
<td>6.9 ± 2.4</td>
<td>0.66</td>
</tr>
<tr>
<td>WHOQOL-BREF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall QOL</td>
<td>3.3 ± 0.6</td>
<td>3.1 ± 0.7</td>
<td>0.28</td>
</tr>
<tr>
<td>General health</td>
<td>2.4 ± 0.9</td>
<td>2.3 ± 0.8</td>
<td>0.83</td>
</tr>
<tr>
<td>Physical domain</td>
<td>12.3 ± 2.0</td>
<td>11.7 ± 1.9</td>
<td>0.37</td>
</tr>
<tr>
<td>Psychological domain</td>
<td>13.0 ± 2.4</td>
<td>11.4 ± 2.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Social domain</td>
<td>13.4 ± 2.4</td>
<td>13.0 ± 2.7</td>
<td>0.64</td>
</tr>
<tr>
<td>Environmental domain</td>
<td>13.4 ± 1.9</td>
<td>12.1 ± 2.0</td>
<td>0.09</td>
</tr>
<tr>
<td>BZTQ</td>
<td>66.6 ± 19.6</td>
<td>67.5 ± 13.5</td>
<td>0.89</td>
</tr>
<tr>
<td>Salivary cortisol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 AM (µg/dL)</td>
<td>0.26 ± 0.21</td>
<td>0.26 ± 0.19</td>
<td>0.99</td>
</tr>
<tr>
<td>9 PM (µg/dL)</td>
<td>0.10 ± 0.14</td>
<td>0.13 ± 0.12</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Values expressed with a plus/minus sign are the mean ± standard deviation.
BMI, body mass index; BZTQ, Buchongyi-Tang questionnaire; FSS, fatigue severity scale; OMMT, oriental medicine music therapy; PSQI, Pittsburgh sleep quality index; RCFS, revised Chalder fatigue scale; VAS, visual analog scale for overall fatigue; WHOQOL-BREF, World Health Organization quality of life scale abbreviated version.

3.9 ± 0.5 versus 3.2 ± 0.6 (p = 0.002); for general health: 3.2 ± 0.8 versus 2.5 ± 0.7 (p = 0.023); for physical domain: 14.5 ± 1.9 versus 11.5 ± 2.1 (p < 0.001); for psychological domain: 14.1 ± 2.0 versus 11.5 ± 2.3 (p = 0.003); for environmental domain: 14.0 ± 2.0 versus 12.0 ± 2.2 (p = 0.013).

However, social domain scores of the OMMT group were not significantly different from those of the waitlist group: 14.2 ± 1.8 versus 12.8 ± 2.5 (p = 0.084; Fig. 3).

Buzhongyiqi-Tang Questionnaire
There were no significant differences of BZTQ scores between the OMMT group and the waitlist group at week 2: 53.0 ± 22.0 versus 64.9 ± 15.0 (p = 0.095; Fig. 2).

Salivary cortisol
There was no significant difference between the concentration of salivary cortisol at 9 AM of the OMMT group and that of the waitlist group at week 2: 0.25 ± 0.13 µg/dL versus 0.22 ± 0.14 µg/dL (p = 0.566) and at 9 PM: 0.09 ± 0.05 µg/dL versus 0.20 ± 0.23 µg/dL (p = 0.109; Fig. 4).

Discussion
The objective of this study was to investigate the effects of OMMT on ICF. The OMMT, the novel music therapy based on the theory of traditional Korean medicine, is recently introduced to complementary and alternative medicine practitioners and researchers as an option for CF in Korea. Most of previous studies on fatigue have used other types of music therapy such as therapeutic instrumental music performance, singing while listening to music, and music combined with progressive muscle relaxation. Those studies involved patients with fatigue related to specific conditions such as orthopedic surgery and cancer, while the present study focused on medically unexplained CF, which has been more commonly seen in the clinical field. The treatments and mechanism of ICF are still a subject of controversy.

