Postprint: Clinical Efficacy of Chaihu Jia Longgu Muli Decoction Combined with Cognitive Behavioral Therapy for Insomnia in the Treatment of Acute Insomnia with Liver Depression Transforming into Fire Pattern

Authors: Yu Xuefang, Zhu Min, Ma Qinglin, Tan Shenlang, Wu Zixing, Jiang Wei, Wu Zixing, Jiang Wei

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Abstract

Background Acute insomnia of the Liver Depression Transforming into Fire pattern originates from emotional dysregulation, leading to heart disturbance and insomnia. The therapeutic principle focuses on soothing the liver and relieving depression, clearing heat and draining fire, and calming the spirit. Chaihu Jia Longgu Muli Decoction possesses sedative and spirit-calming effects, while Cognitive Behavioral Therapy for Insomnia (CBT-I) is recommended as the first-line non-pharmacological treatment for insomnia. Currently, research on the combination of Chaihu Jia Longgu Muli Decoction and CBT-I for acute insomnia of the Liver Depression Transforming into Fire pattern remains scarce.

Objective This study aims to evaluate the clinical efficacy of Chaihu Jia Longgu Muli Decoction combined with CBT-I in patients with acute insomnia of the Liver Depression Transforming into Fire pattern.

Methods A total of 90 patients diagnosed with acute insomnia of the Liver Depression Transforming into Fire pattern who visited the 901st Hospital of the Joint Logistics Support Force of the Chinese People' s Liberation Army between March 2023 and September 2024 were selected as study subjects. Patients were divided into a control group (45 cases) and an observation group (45 cases) using the random number table method. The control group received CBT-I intervention, while the observation group received combined treatment with Chaihu Jia Longgu Muli Decoction on the basis of CBT-I. Both groups underwent 4 weeks of intervention. Study evaluation indicators included: (1) improvement in clinical symptoms (Traditional Chinese Medicine syndrome scores); (2) sleep

quality parameters [Pittsburgh Sleep Quality Index (PSQI) scores, photoplethysmography (PPG) monitoring indices]; (3) emotional state indicators [Hamilton Anxiety Scale (HAMA) scores, Hamilton Depression Scale (HAMD) scores]; (4) serum biomarker levels [tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), 5-hydroxytryptamine (5-HT)]; (5) clinical efficacy and safety.

Results The total clinical effective rate in the observation group [88.89% (40/45)] was significantly superior to that in the control group [66.67% (30/45), $2 = 14.284$, $P < 0.05$]. Intra-group comparisons revealed that, compared with pre-treatment values, both groups exhibited significant increases in total sleep time, sleep efficiency, and 5-HT levels after treatment ($P < 0.05$), along with significant decreases in sleep latency, number of awakenings, PSQI scores, HAMA scores, HAMD scores, Traditional Chinese Medicine syndrome scores, and inflammatory factor (TNF-α, IL-1β) levels ($P < 0.05$). Post-treatment inter-group comparisons demonstrated that all aforementioned indicators in the observation group were significantly superior to those in the control group ($P < 0.05$). No statistically significant difference was observed in the incidence of adverse events between the control and observation groups ($2 = 0.511$, $P > 0.05$).

Conclusion The combination of Chaihu Longgu Muli Decoction and CBT-I is safe and feasible for treating acute insomnia of the Liver Depression Transforming into Fire pattern, effectively improving patients' sleep quality, alleviating emotional disturbances, reducing Traditional Chinese Medicine syndrome scores, regulating neurotransmitter levels, and suppressing inflammatory responses, with therapeutic outcomes superior to CBT-I alone.

