

Effect of Huo Li Su Oral Solution Combined with Zopiclone in the Treatment of Insomnia Symptoms

ABSTRACT

Objective: Insomnia is a common symptom in subhealthy states. In patients, long-term insomnia symptoms can lead to decreased immune function, even mental depression, thus seriously affecting quality of life. Therefore, this study aims to observe the therapeutic effect of huo li su (HLS) oral solution combined with zopiclone in the treatment of insomnia to find suitable drugs for treatment.

Methods: A total of 161 patients with insomnia from January 2017 to March 2022 were selected in this retrospective cohort study. The patients were divided into the observation (82 cases, receiving HLS oral solution and zopiclone) and control (79 cases, receiving zopiclone alone) groups in accordance with therapeutic drug administration. The differences in the scores of the 2 groups on the Sleep Disorder Scale (SDRS), Pittsburgh Sleep Quality Index (PSQI), Fatigue Inventory 14 (FS-14), and traditional Chinese medicine (TCM) syndromes before and after treatment were compared.

Results: No significant differences in age, gender, disease duration, body mass index (BMI), and other general data were found between the 2 groups ($P > .05$). The TCM syndrome, PSQI, FS-14, and SDRS scores before treatment of the 2 groups were not significantly different ($P < .05$). After 4 weeks of treatment, the TCM syndrome, PSQI, FS-14, and SDRS scores of the observation group were significantly lower than those of the control group.

Conclusion: HLS oral solution combined with zopiclone can effectively improve insomnia symptoms and is superior to zopiclone alone.

Keywords: Clinical effect, Huo li su oral solution, insomnia symptoms in traditional Chinese medicine syndromes

Introduction

People with insomnia symptoms are usually dissatisfied with the quality or duration of their sleep.¹ The main clinical manifestations of insomnia include difficulty falling asleep and returning to sleep after waking, inability to sleep deeply, and dreaminess. Long-term insomnia affects the quality of life of patients and leads to fear, anxiety, and other adverse emotions, thus threatening human health.² The pathogenesis of insomnia symptoms in patients has not been fully elucidated yet but may be related to excessive arousal, cytokine, melatonin, and receptor mechanisms.³ The treatment of insomnia symptoms remains dominated by drugs, among which sleeping pills are the first choice because of their rapid effectiveness; however, addiction and dependence on sleeping pills exert as much psychological pressure on doctors and patients as insomnia itself.⁴ Zopiclone is a commonly used drug in the clinical treatment of insomnia symptoms in patients. It can shorten sleep latency, increase sleep duration, reduce the number of night awakenings, and improve sleep quality. Zopiclone, a nonbenzodiazepine drug, has a short half-life and has minimal residual effects on the following day.⁵ However, it can still lead to tolerance, dependence, and withdrawal symptoms.⁶ The sudden discontinuation of zopiclone after long-term use can cause symptoms of rebound insomnia, nausea, vomiting, and anxiety and even muscle tremors and confusion.



Lin Cong¹ 

Zili Zhou² 

¹Department of Dermatology, Sichuan Second Hospital of T.C.M, Chengdu, Sichuan, China

²Department of Gastroenterology, Sichuan Second Hospital of T.C.M, Chengdu, Sichuan, China

Corresponding author:

Lin Cong
✉ 429841267@qq.com

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Huo li su oral liquid (HLS) is composed of *Reynoutria multiflora* (Thunb.) Moldenke, *moldenke* (Polygonaceae; Polygoni Multiflora Radix Praeparata) and *Epimedium brevicornu* Maxim and has the functions of replenishing qi and blood, nourishing the liver and kidney, and calming nerves.⁷ Huo li su oral liquid can increase superoxide dismutase content and play an antiaging role as well as increase the amplitude of human cerebral blood flow and improve cerebral blood flow supply; it is used clinically mainly for the treatment of neurasthenia and insomnia or depression associated with cerebrovascular disease.⁸ As a well-known traditional Chinese medicine (TCM) prescription, HLS has almost no side effects. However, a small number of patients may experience drug allergies when taking HLS.⁹

Studies have shown that the combination of TCM and zopiclone can improve sleep disorders in patients with insomnia.¹⁰ Therefore, we intend to identify the best drug to treat insomnia symptoms by observing the effect of HLS oral liquid combined with zopiclone on insomnia symptoms in patients. Relevant research on this effect does not exist.