The decrease in significant FSS scores in the OMMT group indicated that OMMT relieved overall fatigue of participants. The FSS scores of the OMMT group at week 2 (3.2 ± 1.4) were even close to those of healthy populations in a previous study (3.0 ± 1.1). The significant decrease in VAS of the OMMT group also indicated that OMMT relieved fatigue. However, it is necessary to understand the nature of the items when interpreting the results of the scales. All items of FSS are focused on how respondent’s fatigue affects life, rather than on fatigue itself. On the other hand, VAS is a scale evaluating the severity of fatigue; it was used as an assistant scale of FSS in the present study. Correlation of FSS with VAS was very strongly positive.
RCFS consists of physical domain and psychological domain. A significant decrease in the two domains indicated that both mental and physical fatigue were improved by OMMT. This might be due to its active behavioral process, including stimulating acupoints and playing instruments.

All WHOQOL-BREF domains were significantly improved in the OMMT group compared to the waitlist group except for the social domain. Patients with CF usually experience a reduction in QOL. In the present study, the participants were asked to write down any comments about the study at week 2. The majority of them (73%) wrote about the effect of OMMT. Their thoughts and feelings could be divided into three categories without duplication: (1) Five of the participants (33%) reported an improvement of the quality of sleep after OMMT. Pittsburgh sleep quality index (PSQI), the self-rated questionnaire for quality of sleep, was used to exclude participants with serious insomnia in the present study. Baseline PSQI scores of the study sample were low (mean = 7.3, SD 3.1), which indicated poor quality of sleep. However, it is hard to tell whether OMMT statistically improved quality of sleep of ICF patients due to lack of follow-up data. Further study is needed to investigate the relationship between OMMT and quality of sleep. (2) Five other participants (33%) reported an improvement in QOL and physical lassitude after OMMT. (3) One of the participants (7%) reported an improvement of respiration after OMMT. These experiences suggest that OMMT might also improve overall QOL in ICF.

\[ r = 0.70; \ p < 0.001, \] which is similar to results of the previous study using FSS \( (r = 0.68).^{15} \)

BZTQ scores of the OMMT group did not differ from those of the waitlist group. In fact, baseline BZTQ scores in both groups (66.6 in the OMMT group and 67.5 in the waitlist group) were close to normal values. The participants answered “normal” to the majority of the items tested: most items \( (n = 14) \) are related to accessory symptoms of CFS, whereas only 2 items are directly related to fatigue. Patients

![FIG. 2. Scores on fatigue-related questionnaires at 2 weeks. Error bars indicate standard error of mean. Asterisks indicate the level of statistical significance for intragroup comparisons (compared to baseline) \( (**p < 0.01, \ ***p < 0.001) \). \( p \)-Values represent between-group differences (control group vs. OMMT). BZTQ, Buzhongyiqi-Tang questionnaire; FSS, fatigue severity scale; RCFS, revised Chalder fatigue scale; VAS, visual analog scale.](image)

![FIG. 3. Scores on WHOQOL-BREF at 2 weeks. Error bars indicate standard error of mean. Asterisks indicate the level of statistical significance for intragroup comparisons (compared to baseline) \( (*p < 0.05, \ **p < 0.01) \). \( p \)-Values represent between-group differences (control group vs. OMMT). WHOQOL-BREF, World Health Organization quality of life scale abbreviated version.](image)

![FIG. 4. Concentration of salivary cortisol at 2 weeks. Error bars indicate standard error of mean.](image)
with CFS usually experience more than four accessory symptoms, while patients with ICF experience less than four by definition. This explains why OMMT failed to significantly improve LJS despite marked improvement of fatigue symptoms. An in-depth study with BZTQ is necessary to investigate a possible correlation between LJS and CFS.

In our study, female participants were recruited with preponderance (90%). In the screening test, most male applicants were of the opinion that their heavy workload was the definite cause of fatigue. Their fatigue corresponded to physiological fatigue rather than pathological fatigue such as ICF and CFS. This might be a major contributing factor of gender imbalance in the present study. In the future, a clinical study with larger sample size is needed to overcome gender imbalance.