Full Text

Clinical Efficacy of Bupleurum and Dragon Bone and Oyster Decoction Combined with Cognitive Behavioral Therapy for Insomnia in the Treatment of Acute Insomnia of Liver Qi Stagnation with Fire Transformation Type

YU Xuefang[1], **ZHU Min**[2], **MA Qinglin**[2], **TAN Shenlang**[2], **WU Zixing**[3], ***JIANG Wei***[3]

[1]Department of Traditional Chinese Medicine, the 901st Hospital of the Joint Logistics Support Force of the Chinese People' s Liberation Army, Hefei 230031, China
[2]Graduate School, Wannan Medical College, Wuhu 241003, China
[3]Department of General Practice, the 901st Hospital of the Joint Logistics Support Force of the Chinese People' s Liberation Army, Hefei 230031, China

Corresponding authors: WU Zixing, Attending physician; E-mail: 799285457@qq.com; JIANG Wei, Associate chief physician; E-mail: 2408797210@qq.com

Abstract

Background: Acute insomnia of the liver qi stagnation with fire transformation type originates from emotional imbalance that disturbs the heart and causes sleeplessness. Treatment focuses on soothing the liver, relieving depression, clearing heat, purging fire, and calming the mind. Bupleurum and Dragon Bone and Oyster Decoction has sedative and mind-calming effects, while Cognitive Behavioral Therapy for Insomnia (CBT-I) is recommended as the first-line non-pharmacological treatment for insomnia. Currently, few studies have investigated the combination of Bupleurum and Dragon Bone and Oyster Decoction with CBT-I for this specific pattern of acute insomnia.

Objective: This study aimed to systematically evaluate the clinical efficacy of Bupleurum and Dragon Bone and Oyster Decoction combined with CBT-I in patients with acute insomnia of liver qi stagnation with fire transformation type.

Methods: From March 2023 to September 2024, 90 patients meeting diagnostic criteria for acute insomnia of liver qi stagnation with fire transformation type were enrolled at the 901st Hospital of the Joint Logistics Support Force of the Chinese People' s Liberation Army. Using a random number table method, patients were allocated to either a control group (n=45) or an observation group (n=45). The control group received CBT-I alone, while the observation group received Bupleurum and Dragon Bone and Oyster Decoction in addition to CBT-I. Both groups underwent 4 weeks of intervention. Evaluation indices included: (1) clinical symptom improvement (Traditional Chinese Medicine syndrome scores); (2) sleep quality parameters [Pittsburgh Sleep Quality Index (PSQI) scores and photoplethysmography (PPG) monitoring indices]; (3) emotional status indicators [Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD) scores]; (4) serum biomarker levels [tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and 5-hydroxytryptamine (5-HT)]; (5) clinical efficacy and safety.

Results: The total clinical effective rate in the observation group [88.89% (40/45)] was significantly higher than that in the control group [66.67% (30/45), ^{2}=14.284, P<0.05]. Within-group comparisons revealed that both groups showed significant increases in total sleep time, sleep efficiency, and 5-HT levels after treatment compared with baseline (P<0.05), while sleep latency, awakening frequency, PSQI scores, HAMA scores, HAMD scores, TCM syndrome scores, and inflammatory factor levels (TNF-α, IL-1β) decreased significantly (P<0.05). Between-group comparisons after treatment demonstrated that all these indices were significantly better in the observation group than in the control group (P<0.05). There was no significant difference in adverse event incidence between the two groups (^{2}=0.511, P>0.05).

Conclusion: The combination of Bupleurum and Dragon Bone and Oyster Decoction with CBT-I is safe and feasible for treating acute insomnia of liver qi stagnation with fire transformation type. This approach effectively improves sleep

quality, alleviates emotional disturbances, reduces TCM syndrome scores, regulates neurotransmitter levels, and suppresses inflammatory responses, demonstrating superior therapeutic efficacy compared with CBT-I alone.

Keywords: Sleep initiation and maintenance disorders; Acute insomnia; Liver qi stagnation with fire transformation; Chaihu; Longgu Muli Tang; Cognitive behavioral therapy

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1. Materials and Methods

1.1 General Information

We prospectively enrolled 90 patients who met diagnostic criteria for acute insomnia of liver qi stagnation with fire transformation type at the 901st Hospital of the Joint Logistics Support Force of the Chinese People' s Liberation Army between March 2023 and September 2024. Using the random number table method, patients were divided into a control group and an observation group, with 45 cases in each group. The study protocol was approved by the Medical Ethics Committee of the 901st Hospital of the Joint Logistics Support Force of the Chinese People' s Liberation Army (Ethics Approval No.: 202107001).

