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Shexian Bupleurum Alleviates Insomnia and Improves Symptoms of Anxiety and Depression: A Randomized Double-Blind Placebo-Controlled Clinical Trial

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Abstract: *Objective:* To observe the clinical efficacy of Shexian bupleurum on insomnia based on evaluation scales and polysomnogram (PSG). *Methods:* A total of 260 patients suffering from insomnia admitted to the outpatient department of Handan Central Hospital were included in a randomized, double blind, placebo-controlled trial. The patients were randomly divided into two groups: a control group (receiving placebo, n = 150), and an intervention group (receiving Shexian bupleurum treatment, n = 110). The clinical trial lasted for 4 weeks. The Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Patient Health Questionnaire (PHQ)-9, Generalized Anxiety Disorder (GAD)-7, 17 items of Hamilton Depression Scale (HAMD-17), and Hamilton Anxiety Scale (HAMA) were used to evaluate the patients at baseline as well as two weeks and four weeks after treatment; the Treatment Emergent Symptom Scale (TESS) was used to evaluate adverse reactions; polysomnography (PSG) was used to monitor and analyze their sleep characteristics at baseline and four weeks after treatment. *Results:* The PSQI, ISI, PHQ-9, HAMD-17, and HAMA scores of the intervention group significantly decreased compared to the control group, while the total sleep time, rapid eye movement sleep latency, stage 2 sleep, deep sleep, rapid eye movement sleep, and sleep efficiency of the intervention group significantly increased compared to the control group. The PHQ-9 score of the control group only decreased two weeks after treatment ($p < 0.05$) compared to the intervention group. In addition, there were no obvious adverse events in both the intervention group and the control group. *Conclusion:* Shexian bupleurum not only improves sleep quality, but also relieves depression and anxiety in patients who suffer from insomnia.

Keywords: Clinical trial; Randomized double-blind method; Insomnia; Shexian bupleurum; Polysomnography

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1. Background

Insomnia, as a sleep disorder, is characterized by having trouble falling asleep, waking up intermittently or early, and difficulty in falling asleep again. Journal of the American Medical Association reported the incidence of insomnia to be close to 10% to 20%, in which nearly half of those are chronic patients, with their mood, social function, and life satisfaction being seriously affected [1,2]. A survey conducted by the health department in China revealed that the prevalence of insomnia in China is as high as 27%, reaching

1.2 to 1.4 million [3]. In addition, insomnia, as a mental disorder, also increases the risk of anxiety and depression. According to Baglioni and several other researchers [4], patients suffering from insomnia have a 2.5 times higher risk of depression than those without sleep disorders. Insomnia also increases the risk of drug abuse and even suicide [5,6]. A study reported that 40% of insomnia patients are accompanied by symptoms of mental health disorders [7]; 43% of patients suffering from anxiety, depression, and comorbidities also have symptoms of insomnia [8]. It is gratifying that the effective treatment of insomnia can also positively affect the mood of patients with depression [9]. In addition to symptoms of mental health disorders, insomnia is considered as an independent risk factor of several diseases, such as diabetes [10], hypertension [11], heart failure [12], coronary heart disease [13], and myocardial infarction [14]. Thus, insomnia has been regarded as a global public health issue and one of the leading causes of various common diseases.

Cognitive behavior therapy (CBT) and drug therapy are commonly used to treat insomnia [15]. CBT has fewer side effects and is more cost effective; thus, it is considered the first choice [16]. It cannot be denied that it has inevitable limitations, such as the lack of trained therapists and the low response rate [17]; insomnia still persists in 30% of patients after the complete course of CBT; additionally, 20% to 25% of patients are not sensitive to the therapy and show no signs of improvement in terms of insomnia [18]. Other than that, the efficacy of CBT mainly relies on patients' self-discipline and self-efficacy [19], which marks the limitations of the applicability of CBT in certain populations. Therefore, CBT cannot be used as a completely convincing treatment for insomnia. Since the 1990s, benzodiazepines have been widely used to treat insomnia due to their fast efficacy and remarkable effect. At the same time, drug resistance, addiction, psychomotor disorders, cognitive impairment, and withdrawals all emerged. The clinical application of benzodiazepines is also limited to a certain extent. Therefore, there is an urgent need for innovative methods to treat insomnia with minimal side effects and high benefit-to-risk ratio.

