Effect of Huatan Jieyu granules in treatment of Parkinson's disease patients with sleep disorder identified as symptom pattern of phlegma-heat-stirring wind


Both groups were given basic treatment with prednisone. The experimental group of patients was treated with Huatan Jieyu granules and the control group of patients was treated with only the basic treatment. Treatment lasted for 4 weeks. Sleep polygraph were recorded before the study as well as 3 months and 6 months after treatment.

RESULTS: After treated with Huatan Jieyu granules, the total sleep time, and the percentage of non rapid eye movement 2 (NREM 2), non rapid eye movement 3 (NREM 3) and rapid eye movement (REM) sleep period increased significantly, while the percentage of NREM1 sleep period decreased significantly compared with before treatment (P < 0.05).

CONCLUSION: The treatment of PD patients with sleep disorder by Huatan Jieyu granules can improve their sleep structure and their sleep quality.

Keywords: Parkinson disease; Sleep disorder; Phlegma-heat-stirring wind; Sleep polygraph; Huatan Jieyu granules
the quality of life of PD patients are mental disorders, cognitive dysfunction and sleep disorders, especially sleep disorders. One study showed that the prevalence of sleep disorders in PD patients was 82%. There are mainly five types: insomnia with prolonged sleep latency, wakefulness disorders, Rapid eye movement sleep behavior disorder with clinical manifestations such as rapid eye movement sleep behavior disorder and dysfunction syndrome, sleep-related dyskinesia obstruction and sleep-related respiratory disorders. Insomnia is the most common type, accounting for 68.8%-82.4%. The PD patients with sleep disorders are positively correlated with the progression and the motor symptoms, emotional and cognitive disorders will be worsened. At present, The medicine treatment of sleep disorder is limited, and levodopa preparation is the most effective used as the current treatment of PD. But a long-term application will reduce sleep quality. It is known that sleepiness is one of the side effects of the dopamine agonist drugs used in PD patients, and that it may also be induced by L-Dopamine. Higher doses of dopamine agonists were correlated with more sleepiness in PD patients. However, the pathogenesis of PD is still unclear. Studies have shown that it may be related to factors such as neurodegeneration and dopamine replacement therapy, as well as to patients with motor and non-motor impairment. Recently, Tarça etc. studied a new circuitry for sleep regulation in rats and proposed that the pedunculopontine nucleus, substantia nigra pars compacta, and striatum may be involved in pathophysiology of sleep disturbances. Huatan Jieyu granules (HGs) is a prescription composed of a variety of herbal medicine, could improve sleep, vertigo and depressive symptoms. Our previous research found that Huatan Jieyu granules treating the patients with insomnia in symptom pattern of phlegm-heat disturbing heart were compared with the estazolam treating the patients in the second and third weeks. Another study on Huatan Jieyu granules treatment of mild-moderate depression (in symptom pattern of phlegm-heat disturbing heart), the patients got low score in Hamilton Depression Scale (HADM) and Hamilton Anxiety Scale (HADA). Huatan Jieyu granules could ameliorate anxiety somatization disorder, cognitive impairment, blocking disorder and insomnia. The effect of Huatan Jieyu granules were mainly to increase of 5-hydroxytryptamine (5-HT) and Nor-epinephrine (NE) content in rats’ brain and decrease of adreno-cortico-tropic-hormone (ACTH) and cortisol (CORT) level in rats’ blood serum to regulate the hyperactive HPA axis. It is a kind of decoction with the effect of removing heat-phlegm, promoting Qi and soothing the nerves. It is effective in the treatment of non-motor symptoms of PD, especially sleep disorders including insomnia and wakefulness disorders. This study explored the efficacy and safety of HGs in the treatment of sleep disorders in Parkinson’s disease.

In this study, we aimed to investigate the safety and efficacy of Huatan Jieyu granules in treatment of PD patients with sleep disorder identified as symptom pattern of phlegma-heat-stirring wind in terms of theory of Traditional Chinese Medicine (TCM).

**METHODS**

**Design**

This was a randomized, controlled, double blind, clinical study conducted at one center. The researchers were trained in a unified way. The random grouping scheme is stored in each envelope, the envelopes are opened in sequence according to the grouping sequence, and the grouping condition of patients was determined according to the grouping scheme in the envelopes. The sample size was beyond the minimum sample size for clinical study, and the losing ratio was 20%. The duration of the study was 5 weeks (1 week to allow for patient selection, and 4 weeks for the duration of treatment). This study was approved by the Institutional Review Board of the Teaching Hospital of Chengdu University of Traditional Chinese Medicine, with all patients and their guardians giving signed informed consent.