Cortisol is one of the major hormones produced by the adrenal cortex, activated by the pituitary gland. The hypothalamic–pituitary–adrenal axis is thought to have a key role in resisting to inflammation and defending against stress regulating various hormones, including cortisol. The relevance of hypocortisolism to bodily diseases such as CFS has previously hypothesized. There are several researches observing no attenuation of cortisol level or, indeed, increased cortisol in CFS. The change of cortisol level in patients with fatigue is still unclear and controversial. A recent systematic review and meta-analysis study reported decreased cortisol awakening response and circadian cortisol variation within CFS. An attenuation of diurnal variability concurs with the recent review of endocrine dysfunction in CFS. Although the concentration of salivary cortisol showed no significant difference between the two groups after treatment, the diurnal cortisol slope of the waitlist group became flatter after treatment, which indicated more severe fatigue in previous studies.

Compared with some previous studies measuring cortisol in serum, we measured cortisol in saliva, because measurements of cortisol in saliva are noninvasive and more accurately reflect serum-free cortisol concentrations than do measurements of serum total cortisol. Salivary cortisol levels display diurnal cycles in humans. Generally, cortisol levels are the lowest between 8 PM and 2 AM; levels increase thereafter, with the highest levels shortly after awakening (approximately 8 AM). In the absence of external stimuli, cortisol levels typically decrease throughout the day. In our trial, we tried to check the highest and lowest cortisol level based on circadian pattern. However, considering participants’ compliance, we fixed the time of collection at 9 AM and 9 PM. Fixation of saliva collection time was considered as a better method for participants to memorize and conduct it in this study, because they had some variations at awaking and sleeping times. Another reason why we kept the fixed time of saliva collection was that this trial was not an inpatient setting that enabled to collect saliva individually. We also tried not to change participants’ life style due to saliva collection. Future study should focus on setting the more relevant timing of collecting saliva in order not to affect participant’s diurnal cycle, and consider an inpatient setting if possible.

Aardal et al. have reported that the normal ranges of cortisol in saliva were estimated to 0.17–0.98 µg/dL at 8 AM and <0.22 µg/dL at 10 PM. Though collection time was slightly different, our study showed the similar tendency to the reference range shown in the previous study. The cortisol level is sensitive to outside stimuli such as pain or stress, which could not be controlled fully in this study and slightly vary with age and sex. Therefore, future studies that regulate outside circumstances and consider characteristics of individuals are needed.

The present study has a few limitations. First, follow-up period is not considered in this study. Second, the present study has been conducted with a small sample size.

In conclusion, it is suggested that OMMT might be an alternative treatment for ICF patients. However, further clinical trials with a larger sample size and follow-up are still needed to confirm the effects of OMMT on ICF.

Acknowledgments

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Author Disclosure Statement

The funding organizations had no other role in the study. No competing financial interests exist.

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therapy which was applied to blood cancer patients. J Korean Med Classics 2005;18:15.

Address correspondence to:
Jae-Woo Park, PhD, KMD
Department of Internal Medicine
College of Korean Medicine
Kyung Hee University
J Hoegi-dong, Dongdaemun-gu
Seoul 130-701
Republic of Korea
E-mail: pjw2907@khu.ac.kr

(Appendix follows →)
Appendix 1. *Buzhongyiqi-Tang* Questionnaire

Following is the questionnaire indicating your symptoms. Place mark “✓” in the frequency level on each symptom.

<table>
<thead>
<tr>
<th>Item</th>
<th>7</th>
<th>6</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always</td>
<td>Very frequently</td>
<td>Frequently</td>
<td>Occasionally</td>
<td>Rarely</td>
<td>Very rarely</td>
<td>Never</td>
<td></td>
</tr>
</tbody>
</table>

Do you overwork yourself?
Are you under stress because of your work?
Do you feel pain after working?
Do you feel tired or languid usually?
Are your work hours irregular?
Do you have indigestion?
Do you have poor appetite?
Do you feel heavy or weak in the limbs?
Do you have trouble standing or walking for a long time?
Do you feel weak after skipping a meal?
Do you have a sunken voice?
Does your cold keep up for a long time?
Do you have a hoarse throat after much talking?
Do you feel short of breath after working?
Do you have a pulling down feeling on the anus?
Do you have a fever?