Effect of Lixujieyu recipe in combination with Five Elements music therapy on chronic fatigue syndrome

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Abstract

OBJECTIVE: To observe the clinical effects of the Lixujieyu recipe combined with Five Elements music therapy on chronic fatigue syndrome (CFS) identified as the symptom patterns of liver stagnation and spleen deficiency in terms of Traditional Chinese Medicine.

METHODS: Patients with CFS were randomly divided into treatment group 1 (Lixujieyu recipe combined with Gong-Tune, n = 15); treatment group 2 (Lixujieyu recipe combined with Jiao-Tune, n = 15); treatment group 3 (Lixujieyu recipe combined with Yu-Tune, n = 15); treatment group 4 (Lixujieyu recipe combined with Shang-Tune, n = 15); treatment group 5 (Lixujieyu recipe combined with Zhi-Tune, n = 15); and the control group (Lixujieyu recipe alone, n = 15). Chinese medicine was given twice daily, and music was listened to for 45 minutes daily, 5 days a week. All patients were treated for 4 weeks. Patients were assessed via the Fatigue Scale, the Hamilton Depression Rating Scale, and the Hamilton Anxiety Rating Scale before and after treatment.

RESULTS: Treatment groups 1 and 2 had better effects on relieving the symptoms of physical fatigue related to anxiety and depression than the control group (P < 0.05).

CONCLUSION: Lixujieyu recipe combined with Gong-Tune or Jiao-Tune significantly relieved the symptoms of CFS.

INTRODUCTION

Chronic fatigue syndrome (CFS) is a debilitating and complex disorder characterized by severe chronic fatigue for 6 or more consecutive months. Some patients may also have additional non-specific symptoms including fever, sore throat, muscle pain, neuropsychiatric symptoms, and unrefreshing sleep. CFS is associated with many different stress factors, including ongoing mental stimulation and excessive physiological labor, accompanied by nerve-endocrine-immune dysfunction. The incidence of CFS has been increasing in recent years, and the prevalence in developed coun-
countries is generally higher than in developing countries. A large-scale epidemiological survey in China showed that the CFS prevalence rate was 1.95% in those aged 31-50 years, mainly affecting those engaged in mental cadres, researchers, and students. The major clinical manifestation for CFS patients is recurrent debilitating fatigue and negative emotional states; mood disorders and CFS are related. Our previous studies have found that those with liver stagnation and spleen deficiency in Traditional Chinese Medicine (TCM) are the main type of people diagnosed with CFS. As stated in the TCM classic text the "Lei Zheng Zhi Cai" Melancholia caused by the seven emotions will initially hurt Qi and blood, then eventually become consumptive disease. Therefore, the therapeutic direction for CFS patients is to relieve severe fatigue and eliminate mood disorders.

Five Elements music therapy originates from the Suwen, which states that different tunes of music can help treat different emotional disorders. It is based on theory that the Five Elements music connects the five pentameters (Jiao, Zhi, Gong, Shang, and Yu), the internal organs (liver, heart, spleen, lung, and kidney), and the five emotions (anger, joy, anxiety, worry, and fear). For example, the Gong-tune is melodious and harmonious, and can relieve an oversprung mood and help the spleen to transform and transport cerebral nutrients smoothly. Five Elements music corresponds with "do, re, mi, so, la" in the modern musical scale. Five Elements music therapy is an effective treatment for emotional disorders. Immersing in the beautiful and soothing melodies helps relieve insomnia, depressed spirits, fatigue, dysphoria and rage.

This study builds on our earlier study on treating CFS with Lixujieyu recipe and combines with our other earlier study on Five Elements music therapy. This study will evaluate the fatigue and mood disorders of patients with CFS before and after treatment with Five Elements music therapy, and determine which treatment can improve the clinical symptoms of CFS. Hence, this study aims to form a comprehensive treatment program combining music with medicine for CFS treatment.

MATERIALS AND METHODS

Study design
Based on the completely random method, the subjects were randomly assigned to either the control group (Lixujieyu recipe alone) or the treatment groups (Lixujieyu recipe combined with Five Elements music therapy) according to the proportion of 1:5. We adopted a group sequential design, and checked the experimental data at the midterm examination. The experiment was ongoing while statistics were being analyzed; hence, if significant statistical conclusions appeared that met the demands of our project, the experiment would be stopped.