For thousands of years, Chinese herbal medicine (CHM) has been used to treat insomnia since ancient China. Among many treatments, traditional Chinese medicine treatment have the advantages of stable therapeutic effect with minimal side effects [20,21]. With the improvement of Chinese herbal medicine dosage forms and processing techniques, many Chinese herbal medicine patents have been found to have more clinical use. As a local specialty, bupleurum, which originated from Shexian County, Handan, is characterized by its thick roots and its cylindrical or long conical shape. Its root head is expanded, its stem base or short fibrous leaf base remains at the top, and its lower part is branched. It can be dark brown or light brown in color. It is difficult to break since it is hard and tough. It smells slightly fragrant and tastes slightly bitter. Its main active ingredient is saikosaponin. The total amount of saikosaponin A and D in bupleurum is 0.69%, which is 2.3 times that specified in the 2021 Chinese Pharmacopoeia 2021 (0.30%), and its extract is 18.3%, which is 1.67 times that specified in the Pharmacopoeia (11.0%). The efficacy of bupleurum on insomnia has also been confirmed in a number of randomized controlled trials [22]. However, these studies only focused on scale scores to evaluate insomnia and the efficacy of the treatment. The use of polysomnography (PSG) to evaluate the sleep characteristics of the subjects has not been reported. Since PSG is regarded as the gold standard for monitoring and evaluating sleep disorders [23,24], this study aims at evaluating the efficacy of Shexian bupleurum in the treatment of insomnia by using both, PSG and a scale score.

2. Data and methods

2.1. General information

The clinical trial was a randomized, double-blind, placebo-controlled study. A total of 970 insomnia patients from the outpatient department of Handan Central Hospital were enrolled in the trial, of which 710 cases were excluded (490 cases did not meet the inclusion and exclusion criteria; 150 cases refused to participate in the clinical trial; 70 cases were excluded for other reasons), with 260 cases finally included.

There were 110 cases in the intervention group, comprising of 60 female patients and 50 male patients, with a mean age of (51.64 ± 3.71), and a BMI of (22.89 ± 0.90). There were 150 cases in the control group, comprising of 120 female patients and 30 male patients, with a mean age of (44.53 ± 3.53), and a BMI of (23.86 ± 1.86). There was no significant difference in terms of age, gender, and BMI between the intervention group and the control group ($p > 0.05$).

2.2. Inclusion criteria

According to the diagnostic criteria in western medicine, the inclusion criteria for patients with insomnia who came to the hospital or were recruited through clinical trials due to insomnia were as follows: (1) age ranging between 18 and 65; (2) insomnia diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (3) Hamilton Anxiety Scale (HAMA) < 14 items, Hamilton Depression Scale (HAMD-17) < 17 items, and Pittsburgh Sleep Quality Scale (PSQI) > 8 items; (4) no serious systemic complications; (5) no drugs that affect sleep were taken two months before the test; (6) informed consent signed before the trial.

2.3. Exclusion criteria

Patients who met the following criteria were excluded: (1) secondary insomnia (resulted from or accompanied by moderate depression, acute stress, or anxiety), or other sleep disorders (for example, sleep apnea syndrome); (2) pregnant or lactating women; (3) severe physical diseases, such as serious liver, heart, or kidney dysfunction, or malignant tumors; (4) history of drug abuse, or drug or alcohol dependence; (5) allergic to Shexian bupleurum; (6) patients who had taken hypnotics, anxiolytics, or antidepressants.

2.4. Methods of intervention

2.4.1. Randomized double-blind design

The control group and the intervention group were equally divided in a 1:1 ratio. According to the random number grouping table and the numbering standard on the packaging bag, all enrolled subjects were randomly treated with either Shexian bupleurum or a placebo over 4 weeks, and every two weeks, they returned to the hospital for evaluation. All the patients were told to take Shexian bupleurum an hour prior to bed after dinner.