Diagnostic Criteria: (1) Western medicine diagnosis followed the clinical diagnostic criteria for acute insomnia in the *International Classification of Sleep Disorders (Third Edition)* [10]. (2) Traditional Chinese medicine diagnosis referred to the "Insomnia" section of the *Diagnostic and Therapeutic Criteria of TCM Diseases* (Standard No. ZYT001.1-94), with specific pattern differentiation criteria established for liver qi stagnation with fire transformation type. The main symptoms were defined as: insomnia (difficulty falling asleep) and restlessness preventing sleep. Secondary symptoms included: irritability and anger, chest tightness and hypochondriac pain, headache, flushed face and red eyes, bitter taste in mouth, constipation, and dark urine. Tongue and pulse manifestations: red tongue tip with yellow coating, wiry and rapid pulse. Insomnia and tongue/pulse signs were required, plus 3-4 additional main or secondary symptoms for diagnosis.

Inclusion Criteria: (1) Age 18-65 years; (2) Insomnia symptoms $ $3 times per week with duration <3 months; (3) PSQI score >7; (4) No prior treatment for insomnia; (5) Ability to cooperate with the study and provide informed consent.

Exclusion Criteria: (1) Alcohol or drug dependence; (2) Comorbid serious heart, lung, liver, or kidney disease; (3) Psychiatric disorders or severe emotional disturbances (HAMA score $ $29 or HAMD score $ $24); (4) Pregnancy or lactation; (5) Allergy to study medications.

Baseline comparisons showed no significant differences between the two groups in age, sex, BMI, disease duration, or education level (P>0.05) .

1.2 Treatment Methods

1.2.1 Control Group Treatment The control group received CBT-I intervention consisting of: (1) Sleep hygiene education: researchers provided patients with the *Sleep Hygiene Education Guide* and instructed them to study its contents carefully to enhance sleep cognition; (2) Stimulus control therapy: limiting time spent in bed or bedroom while awake to strengthen the association between bed, bedroom, and sleep; (3) Sleep restriction therapy: individualizing sleep schedules to balance time in bed with average total sleep time; (4) Relaxation training: implementing muscle relaxation techniques; (5) Cognitive therapy: maintaining communication with patients to correct erroneous cognitions.

1.2.2 Observation Group Treatment The observation group received Bupleurum and Dragon Bone and Oyster Decoction in addition to CBT-I. The herbal formula consisted of: Bupleurum 24 g, Scutellaria, Ginger, Ginseng, Concha Margaritifera, Poria, Cinnamomum, Calcined Dragon Bone and Oyster Shell each 9 g, Pinellia 15 g, Rheum palmatum 12 g, and Jujube 6 pieces. The decoction was administered warm at 200 mL per dose, twice daily. Both groups received continuous treatment for 4 weeks.

1.3 Evaluation Indices

1.3.1 Clinical Efficacy Assessment Clinical efficacy was classified as cured, markedly effective, effective, or ineffective. *Cured*: complete resolution of sleep disturbance symptoms, ability to fall asleep rapidly with no nocturnal awakenings, PSQI score reduction $ $75%; *Markedly effective*: significant improvement in sleep quality, shortened sleep latency with occasional 1-2 nocturnal awakenings, PSQI score reduction 50%-<75%; *Effective*: improved sleep status but without significant change in sleep latency, PSQI score reduction 25%-<50%; *Ineffective*: no improvement in insomnia symptoms, unchanged sleep latency, PSQI score reduction <25%. Total effective rate = (cured + markedly effective + effective cases)/total cases $×$100%.

1.3.2 Objective Sleep Quality Monitoring Photoplethysmography (PPG, Morpheux Ox model) was used for overnight sleep quality monitoring (22:00-06:00). Data were collected before treatment and after 4 weeks of intervention. All PPG signals were transmitted via cloud server and automatically processed by Morpheux Ox professional analysis software to obtain key sleep parameters including total sleep time, sleep latency, sleep efficiency, and awakening frequency.