Estimation of sample size
According to the results of our previous study, the efficacy rate of patients treated with Lixujieyu recipe was 95%. Medical Statistics was used for sample size estimation; the Inspection Level was set at 0.05 and the Power of Test was 0.10 in this two-tailed test. The formula was parameterized with data from our previous study. The result indicated that this project needed 12 participants in each group. Assuming a 20% dropout rate, the sample size was expanded to 15 patients in each group, and therefore the total sample size was 90.

Participants
All participants were either hospitalized patients or outpatients of the CFS specialist outpatient unit of Shanghai University of Traditional Chinese Medicine, Yueyang Hospital from November 2010 to October 2011.

Inclusion criteria
(a) Patients meeting the diagnostic criteria of CFS, and the TCM definition for liver stagnation and spleen deficiency syndrome. (b) Males or females aged from 15 to 60 years. (c) CFS symptoms had persisted or recurred for 6 or more consecutive months. (d) Patients who had undergone state examination and routine physical examination, including a blood test, urine test, erythrocyte sedimentation rate, electrolyte levels, glucose levels, liver function, kidney function, and thyroid-stimulating hormone levels, to exclude other diseases that cause chronic fatigue. (e) Patients who loved music, and would listen to music at least 5 hours per week. (f) Patients who received the treatments voluntarily and provided written, informed consent.

Exclusion criteria
(a) People aged under 15 or over 60 years. (b) Patients in whom chronic fatigue could be explained by other primary diseases. (c) Patients with mental disorders including bipolar disorder, schizophrenia, delusional disorder, dementia, and anorexia nervosa. (d) People with hearing disorders who could not hear the rhythm of the music. (e) Those who did not like music and did not have a habit of listening to music. (f) Hamilton Depression Scale (HAMD) score ≥ 17 points, indicating depression. (g) Hamilton Anxiety Scale (HAMA) score ≥ 14 points, indicating an anxiety disorder. (h) Pregnant women, those who had given birth less than 1 year prior, and those who had undergone surgery in the last year. (i) Obese patients whose body mass index was more than 40. (j) Patients who had undergone other relevant treatments. (k) Patients who were mentally challenged. (l) Patients who were allergic to the recipe used in this study.

Intervention
The enrolled patients were randomly assigned to six groups, with 15 patients in each group. They were assigned as treatment group 1 (Lixujieyu recipe combined with Gong-Tune), treatment group 2 (Lixujieyu...
recipe combined with Jiao-Tune), treatment group 3 (Lixujieyu recipe combined with Yu-Tune), treatment group 4 (Lixujieyu recipe combined with Shang-Tune), treatment group 5 (Lixujieyu recipe combined with Zhi-Tune), and the control group (Lixujieyu recipe alone). All patients were separately treated for 4 weeks.

**Outcome measurements**

The Fatigue Scale used was based on the British Chalder Fatigue Scale,17 referring to the diagnostic criteria for CFS Centers for Disease Control (1994).15 The HAMD15 and the HAMA15 were used to assess the depression and anxiety of the patients, respectively.

**Quality control of the Lixujieyu recipe**

Ingredients: Huangqi (Radix Astragali Mongolici), Ge-gen (Radix Puerariae Lobatae), Sanqi (Radix Notoginseng), Yinyanghuo (Herba Epimedi Beovirus), Yujin (Radix Curcumae Wenyujin), and Shichangpu (Rhizoma Acori Tatarinowii). The Chinese medicine was prescribed on the basis of our patent registered with the State Intellectual Property Office of China (No. 201210197606.X), which included the directions for use and dosage.

**Decoction method**

The recipe decoction was prepared by our pharmacy department, with 300 mL designated as one dose. Half the dose was administered in the morning and the other half in the evening.