2.4.2. Intervention

The patients received the 4-week dose of placebo or Shexian bupleurum in two rounds; the first time was on the day of enrollment, and the second was at the end of the two-week treatment. Other personnel who did not participate in the clinical trial and evaluation were responsible for drug distribution. Any drugs (including herbs), food, drinks, or health products were not allowed to be consumed with the treatment, in order to avoid hypnotic or insomnia effects.

2.5. Observation

PSQI [25], Insomnia Severity Index (ISI) [26], and 7 items of Generalized Anxiety Disorder (GAD-7) [27] self-rated scales were used as indicators for assessing the severity of insomnia, anxiety, and depression. The severity of insomnia was evaluated by using the first two scales, and the severity of anxiety and depression was evaluated by the latter two scales. Although the severity of depression and anxiety was evaluated by HAMD and HAMA, the safety of treatment was evaluated by the TESS. All of these scales were used at baseline as well as two and four weeks after the treatment.

The main innovation of this study was the use of polysomnography (PSG), which was recorded and analyzed based on the standards of the American Academy of Sleep Medicine (AASM) [28]. The detection

indexes include sleep latency, sleep efficiency, sleep maintenance efficiency, rapid eye movement sleep latency, total sleep time, and the time spent in each sleep stage (stage I, stage II, deep sleep, and rapid eye movement stage). Each subject was monitored at baseline and four weeks after treatment. Two PSG tests were conducted, respectively, and the time for each test was 8 hours or more.

2.6. Statistical analysis

All data were analyzed by using SPSS 22.0 (IBM, Armonk, NY, USA). Measurement data were expressed as $\bar{x} \pm s$, the data followed a normal distribution, Kolmogorov-Smirnov test was used for data analysis, and independent sample T test was also used. When the data did not follow a normal distribution, nonparametric test was used; meanwhile, paired sample t-test was used for comparison of the numerical data in the group. Categorical variables were represented by numbers, and χ^2 test was used to test the standard $\alpha = 0.05$; $p < 0.05$ indicated a statistically significant difference.

3. Results

3.1. Comparison of efficacy

Finally, a total of 260 patients with insomnia were included, with 110 cases in the Shexian bupleurum intervention group, and 150 cases in the placebo group.

Figure 1 shows a detailed flowchart of the grouping process. After two weeks of treatment, 20 patients from the placebo group and 10 patients from the intervention group withdrew because of the lack of efficacy. There was no significant difference in terms of the withdrawal rate between the two groups (9.09% versus 13.33%, $p = 0.369$). After four weeks of treatment, 20 patients from the placebo group (10 withdrew voluntarily, and the other 10 rejected the test process) and 20 patients from the intervention group (voluntary withdrawal) withdrew. There was no significant difference in terms of the withdrawal rate between the two groups (27.27% versus 26.67%, $p = 0.973$). Finally, 80 patients from the intervention group and 110 patients from the control group underwent three rounds of evaluation and two rounds of PSG monitoring procedures, and the effectiveness of the monitoring was verified.