1.3.3 Sleep, Anxiety, and Depression Scale Assessments PSQI, HAMA, and HAMD scales were administered before treatment and after 4 weeks. The PSQI contains 7 dimensions assessing subjective sleep quality over the past month, with total scores ranging 0-21; scores $ $7 indicate good sleep quality,

with higher scores reflecting more severe sleep disturbance. The HAMA comprises 14 items using a 5-point scoring system (0-4). Anxiety severity is classified as: <7 = no anxiety, 7-13 = possible anxiety, 14-20 = definite anxiety, 21-28 = prominent anxiety, $ $29 = severe anxiety. The HAMD consists of 17 items using the same 5-point scoring system, with depression severity classified as: <7 = no depression, 7-16 = possible depression, 17-23 = mild to moderate depression, $ $24 = severe depression.

1.3.4 Traditional Chinese Medicine Syndrome Score Assessment TCM syndrome scores were recorded before treatment and after 4 weeks. We developed the *TCM Syndrome Grading and Quantification Scale* to quantify main symptoms (difficulty falling asleep, chest tightness and hypochondriac pain, irritability) and secondary symptoms (headache with flushed face, bitter taste, red eyes, dark urine and constipation). Symptom severity was graded using a 4-level system (none, mild, moderate, severe), with main symptoms scored 0, 2, 4, 6 points and secondary symptoms/tongue-pulse manifestations scored 0, 1, 2, 3 points; higher scores indicated more severe clinical symptoms.

1.3.5 Serum Biomarker Level Determination Fasting venous blood samples (5 mL) were collected in the morning at baseline and after 4 weeks of treatment. Samples were left at room temperature for 30 minutes, then centrifuged at 3,000 rpm for 5 minutes (radius 15 cm). Serum was aliquoted and stored at -80°C until analysis. ELISA was used to quantitatively detect serum TNF-α, IL-1β, and 5-HT levels. All assay kits were purchased from Wuhan GeneMay Biotechnology Co., Ltd., and experiments were performed strictly according to the manufacturer' s standard operating procedures.

1.3.6 Safety Assessment Adverse events during treatment were recorded for both groups to evaluate safety.

1.4 Statistical Methods

SPSS 22.0 software was used for data analysis. Normality of quantitative data was tested using the Shapiro-Wilk test. Normally distributed data are expressed as mean ± standard deviation ($\bar{x}\pm s$), with within-group comparisons using paired samples t-test and between-group comparisons using independent samples t-test. Categorical data are expressed as percentages or constituent ratios, with between-group differences analyzed using ^{2} test. All statistical tests were two-tailed, with significance level set at α=0.05 and P<0.05 considered statistically significant.

2. Results

2.1 Comparison of Clinical Efficacy Between Groups

The total effective rate in the observation group (88.89%, 40/45) was significantly higher than in the control group (66.67%, 30/45), with statistically significant difference (^{2}=14.284, P<0.05) .

2.2 Comparison of PPG Sleep Monitoring Parameters Before and After Treatment

Before treatment, no significant differences were observed between groups in total sleep time, sleep latency, sleep efficiency, or awakening frequency (P>0.05). After treatment, the observation group showed increased total sleep time and sleep efficiency, and decreased sleep latency and awakening frequency compared with the control group (P<0.05). Within-group comparisons revealed that both groups demonstrated increased total sleep time and sleep efficiency, and decreased sleep latency and awakening frequency after treatment (P<0.05) .

2.3 Comparison of Sleep, Anxiety, and Depression Scale Scores Before and After Treatment

Before treatment, no significant differences were found between groups in PSQI, HAMA, or HAMD scores (P>0.05). After treatment, the observation group showed significantly lower PSQI, HAMA, and HAMD scores compared with the control group (P<0.05). Within-group comparisons demonstrated that both groups had significantly reduced PSQI, HAMA, and HAMD scores after treatment (P<0.05) .