**Quality control of the five elements music therapy**

The Five Elements music therapy was based on the long-term clinical practice of our research group and the requirements of music therapy. Patients were required to listen to the music for 5 days and have a rest for 2 days each week, choosing a starting time of 12:00 or 19:00 each day.13 Each session continued for 45 minutes at a volume of 55-65 dB. All music was from the Five Element Music compact disc (composed by Shi Feng, pioneer of music for health-maintenance; advised by Hao Wanshan; implemented by the philharmonic of the Central Conservatory of Music). The environment was kept quiet to avoid the influence of external sounds. The tape recorders, the patient’s local-

### Table 1 Comparison of baseline data among groups ($\bar{x} \pm s$)

<table>
<thead>
<tr>
<th>Item</th>
<th>Control group (n=15)</th>
<th>Treatment group 1 (n=15)</th>
<th>Treatment group 2 (n=15)</th>
<th>Treatment group 3 (n=15)</th>
<th>Treatment group 4 (n=15)</th>
<th>Treatment group 5 (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.2±13.1</td>
<td>42.3±12.0</td>
<td>45.8±12.0</td>
<td>44.3±11.3</td>
<td>44.9±12.2</td>
<td>4.1±12.0</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>10.8±3.0</td>
<td>11.0±3.7</td>
<td>10.9±3.2</td>
<td>11.7±2.0</td>
<td>11.0±3.7</td>
<td>10.8±3.1</td>
</tr>
<tr>
<td>Fatigue scale (points)</td>
<td>22.6±2.9</td>
<td>19.6±3.8</td>
<td>22.1±3.1</td>
<td>21.4±3.7</td>
<td>20.1±4.7</td>
<td>20.9±3.8</td>
</tr>
<tr>
<td>HAMD (points)</td>
<td>11.7±3.2</td>
<td>13.2±2.3</td>
<td>13.3±2.4</td>
<td>13.1±2.2</td>
<td>11.8±3.0</td>
<td>11.4±3.4</td>
</tr>
<tr>
<td>HAMA (points)</td>
<td>11.4±1.3</td>
<td>11.2±1.3</td>
<td>11.6±1.3</td>
<td>11.4±1.6</td>
<td>11.2±1.7</td>
<td>10.8±1.7</td>
</tr>
</tbody>
</table>

Notes: control group: patients treated with Lixujieyu recipe only; treatment group 1: patients treated with Lixujieyu recipe and Gong-Tune music; treatment group 2: patients treated with Lixujieyu recipe and Jiao-Tune music; treatment group 3: patients treated with Lixujieyu recipe and Yu-Tune music; treatment group 4: patients treated with Lixujieyu recipe and Shang-Tune music; treatment group 5: patients treated with Lixujieyu recipe and Zhi-Tune music; HAMD: hamilton depression scale; HAMA: hamilton anxiety scale.

**Comparison of baseline data**

The age, duration, scores of the Fatigue Scale, the HAMD and the HAMA of each group before treatment were examined for normal distribution (Table 1, $P < 0.05$).

**Comparison of fatigue classification**

After 4 weeks of treatment, the total Fatigue Scale score in treatment groups 1 and 2 had decreased significantly compared with the control group ($P < 0.05$). There was no statistically significant difference between treatment groups 1 and 2 (Table 2, $P > 0.05$).

**Relief of the symptoms of depression and anxiety**

Compared with the control group, both the HAMD and HAMA score decreased in treatment groups 1 and 2.
CFS has prominent clinical manifestations in chronic fatigue and mood disorders that are associated with spleen and liver dysfunction. The spleen is related to our capacity for thinking, the ascent or descent of Qi, and the muscles and the four limbs. If the spleen is weak, the limbs and muscles will not be nourished and will become tired. The main role of the liver is to control conveyance and dispersion of Qi, maintain free flow of Qi, and adjust the emotions. Hyperactivity of the liver or stagnation of liver Qi causes poor mood and emotional disorders such as anxiety and depression. Spleen deficiency causes over-restraint of the liver, and emotional disorders such as anxiety and depression.”

DISCUSSION

CFS is categorized by TCM as "melancholia" or "consumption". We have observed clinically that a combination of TCM treatment and Five Elements music therapy can relieve the somatic symptoms of chronic fatigue and mood disorders for CFS patients with liver stagnation and spleen deficiency.