**Participants**

Totally 107 patients with Parkinson’s disease and sleep disorders who met the diagnostic criteria of Parkinson’s Disease with Sleep Disorder were selected from the department of neurology and inpatient department of the hospital of Chengdu university of Chinese medicine, from July 2015 to December 2017. The patients were selected and randomly divided into the experimental group (55 cases) and the control group (52 cases).

**Inclusion criteria**

The inclusion criteria were as follows: (a) patients with primary Parkinson’s disease, diagnosed according to MSD’s diagnostic criteria for Parkinson’s disease (2015); (b) patients with pattern of phlelgma-heat-stirring wind; The patients maybe exhibit some symptoms of head shaking, tremor, hand inability to hold objects, dizziness, fullness and tightness in chest and abdomen, bitterness and stickiness, or even spitting and salvation. The body of the tongue is fat, with teeth marks, red tongue, yellow and greasy tongue coat. (c) patients with sleep disorders at the same time; (d) patients with more than 5 years of education; (f) an age range of 15-70 years; (g) signed the informed consent form and voluntarily participate in this research project.

**Exclusion criteria**

The exclusion criteria were as follows: (a) patients with essential tremor; (b) patients with secondary Parkinson’s disease and Parkinson’s superposition syndrome; (c) patients with other mental disorders and serious
heart and lung diseases affect sleep; (d) patients are participating in other clinical trials.

Medications
The experimental group of patients were treated with basic treatment and HGs (prepared by Hospital of Chengdu University of Traditional Chinese Medicine, with 9 g/bag, HGs contained Coptis chinensis, Tangerine peel, Tuckahoe, Liquorice, Immature bitter orange, Bamboo shavings, Tuber fleeceflower stem, Semen bioricome, Semen ziziphi spinae, Ligusticum chuanxiong and Acorus gramineus.) (Huanglian (Rhizoma Coptidis), Chenpi (Pericarpium Citri Reticulatae), Fuling (Porridge), Gancao (Radix Glycyrrhizae), Zhishi (Fructus Aurantii Immaturi), Zhurui (Caulis Bambusae in Tae-niam), Shouwuteng (Caulis Polygoni Multiflori), Baiziren (Semen Platycladi), Suanzaoren (Semen Ziziphi Spinae), Chuanxiong (Rhizoma Chuanxiong), Shichangpu (Rhizoma Acori Tatarinowii) were taken orally three times daily, 9 g/bag a dose. The control group of patients was treated with basic treatment (Therapeutic drugs including Madopar® between 0.5 g and 1 g were taken 3 to 4 times per day, Sifrol® between 0.375 to 4.5 mg were taken 3 times per day, Benzhexol Hydrochloride Tablets between 8 and 12 mg were taken 3 times per day, and Amantadine Hydrochloride (prepared by Jiangsu pengyao pharmaceutical Co., Ltd., Yixing, China) were taken twice a day, 100 mg.

Outcome measures
Data were captured before beginning drug administration and at before treatment and after treatment 4 weeks.

Endpoints
The outcomes were the Sleep polygraph (PSG). The subjects went to the electroencephalogram room at least 2 h earlier at night according to the usual sleep time, were familiar with the sleep monitoring environment and informed the subjects of the purpose and method of the examination in order to relieve the tension of the subjects. The electrode was installed and the electrode impedance was measured. The subjects were continuously monitored by Sleep polygraph (PSG) all night (≥ 8 h). According to the international calibration method: the surface discoid electrode was used to record F3-A2, F4-C1, C3-A2, C4-A1, O1-A2 and O2-A1. The electroencephalogram signals of patients were recorded by two surface electrodes, and the left and right lateral canthus and upper and lower sides of the mental region were recorded by the electromyography of the mental region and the left and right lateral canthus. One electrode was placed at cm to record the eye movement of the left and right eyes, and the impedance chest and abdominal motility sensor was used to record the eye movement of the left and right eyes respectively. The respiratory motility of chest and abdomen was recorded by pressure sensor placed in nasal vestibule, snoring, limb movement was recorded by bilateral calf fixed displacement sensor, and posture and potential of body were measured by chest fixed sensor. The blood oxygen saturation of the right index finger was monitored synchronously by blood oxygen saturation sensor.