2.4 Comparison of TCM Syndrome Scores Before and After Treatment

No significant differences were observed between groups in main symptom, secondary symptom, or tongue-pulse syndrome scores before treatment (P>0.05). After treatment, both groups showed significantly reduced TCM syndrome scores compared with baseline (P<0.05), with the observation group demonstrating significantly greater reductions than the control group (P<0.05) .

2.5 Comparison of Serum TNF-α, IL-1β, and 5-HT Levels Before and After Treatment

No significant differences were found between groups in serum TNF-α, IL-1β, or 5-HT levels before treatment (P>0.05). After treatment, the observation group showed significantly decreased TNF-α and IL-1β levels and increased 5-HT level compared with the control group (P<0.05). Within-group comparisons revealed that both groups had significantly reduced TNF-α and IL-1β levels and increased 5-HT level after treatment (P<0.05) .

2.6 Safety Assessment

During the study, no adverse events such as dizziness, nausea, or vomiting were observed in the control group. In the observation group, one case of dizziness and one case of nausea occurred (4.44%). No statistically significant difference was found between groups (^{2}=0.511, P>0.05).

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3. Discussion

Acute insomnia is a common condition that often has clear precipitating factors and may resolve spontaneously, leading to insufficient clinical attention. However, epidemiological studies abroad have reported an annual incidence of acute insomnia of approximately 36% in the general population, with nearly 40% of cases progressing to persistent sleep disorders [11-12]. These data indicate that acute insomnia not only has high prevalence but also significant chronicity potential, necessitating active clinical intervention. In Traditional Chinese Medicine, insomnia belongs to the category of "non-sleep" (不寐), with etiology primarily related to emotional disturbance, improper diet, and imbalance between work and rest [13-14]. Acute insomnia of liver qi stagnation with fire transformation type specifically stems from emotional dysregulation causing liver qi constraint, which transforms into fire over time; this fire then disturbs the heart, leading to loss of mental tranquility and resulting in insomnia [15].

Current pharmacological treatment for insomnia primarily relies on benzodiazepine sedative-hypnotic agents, which carry risks of dependence, cognitive impairment, tolerance, and concurrent anxiety or depression with long-term use, limiting their clinical application [16-17]. CBT-I aims to help patients establish good sleep hygiene habits and is recommended as the first-line non-pharmacological approach, but it demands high patient cooperation and adherence. Clinical practice shows that many insomnia patients have poor compliance, with studies indicating that CBT-I alone achieves only 60% effectiveness [18]. Bupleurum and Dragon Bone and Oyster Decoction, first recorded in the *Treatise on Cold Damage Diseases* (伤寒论), addresses the fundamental pathomechanism of phlegm-heat disturbing the spirit. In this formula, Bupleurum and Scutellaria harmonize the Shaoyang; Pinellia and Ginger regulate the middle-jiao and spleen-stomach pivot; Ginseng and Jujube support upright qi to expel pathogenic factors and harmonize the middle; Dragon Bone, Oyster Shell, and Concha Margaritifera are heavy settling substances that calm the spirit, suppress liver yang, and tranquilize the mind; Poria is a light seeping agent that also calms the heart spirit; Cinnamomum frees yang and transforms qi, while Rheum palmatum drains heat from the bowels. These two medicinals together facilitate the Triple Burner, allowing constrained heat in the bowels to be vented. The combined formula disperses constrained heat from Shaoyang, heavily settles and calms the spirit, and expels pathogenic factors while harmonizing the middle, precisely matching the fundamental pathomechanism of liver qi stagnation

with fire transformation insomnia [19-20].

Therefore, this study employed Bupleurum and Dragon Bone and Oyster Decoction combined with CBT-I for patients with acute insomnia of this pattern. Clinical data revealed that the combined treatment group achieved a total effective rate of 88.89%, significantly higher than the 66.67% in the CBT-I alone group. Furthermore, TCM syndrome score assessments showed significant reductions from baseline in both groups, with the combined treatment group demonstrating markedly superior symptom improvement compared with CBT-I monotherapy. These findings confirm that the synergistic treatment approach yields superior clinical efficacy for acute insomnia of liver qi stagnation with fire transformation type.