Our Lixujieyu recipe was created by a veteran doctor of TCM, Professor Xiaxiang, and summarized according to many years of clinical experience. The recipe was created on the principle of adjusting Qi and blood together, clearing stasis, and treating both essence and appearance. Modern medical surveys have found that this recipe can regulate cortisol and 5-hydroxytryptamine levels in the blood, and affects the hypothalamic-pituitary axis,” which can satisfactorily relieve fatigue symptoms. According to the Five Elements Theory, Five Emotions Theory, and Five Zang Viscera Theory, each internal organ has its corresponding emotional activity characteristics. Abnormal changes in emotion can damage the physiological functions of the corresponding viscera. CFS has prominent clinical manifestations in chronic fatigue and mood disorders that are associated with spleen and liver dysfunction. The spleen is related to our capacity for thinking, the ascent or descent of Qi, and the muscles and the four limbs. If the spleen is weak, the limbs and muscles will not be nourished and will become tired. The main role of the liver is to control conveyance and dispersion of Qi, maintain free flow of Qi, and adjust the emotions. Hyperactivity of the liver or stagnation of liver Qi causes poor mood and emotional disorders such as anxiety and depression. Spleen deficiency causes over-restraint of the liver, and liver hyperactivity causes mutual restraint of the spleen. According to TCM, the chronic fatigue and emotional disorders in CFS are related, so treatment must be based on strengthening the spleen as well as soothing the liver.

The spleen is one of the five Zang viscera; it belongs to the Earth element and corresponds to the Gong-tune of the five tunes. Gong-tune music is quiet and melodious, considered to be as honest and sincere as the Earth, and can help the spleen to transport nutrients. The liver is also one of the five Zang viscera; it belongs to the Wood element and corresponds to the Jiao-tune. Jiao-tune music is bright and comforting, considered to be as germinal as the Wood, and can maintain free flow of Qi and regulate the emotions. Thus Gong-tune music has a calming effect.

Notes: control group: patients treated with Lixujieyu recipe only; treatment group 1: patients treated with Lixujieyu recipe and Gong-Tune music; treatment group 2: patients treated with Lixujieyu recipe and Gong-Tune music; treatment group 3: patients treated with Lixujieyu recipe and Yu-Tune music; treatment group 4: patients treated with Lixujieyu recipe and Shang-Tune music; treatment group 5: patients treated with Lixujieyu recipe and Zhi-Tune music. *P < 0.05, compared with the control group.

Table 2 Total score of Fatigue Scale (points, ± ± ±)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>15</td>
<td>22.6±2.8</td>
<td>20.2±4.0</td>
</tr>
<tr>
<td>Treatment group 1</td>
<td>15</td>
<td>19.8±5.6</td>
<td>12.5±2.8</td>
</tr>
<tr>
<td>Treatment group 2</td>
<td>15</td>
<td>22.1±3.1</td>
<td>14.2±2.8</td>
</tr>
<tr>
<td>Treatment group 3</td>
<td>15</td>
<td>20.1±4.7</td>
<td>18.9±4.4</td>
</tr>
<tr>
<td>Treatment group 4</td>
<td>15</td>
<td>21.0±3.1</td>
<td>20.9±1.7</td>
</tr>
<tr>
<td>Treatment group 5</td>
<td>15</td>
<td>19.6±4.8</td>
<td>21.2±6.2</td>
</tr>
</tbody>
</table>

Notes: control group: patients treated with Lixujieyu recipe only; treatment group 1: patients treated with Lixujieyu recipe and Gong-Tune music; treatment group 2: patients treated with Lixujieyu recipe and Gong-Tune music; treatment group 3: patients treated with Lixujieyu recipe and Yu-Tune music; treatment group 4: patients treated with Lixujieyu recipe and Shang-Tune music; treatment group 5: patients treated with Lixujieyu recipe and Zhi-Tune music. *P < 0.05, compared with the control group.