Methods

Patient Selection

A total of 161 patients with insomnia symptoms were selected on the basis of electronic medical records in our hospital from January 2017 to March 2022 to join this retrospective cohort study. The patients were divided into the observation (82 cases) and control (79 cases) groups in accordance with the administration of different therapeutic drugs. The control group was treated with conventional zopiclone, and the observation group was treated with HLS oral solution combined with zopiclone. Clinicians reassessed the sleep conditions and clinical data of the patients before the start of the study. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Sichuan Second Hospital of Traditional Chinese Medicine (2023Lunshen-76), and the recruited patients were informed and signed informed consent forms. The diagnostic criteria for insomnia symptoms and inclusion and exclusion criteria for patients are given below.

Diagnostic Criteria

The diagnostic criteria in the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) were adopted, as follows¹¹: (1) Symptom criteria: Insomnia is almost the only symptom and includes difficulties falling asleep, maintaining sleep, returning to sleep, and falling asleep again after waking up early; discomfort after waking up; fatigue; daytime sleepiness; or poor sleep quality. (2) Serious criteria: The dissatisfaction of the patient with their sleep

time and quality causes obvious distress and impaired social function. The patient focuses on their insomnia day and night and worries excessively about the consequences of insomnia, and their dissatisfaction with the quantity and quality of their sleep causes considerable distress and affects social and occupational functioning. (3) Disease course criteria: The patient sleeps for less than 4 hours. Their disease course is more than 3 years. They did not use antidepressants or sedative and hypnotic drugs 2 weeks before treatment. They experience more than 3 episodes per week with at least 1 month of onset.

Inclusion Criteria

1. All patients aged 40-65 (including 40 and 65) years old have primary insomnia and a total Pittsburgh Sleep Quality Index (PSQI) score > 7.
2. Patients who take medication as required and do not take other sleep aids or receive other treatments.
3. All enrolled patients gave informed consent and signed informed consent forms. Patients complied with the treatment plan and visited doctors for review on time during the trial.

Exclusion Criteria

1. Patients with incomplete clinical information.
2. People with serious brain, heart, liver, kidney, and other physical diseases; pregnant or lactating women; people with severe mental illness and alcohol and drug dependence; and people with allergic constitution and who are allergic to the drug given in this study.
3. People with complications of other mental diseases, organic brain diseases, drug poisoning, and posttraumatic brain injury syndrome and who used antipsychotics, antianxiety, and depression drugs in the week prior to treatment.
4. People who did not take the medicine as prescribed, for whom efficacy cannot be determined, or have incomplete data.

Exposure Factors

The control group received conventional zopiclone treatment as follows: one 7 mg zopiclone (Qilu Pharmaceutical Co. National, drug approval number: H10980162) tablet was given orally every night for 1 week as the course of treatment for 4 continuous courses. The exposure group was treated with HLS oral liquid (Chengdu Huashen Technology Group Co. Z51020209) on the basis of the control group. Patients in the exposure group received 10 mg of HLS oral liquid orally every night for 1 week as the course of treatment for 4 continuous courses. The main ingredients of HLS oral liquid are *Herba Epimedii*, *Polygonatum sibiricum*, wolfberry, *Astragalus*, and *Salvia miltiorrhiza* Bunge. The specific preparation methods are as follows: (1) *Fallopia multiflora* Harald, *S. miltiorrhiza* Bunge, and wolfberry were boiled with water 3 times. The combined decoction was then filtered. The filtrate was concentrated into a syrup and added with ethanol to increase its alcohol content to 80%. The pH of the decoction was adjusted to 7.0 with 10% sodium hydroxide solution. Ethanol was recovered, and the liquid medicine was used. (2) *Herba Epimedii* and *P. sibiricum* were boiled twice with water. The supernatant was concentrated to an appropriate amount. Ethanol was added until the alcohol content of the decoction reached 80%. The pH of the decoction was adjusted to 7.0 with 10% sodium hydroxide solution. Ethanol was recovered, and the liquid medicine was used. (3) *Astragalus* was boiled in water 3 times. The filtrate was concentrated to a volume of approximately 95 mL. The liquid medicine was

MAIN POINTS

- Huo li su oral solution combined with zopiclone has a certain effect on insomnia symptoms.
- HLS oral solution combined with zopiclone can improve sleep quality and relieve fatigue in patients with insomnia symptoms.
- HLS oral solution combined with zopiclone can improve the daytime function of patients with insomnia symptoms.
- No related adverse reactions occurred during treatment with HLS oral solution.

set aside. The above spare liquid medicine was mixed, stirred evenly, refrigerated, brought to 1000 mL with water, and added with an appropriate amount of sugar-free sweetener. The pH of the filtrate was adjusted to 7.0-7.5 with 10% sodium hydroxide solution.