The polysomnography and AnalysisManager sleep analysis soft (The N7000 60, produced by Rembrandt Embla Company, America). Monitoring items include electroencephalogram, eye movement electrogram, submental electromyography, snoring, mouth and nose airflow, and blood oxygen saturation and degree, electrocardiogram, leg electricity, somatosensory, synchronous video recording attention to the behavior of patients during sleep at night. The total sleep time, sleep efficiency, the percentage of sleep in total sleep time, wake-up index and so on were analyzed. After manual correction, the relevant data should be calculated automatically.

Safety indices
General medical examination, regular blood and urine tests, electrocardiography (ECG), liver function, renal function and adverse events (signs and symptoms) were recorded before the study as well as 4 weeks.
Statistics analysis
All data were processed with SPSS 21.0 (IBM Corp. Released 2012. IBM Statistics for Windows, Version 21.0. Armonk, NY, USA). Quantitative data fitting a normal distribution was expressed as mean ± standard deviation (\( \bar{x} \pm s \)), while ill-fitting data were analyzed using non-parametric tests. The \( \chi^2 \) test was used for enumerated data. An independent sample t-test was used for quantitative data fitting a normal distribution when there was equal variance between two groups. A paired sample t-test was used to compare the data from the two groups before and after treatment. Quantitative data not fitting a normal distribution or data with an unequal variance was analyzed using a Wilcoxon rank sum test. \( P < 0.05 \) was considered as a statistically significant difference.

RESULTS
Enrollment and completion
In total, 130 cases of Parkinson’s disease and sleep disorders were preliminarily selected. Reasons for withdrawal during enrollment were as follows. There were 5 cases that did not meet the inclusion criteria. Two patients declined to participate. Three cases were withdrawn for other reasons. Thereafter, 125 cases were randomly divided into two groups by simple randomization using random number tables, with 63 cases assigned to the treatment group and 62 cases to the control group. 4 patients withdrew from the treatment group and 6 patients withdrew from the control group. Reasons for withdrawal during the test were as follows. 4 cases were unable to tolerate the PSG from the treatment group and 6 cases were unable to tolerate the PSG from the control group. 4 cases from the treatment group were lost to follow-up. 4 cases from the control group were lost to follow-up. As a result, 107 patients completed the study, with 55 cases in the treatment group and 52 cases in the control group (Figure 1).

Baseline comparison
Among the two groups there were no significant differences in sex and age (\( P > 0.05 \), Table 1). There is no statistically significant difference in total sleep time, the non-rapid eye movement sleep (NREM) comprised (N1, N2, N3); and rapid eye movement sleep (REM) and the number of wakefulness between the two groups (\( P > 0.05 \), Table 1).

Comparison of the PSG index
Both of the in this study, the pre-treatment levels of

![Consolidation Flow Chart](https://www.journaltcm.com)
that the combination of the TCM and Western Medicine meta-analysis of the treatment of Parkinson’s disease body disturbed mind excessively lead to insomnia. A in PD patients. So, Phlegm-Dampness retention in the
12%, which is the common symptom pattern found.

8% the factor that makes the disease worse. Among them, 23% for non rapid eye movement 1; N2: non rapid eye movement 2; N3: non rapid eye movement 3; REM: rapid eye movement. *P > 0.05, compared with control group.

Studies on the distribution of PD symptom patterns also show that kidney deficiency and spleen deficiency are the keys to the pathogenesis. The spleen and kidney deficiency pattern accounts for 22.4%, and the spleen and kidney Yang deficiency pattern accounts for 16%, but it is damp. The blood stasis is the factor that makes the disease worse. Among them, the hot air pattern type accounts for 12.8%, which is the common TCM symptom pattern in PD patients. However, the body of the dampness is so disturbing that it is not disturbing. “Medical Standards of Orchid Chamber, The Royal Library” said “The doctor must first recognize the name of the disease, and then consider its treatment. Different diseases can have their own special prescriptions and special drugs. The treatment of diseases should be based on its essence, combined with disease and symptom pattern, and cannot be used blindly, subjectively and randomly. The treatment of diseases should be based on its essence, combined with disease and symptom pattern, and cannot be used blindly, subjectively and randomly. We find that clinically, PD patients with sleep disorders are mostly identified as with hot-wind pattern. Phlegm resolve depres-

Evaluation of safety
The adverse reactions in the control group and the experimental group were similar. In the experimental group, 3 patients suffered from mild nausea and 2 patients had abdominal distension. In the control group, 2 patients suffered from mild nausea, 1 experienced moderate diarrhea, and 1 patient had abdominal distension. There was no significant difference in the number of adverse reactions between the two groups (*P > 0.05).