Current insomnia practice relies heavily on subjective scales, lacking objective assessment methods. Although polysomnography (PSG) is the gold standard for evaluating sleep quality and architecture, its complexity, high cost, and poor patient comfort limit widespread clinical use. Photoplethysmography (PPG) monitoring offers advantages of simplicity, non-invasiveness (requiring only a wrist-worn device), and high patient acceptance, showing good clinical application prospects. Previous studies have confirmed significant consistency between PPG and PSG across multiple sleep parameters [21]. This study used PSQI and PPG monitoring to assess subjective and objective sleep quality before and after treatment. After 4 weeks of intervention, both groups showed significant improvements, including increased total sleep time, reduced sleep latency, improved sleep efficiency, and decreased nocturnal awakenings. Notably, the combined treatment was significantly superior to CBT-I alone in improving total sleep time, sleep efficiency, sleep latency, and awakening frequency.

Additionally, HAMA and HAMD scales were used to quantify anxiety and depression. The combined treatment group showed significantly greater reductions in HAMA and HAMD scores compared with CBT-I alone, indicating that the integrated approach not only improved sleep quality but also effectively alleviated emotional disturbances. This suggests that improving sleep quality may be an important pathway for relieving emotional disorders, a finding consistent with previous research emphasizing the interplay between sleep, depression, and anxiety [22].

Advancing research on sleep physiology has revealed the crucial role of inflammatory mediators and neurotransmitter secretion imbalance in sleep regulation. Multiple studies have demonstrated that functional abnormalities in pro-inflammatory cytokines and neurotransmitter systems significantly impact sleep-wake cycle formation and maintenance [23]. The IL-1 superfamily of cytokines has been identified as genes involved in sleep homeostasis, with IL-1β serving as an important inflammatory regulator in sleep pathophysiology [24]. Research has shown that elevated serum IL-1β correlates with impaired sleep quality in elderly women [25], and that improvement in insomnia symptoms in major depressive patients is associated with decreased serum IL-1β [26]. TNF-α, a key trigger of inflammatory cascades, induces release of various inflammatory

factors during early inflammatory responses and regulates sleep quality [27]. Studies indicate that higher TNF-α expression correlates with increased slow-wave sleep proportion [28], and our previous research demonstrated that serum TNF-α concentrations in elderly insomnia patients correlate positively with disease severity [29]. These findings collectively highlight the important role of IL-1β and TNF-α in sleep regulation.

This study demonstrated that effective treatment significantly alleviated not only sleep disturbances and emotional problems but also markedly reduced serum levels of specific inflammatory factors (TNF-α, IL-1β). Furthermore, 5-HT, as a crucial neurotransmitter, plays a key role in regulating sleep-wake rhythms and has been confirmed by multiple studies to promote sleep [30]. Clinical evidence shows that 5-HT significantly enhances slow-wave sleep depth, thereby improving overall sleep architecture and efficiency [31-32]. Our data revealed that the combined treatment group showed a more pronounced increase in serum 5-HT level compared with CBT-I alone, providing strong evidence for the neuroendocrine and sleep quality benefits of this integrated approach. Related research has also found that this formula can upregulate dopaminergic neurotransmitter concentrations in the cerebral cortex while significantly increasing 5-HT levels in the striatum [33], consistent with our observations.

In conclusion, Bupleurum and Dragon Bone and Oyster Decoction combined with CBT-I is safe and feasible for treating acute insomnia of liver qi stagnation with fire transformation type. This integrated approach effectively improves sleep quality, alleviates emotional disturbances, reduces TCM syndrome scores, regulates neurotransmitter (5-HT) levels, and suppresses inflammatory responses (TNF-α, IL-1β),

Note: Figure translations are in progress. See original paper for figures.