Table 3 Hamilton Depression Scale and Hamilton Anxiety Scale scores before and after treatment (Points, ± ± ±)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>15</td>
<td>11.7±3.2</td>
<td>11.5±3.2</td>
<td>11.4±1.3</td>
<td>10.5±1.8</td>
</tr>
<tr>
<td>Treatment group 1</td>
<td>15</td>
<td>13.3±2.3</td>
<td>7.7±1.8’</td>
<td>11.3±1.3</td>
<td>7.9±1.7’</td>
</tr>
<tr>
<td>Treatment group 2</td>
<td>15</td>
<td>13.3±2.4</td>
<td>7.9±2.0’</td>
<td>11.6±1.3</td>
<td>7.8±1.6’</td>
</tr>
<tr>
<td>Treatment group 3</td>
<td>15</td>
<td>13.1±2.2</td>
<td>11.2±2.2</td>
<td>11.4±1.6</td>
<td>9.5±1.3</td>
</tr>
<tr>
<td>Treatment group 4</td>
<td>15</td>
<td>11.8±3.0</td>
<td>13.0±3.2</td>
<td>11.2±1.7</td>
<td>10.9±1.3</td>
</tr>
<tr>
<td>Treatment group 5</td>
<td>15</td>
<td>11.4±3.4</td>
<td>12.1±2.0</td>
<td>10.8±1.7</td>
<td>11.0±1.6</td>
</tr>
</tbody>
</table>

Notes: control group: patients treated with Lixujieyu recipe only; treatment group 1: patients treated with Lixujieyu recipe and Gong-Tune music; treatment group 2: patients treated with Lixujieyu recipe and Gong-Tune music; treatment group 3: patients treated with Lixujieyu recipe and Yu-Tune music; treatment group 4: patients treated with Lixujieyu recipe and Shang-Tune music; treatment group 5: patients treated with Lixujieyu recipe and Zhi-Tune music; HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale. *P < 0.05 compared with the control group.

2 after 4 weeks of treatment, while in treatment group 4 and 5 the scores increased (Table 3, P < 0.05).
combined with Lixujieyu recipe and Jiao-tune combined with Lixujieyu recipe both have good clinical effectiveness in treatment of CFS. Further research is needed to determine which tune produces a better outcome.

From the view of the Five Zang Viscera, Five Elements, Five Tunes, and Five Minds in TCM theory, all five tunes can relieve mood disorders such as dysphoria, irritability, sorrow and depression. However, the combination of Lixujieyu recipe and Yu-tune, Lixujieyu recipe and Shang-tune, and Lixujieyu recipe and Zhi-tune did not relieve the symptoms of CFS in this study, probably because the CFS patients had liver stagnation and spleen deficiency.

The Yu-tune corresponds with the kidney, and belongs to fear in the Five Minds Theory. In TCM, the kidney is the congenital foundation; it governs bones, and stores the essence and marrow. The main clinical manifestation of patients with CFS is weakness or tiredness in their limbs and muscles, anxiety and depression; however, fear is rarely seen. Therefore, the Yu-tune music combined with Lixujieyu recipe was not likely to relieve symptoms in patients with liver stagnation and spleen deficiency.

The Shang-tune corresponds with the lung, and belongs to sorrow in the Five Minds. The Shang-tune music is cloistered and astringent. Based on the inter-promoting and inter-restraining relationships among the viscera theory that Metal restricts Wood, the Shang-tune is used mainly for syndromes of Qi flow reversal when liver restricts lung due to rage. Patients with CFS have symptoms of chronic fatigue, anxiety and depression, but not rage or anger. Therefore, the astringent Shang-tune music combined with Lixujieyu recipe may cause further depression.

The Zhi-tune corresponds with the heart, and belongs to joy in the Five Minds. Zhi-tune music is lively and fast-paced, and mostly played by Qin, Gu-zheng and percussion music; it flames and rises up like fire, and could excite derailed feelings such as anxiety and dysphoria for patients with CFS. So Zhi-tune music combined with Lixujieyu recipe may also result in the opposite effect to that desired for CFS treatment.

In conclusion, Lixujieyu recipe combined with Gong-tune or Jiao-tune significantly improved CFS symptoms. Five Elements music therapy must be based on the individual clinical features; the tune selected needs to be appropriate for the TCM syndrome of the CFS patient to achieve a better clinical effect than the Lixujieyu recipe alone.

REFERENCES


3 Yao RM. Qiu MY. A preliminary epidemiological study and discussion on TCM pathogenesis of Chronic Fatigue Syndrome in Hong Kong. Zhong Xi Yi Jie He Za Zhi 2006; 3(10): 359-362.


16 Zheng XY. The clinical research guiding principles for new medicine in TCM. Beijing: China Science and Technology Press of Traditional Chinese Medicine, 2002: 364.