DISCUSSION
Studies on the distribution of PD symptom patterns show that kidney deficiency and spleen deficiency is the key to the pathogenesis. The spleen and kidney deficiency pattern accounts for 22.4%, and the spleen and kidney Yin deficiency pattern accounts for 18.4%, and the spleen and kidney Yang deficiency pattern accounts for 16%, but it is phlegm-dampness, the static blood is the factor that makes the disease worse. Among them, the pheclegm-dampness retention in the body disturbed mind excessively lead to insomnia. A meta-analysis of the treatment of Parkinson’s disease sleep disorders by TCM and Western Medicine shows that the combination of the TCM and Western Medicine is superior to the treatment of Western Medicine alone, and in terms of safety assessment, the incidence of adverse events in the treatment group is significantly lower than that of Western Medicine alone. A meta-analysis of TCM assisted levodopa treating Parkinson’s disease indicated that TCM combined with levodopa could alleviate the progression of Parkinson’s disease and improve the movement state of patients. Studies on the distribution of PD symptom patterns also show that kidney deficiency and spleen deficiency are the keys to the pathogenesis. The spleen and kidney deficiency pattern accounts for 22.4%, and the spleen and kidney Yang deficiency pattern accounts for 16%, but it is damp. The blood stasis is the factor that makes the disease worse. Among them, the hot air pattern type accounts for 12.8%, which is the common TCM symptom pattern in PD patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>N (M/F)</th>
<th>Mean age (years)</th>
<th>Total sleep time</th>
<th>N1 (%)</th>
<th>N2 (%)</th>
<th>N3 (%)</th>
<th>REM (%)</th>
<th>Arousal index (time/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>27/28</td>
<td>67±10</td>
<td>328±10</td>
<td>58±20</td>
<td>30±15</td>
<td>2±5</td>
<td>9±5</td>
<td>10±6</td>
</tr>
<tr>
<td>Control</td>
<td>25/27</td>
<td>66±11</td>
<td>322±87</td>
<td>58±14</td>
<td>33±9</td>
<td>2±4</td>
<td>8±5</td>
<td>10±5</td>
</tr>
</tbody>
</table>

Notes: patients in the experimental group were treated with HGs (orally three times daily, 9 g/bag a dose, for 4 weeks). Patients in the control group were treated with HGs analogue agent (orally three times daily, 9 g/bag a dose, for 4 weeks). M: male; F: female; N1: non rapid eye movement 1; N2: non rapid eye movement 2; N3: non rapid eye movement 3; REM: rapid eye movement. *P > 0.05, compared with control group.

Table 1 Comparison of basic clinical characteristics and the PSG parameters between the two groups ( ± s)

<table>
<thead>
<tr>
<th>Group</th>
<th>Total sleep time</th>
<th>N1 (%)</th>
<th>N2 (%)</th>
<th>N3 (%)</th>
<th>REM (%)</th>
<th>Arousal index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>356±88</td>
<td>39±13</td>
<td>46±10</td>
<td>3±5</td>
<td>13±6</td>
<td>8±4</td>
</tr>
<tr>
<td>Control</td>
<td>321±87</td>
<td>56±12</td>
<td>34±9</td>
<td>1±3</td>
<td>8±5</td>
<td>9±5</td>
</tr>
</tbody>
</table>

Notes: patients in the experimental group were treated with HGs (orally three times daily, 9 g/bag a dose, for 4 weeks). Patients in the control group were treated with HGs analogue agent (orally three times daily, 9 g/bag a dose, for 4 weeks). N1: non rapid eye movement 1; N2: non rapid eye movement 2; N3: non rapid eye movement 3; REM: rapid eye movement 1; *P > 0.05, *P < 0.05, compared with control group.
quality of patients. The mechanism behind the action of HGs on PD sleep disorder needs to be further studied, especially for insomnia and Rapid eye movement sleep behavior disorder. However, it has good clinical efficacy and safety for patients with PD sleep disorders.

REFERENCES


13. Li Q. Experimental research on the influence of Huatanjiejuyu prescriptions on expression of HPA and central neurotransmitter 5-HT and NE caused by CUMS. Chengdu: Chengdu university of Traditional Chinese Medicine, 2016: 24-35.