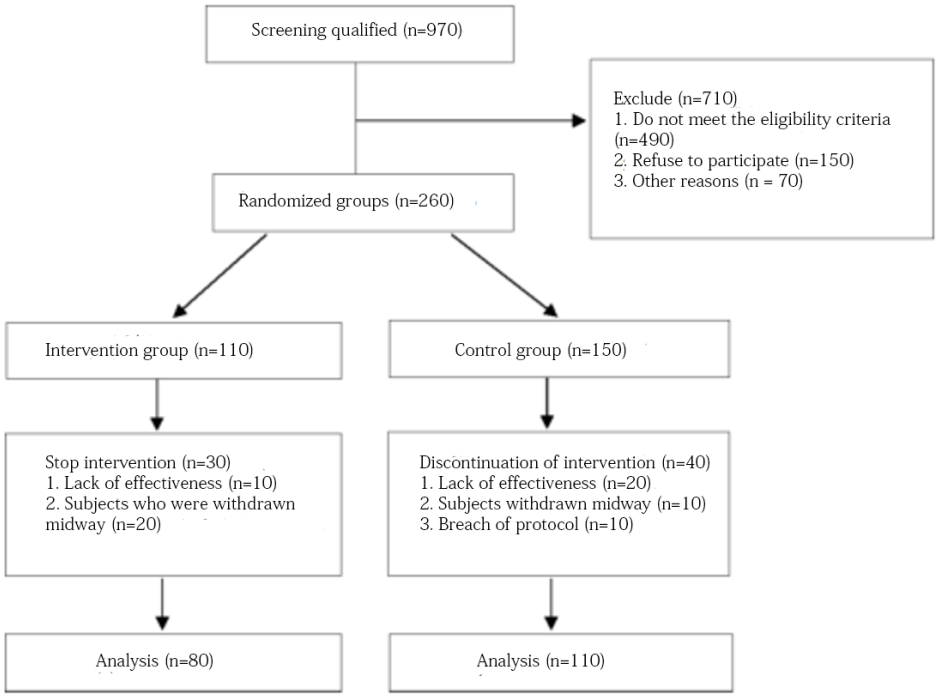

Figure 1. Flowchart showing the progress of enrollment of the two groups in each stage (subject recruitment, intervention group, follow-up, and data analysis)

Table 1 shows the baseline clinical and demographic data of the two groups, including gender, age, years of education, marital status, age of onset of insomnia, duration of insomnia, family history of insomnia, and other psychiatric disorders; the scale scores (PSQI, ISI, PHQ-9, GAD-7, HAMD-17, HAMA) and the PSG correlates (sleep latency, sleep efficiency, REM sleep latency, overall sleep duration, as well as duration of stage 1/2 sleep, deep sleep, and REM sleep) ($p > 0.05$).

Table 1. Baseline indicators of subjects

Parameter	Intervention group	Control group	t/Z/x²	P-value
Gender (female/male) a	60/50	120/30	3.346	0.067
Age b	51.64 ± 3.71	44.53 ± 3.53	1.364	0.185
Years of education b	12.27 ± 1.38	15.33 ± 1.07	−1.782	0.087
BMI b	22.89 ± 0.90	23.86 ± 1.86	−0.419	0.679
Age of onset b	42.73 ± 3.69	38.73 ± 3.25	0.809	0.426
Marital Status (single/married)a	10/100	40/110	1.262	0.261
Duration of insomnia (months)b	107.25 ± 34.24	72.27 ± 22.74	0.886	0.385
Family history of insomnia or other mental illness (yes/no)b	20/90	60/90	1.418	0.234
PSQI_OW (score)a	21.91 ± 1.86	20.80 ± 1.38	0.490	0.628
ISI_OW (score)b	15.73 ± 1.71	15.07 ± 1.12	0.338	0.739
PHQ-9_ow (score) b	8.55 ± 1.32	8.60 ± 1.40	−0.027	0.978
GAD-7_ow (score) b	5.18 ± 1.67	5.73 ± 1.54	−0.240	0.812
Hamd-17_0w (score) b	8.64 ± 0.66	7.80 ± 1.17	0.133	0.579
HAMA_OW (score)b	7.45 ± 0.53	7.13 ± 1.11	0.261	0.797
HAMA_OW (score) b	361.64 ± 15.27	351.93 ± 21.77	0.338	0.738
Total sleep time _0W(score) b	27.70 (27.70)	33.90 (85.10)	−0.289	0.772
Wait time before falling asleep _OW (score) c	104.50 (135.63)	79.00 (49.00)	−1.115	0.265
REM delay _0W (score) c	33.75 (23.75)	33.00 (40.00)	−0.495	0.620
Stage 1 sleep _OW (score) c	211.18 ± 14.10	235.37 ± 19.52	−0.935	0.359
Stage 2 sleep _OW (score) b	28.45 ± 6.88	30.83 ± 6.13	−0.257	0.800
Deep sleep _OW (score) b	60.25 (20.25)	34.5 (43.50)	−1.899	0.058
REM sleep _OW (score)c	74.40 (16.93)	84.90 (19.90)	−1.239	0.215
Sleep efficiency _OW (score) c	75.22 ± 3.38	88.41 ± 2.19	−3.422	0.002
Sleep maintenance efficiency _OW (score)c				