Observation Indices

Traditional Chinese Medicine Syndrome Score: Traditional Chinese medicine syndrome symptoms¹² included difficulty falling asleep, waking up easily/early waking, difficulty sleeping through the night, mental fatigue, pale or yellowish complexion, dizziness, dry eyes, blurred vision, and numbness of hands and feet. Each symptom received a score of 0-3 with a total score of 27. A high assessment score is associated with severe insomnia symptoms.

Sleep Disorder Scale: Scores of more than 20 on the Sleep Disorder Scale¹³ (SDRS) indicate severe sleep disturbance, those between 5 and 20 indicate good sleep quality, and those below 5 indicate relatively poor sleep quality. The reduction rate of the total SDRS before and after treatment was used as an index for determining efficacy. Reduction rate = (total score before treatment – total score after treatment)/total score before treatment. Reduction rates of more than 50% were considered effective, those of 25-49% were considered improved, and those less than 25% was considered ineffective.

Pittsburgh Sleep Quality Index: The Pittsburgh Sleep Quality Index¹⁴ (PSQI) is used to evaluate sleep quality in patients with sleep disorders, patients with psychiatric disorders, and the general population. It consists of 19 self-assessment entries and 5 other assessment entries, wherein the 19th self-assessment entry and 5 other assessment entries are not involved in scoring. Only the 18 self-assessment entries involved in scoring are presented here. The total score on the PSQI ranges from 0 to 21, with high scores indicating poor sleep quality.

Fatigue Scale 14: The maximum total score on the Fatigue Scale 14¹⁵ (Fatigue Scale-14 [FS-14]) is 14, and a high total fatigue score is indicative of severe fatigue.

Statistical Analysis

SPSS 26.0 statistical software (IBM Corporation, Armonk, NY, USA) was used for inductive statistics. Clinical data, such as age and disease course, and measurement data, such as SDRS, PSQI, FS-14, and TCM syndrome scores, were expressed as mean ± standard deviation (SD). D'Agostino Pearson normality test was used to determine whether data were normally distributed. Independent samples t-test was used for data analysis. Insomnia symptoms in patients, such as gender and sleep quality efficiency, were expressed as integers or percentages. Chi-square test was used for data analysis. Differences were considered to be statistically significant when P-value <.05.

Results

Comparison of General Information

No significant difference in age, gender, disease duration, body mass index, and other general data was found between the 2 groups (P > .05) (Table 1).

Comparison of Traditional Chinese Medicine Syndrome Scores

The TCM syndrome scores of both groups were analyzed by using telephone follow-up data collected after 4 weeks of treatment. The TCM syndrome scores of the observation and control groups before

Table 1. Comparison Between the General Information of the 2 Groups of Patients (mean ± SD)

Project	Observation Group (n = 82)	Comparison Group (n = 79)	t/x ²	P
Age (years)	56.13 ± 3.61	55.71 ± 3.65	0.734	.430
Gender (male/female)	53/29	51/28	<0.001	.992
Course of disease (month)	3.65 ± 0.23	3.68 ± 0.22	0.845	1.000
BMI (kg/m ²)	28.74 ± 3.73	28.13 ± 3.67	1.039	.295
Occupation			0.752	.861
Company staff	54	57		
Farmer	15	12		
Self-employed business owner	9	7		
Unemployed or retired	4	3		
Comorbidity (yes/no)	22/60	18/61	0.352	.553
Marital status (married/single or divorced)	75/7	74/5	0.284	.594
Education level			0.742	.690
Elementary school or below	24	21		
Junior/high school	35	39		
College and above	23	19		

SD, standard deviation.

treatment were 19.80 and 18.64, respectively, and did not significantly differ (P > .05). After 4 weeks of treatment, the TCM syndrome score of the observation group was 8.74, whereas that of the control group was 13.42. The TCM syndrome score of the observation group was significantly lower than that of the control group (t = 7.82, P = .037) (Figure 1).

Comparison of Pittsburgh Sleep Quality Index Scores

The PSQI scores of the 2 groups were statistically analyzed. The PSQI scores of the observation and control groups before treatment were 12.98 and 13.06, respectively, and were not significantly different (P > .05). After 4 weeks of treatment, the PSQI score of the observation group was 5.40, whereas that of the control group was 7.66. The PSQI score of the observation group was significantly lower than that of the control group (t = 6.14, P = .028) (Figure 2).

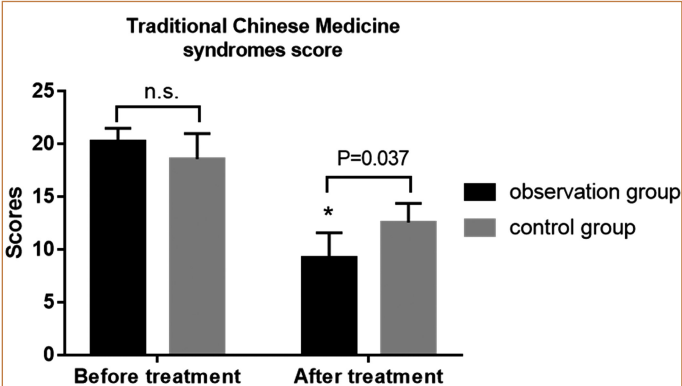


Figure 1. Comparison of traditional Chinese medicine syndrome scores. n.s, non-significant.

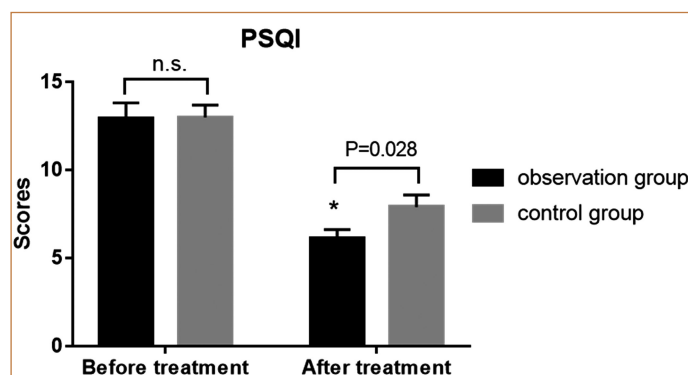


Figure 2. Comparison of Pittsburgh Sleep Quality Index Scores. n.s., non-significant; PSQI, Pittsburgh Sleep Quality Index.

Comparison of Sleep Disorder Scale Scores

The SDRS scores of the observation and control groups before treatment were 25.14 and 24.62, respectively, and did not significantly differ ($P > .05$). After 4 weeks of treatment, the SDRS score of the observation group was 9.23, whereas that of the control group was 18.61. The SDRS score of the observation group was significantly lower than that of the control group ($t = 16.05$, $P = .001$) (Figure 3).

Comparison of Fatigue Scale-14 Scores

The FS-14 scores of the observation and control groups before treatment were 8.82 and 9.05, respectively. The FS-14 scores of the 2 groups before treatment were not significantly different ($P > .05$). After 4 weeks of treatment, the FS-14 score of the observation group was 2.10, whereas that of the control group was 6.37. The FS-14 score of the observation group was significantly lower than that of the control group ($t = 31.84$; $P = .027$) (Figure 4).

Discussion

Our study found that HLS oral solution combined with zopiclone was effective in improving sleep quality and daytime function and relieving fatigue symptoms in patients with insomnia symptoms. Huo li su oral solution can induce sedation and hypnosis, regulate antiperoxidation balance, delay aging, and improve immune function.^{16,17}

Our study found that after treatment, the TCM syndrome, PSQI, SDRS, and FS-14 scores of the observation group became significantly

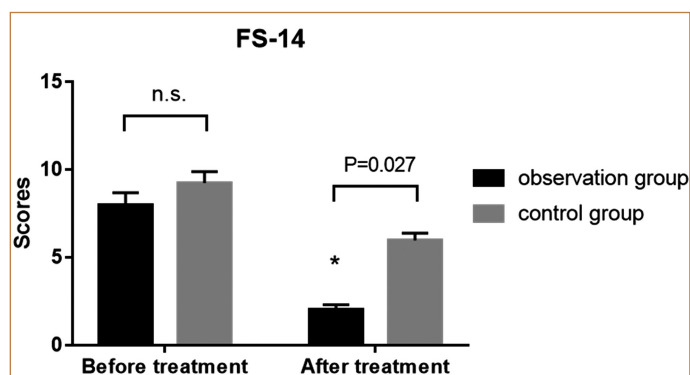


Figure 4. Comparison of Fatigue Scale-14 Scores. n.s., non-significant, FS-14, Fatigue Scale-14.

lower than those of the control group, indicating that the combined treatment of insomnia with HLS oral solution and zopiclone is more effective than treatment with zopiclone alone. Zopiclone is a drug that is commonly used in the clinical treatment of insomnia symptoms and has severe adverse reactions, withdrawal reactions, and rebounds.¹⁸ A previous study demonstrated that the efficacy of zopiclone in combination with TCM decoction, Chinese patent medicine, TCM external treatment, and antidepressants was superior to that of its use alone.¹⁹ The combination of Baolemian capsule and zopiclone had a good effect on insomnia.²⁰ Zhuo Zhihai implemented Nighe Jiannao tablet combined with dexzopiclone tablet in the treatment of patients with insomnia; this combined treatment can improve the sleep quality of patients, sleep disorders, and the total effective rate of treatment and reduce the occurrence of complications.²¹ Huo li su oral solution can regulate the antiperoxide balance of the body; delay aging; improve the immune function of the body; and protect the functions of the brain, liver, endocrine system, and other important tissues and organs.²² Huo li su oral solution also improves immunity, reduces blood lipids, delays aging, and exerts antiatherosclerosis effects.²³ In patients with cancer, HLS oral solution can reduce toxicity and side effects, prevent leukopenia, and regulate immune function when combined with chemotherapy.²⁴

Huo li su oral solution is mainly composed of *Polygonatum dibiricum*, wolfberry, *Astragalus*, and *Herba Epimedii*.²⁵ Wolfberry can promote hematopoietic cell proliferation, increase the number of white blood cells, and enhance human hematopoietic function.^{26,27} *Astragalus* can enhance the physiques of patients; this effect can effectively enhance immunity, improve the patients' mental state, and cause shortness of breath to disappear gradually.²⁸ Pharmacological experiments have shown that *Herba Epimedii* can increase cardiovascular and cerebrovascular blood flow and promote hematopoietic function, immune function, and bone metabolism and has antiaging and antitumor effects.²⁹ *Herba Epimedii* has a regulatory effect on the function of the hypothalamic-pituitary-gonadal axis and regulates the body's immune function.³⁰ It can also delay aging and has a strong anti-HSVii effect.³¹ When used together, the above herbs benefit the liver and kidney by invigorating qi and replenishing blood. *Polygonatum sibiricum* can inhibit angiotensin-converting enzymes and reduce blood pressure.³² It can increase Superoxide dismutase (SOD) activity in the liver, reduce lipofuscin content in the myocardium, and fight against the damage caused by free radicals and their metabolites to the body. It has antiaging and antifatigue effects.³³ The mechanism of HLS oral

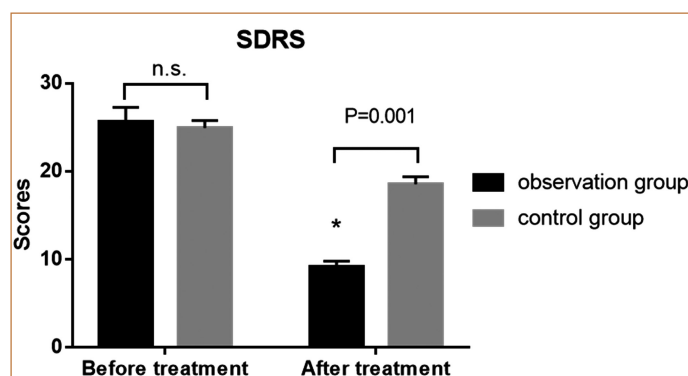


Figure 3. Comparison of sleep disorder scale scores. n.s., non-significant.

solution in the treatment of insomnia symptoms lies in regulating the antiperoxidation balance of the body; delaying aging; regulating and improving the body's immune function; protecting the functions of the brain, liver, endocrine system, and other important tissues and organs; resisting fatigue; and improving cerebral blood flow supply.³³

The short course of treatment and lack of long-term follow-up in our study affected the quality of efficacy evaluation. In the future, the above deficiencies should be overcome actively, and the clinical efficacy of HLS oral solution in resolving insomnia symptoms should be further observed in detail with a large sample size. In addition to evaluating the efficacy of HLS oral solution in improving insomnia symptoms, the mechanism of action of this effect should be discussed to provide high-quality medical evidence and improve clinical guidance.

Huo li su oral solution combined with zopiclone showed considerable efficacy in the treatment of insomnia symptoms and is superior to zopiclone alone in ameliorating sleep disorders, sleep quality, and fatigue.

Availability of Data and Materials: The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Sichuan Second Hospital of Traditional Chinese Medicine (2023Lunshen-76).

Informed Consent: The written informed consent was obtained from the patients/patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – L.C., Z.Z.; Design – L.C., Z.Z.; Supervision – L.C.; Resources – L.C.; Materials – Z.Z.; Data Collection and/or Processing – L.C., Z.Z.; Analysis and/or Interpretation – L.C., Z.Z.; Literature Search – Z.Z.; Writing – L.C., Z.Z.; Critical Review – Z.Z.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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