a Chi-square test: b T-pole of independent sample: c Higher seni U test
Abbreviations: PSQI, Pittsburgh sleep quality scale; ISI, insomnia severityindex; PHQ-9,9 patient health questionnaire; GAD-7, 7 generalized anxiety disorder; HAMD-17, 17-item Hamilton Depression Scale; HAMA, Hamilton anxiety scale; REM, REM sleep

3.2. Comparison of safety and effectiveness

3.2.1. Subjective sleep evaluation

It can be seen from **Figure 2** and **Table 2** that after two and four weeks of intervention, the PSQI scores in the intervention group significantly decreased compared with the control group ($p < 0.001$ and $p = 0.040$, respectively). After two weeks of intervention, the ISI score in the intervention group significantly decreased ($p = 0.002$) compared with the control group. However, within the control group, there was no significant difference in either PSQI scores or ISI scores, either at two or four weeks ($p > 0.05$).

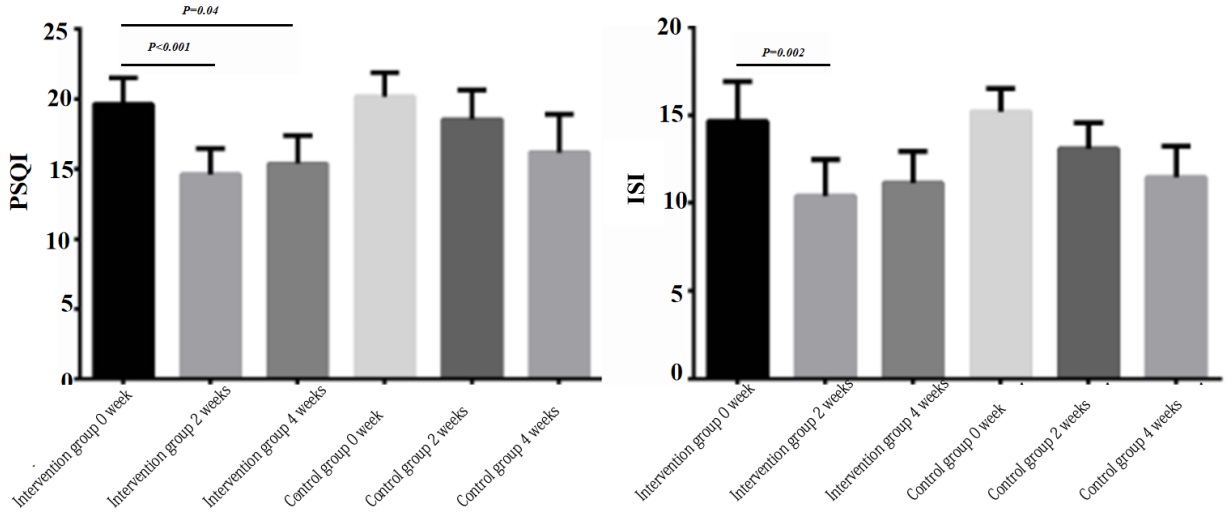

Figure 2. PSQI and ISI scores of the intervention and control groups before and after treatment

Table 2. Pretreatment and post-treatment scores of the intervention group and control group under different evaluation scales

Variable	Intervention group (n=80)			Control group (n=110)			P_1	P_2	P_3	P_4	P_5
	Pre-treatment	2 weeks	4 weeks	Pre-treatment	2 weeks	4 weeks					
PSQI	19.63±5.37	14.63±5.21	15.38±5.66	20.18±5.67	18.55±6.92	16.18±9.02	<0.001	0.040	0.218	0.081	0.832
ISI	14.63±6.39	10.38±5.88	11.13±5.11	15.18±4.38	13.09±4.87	11.45±5.85	0.002	0.111	0.066	0.073	0.824
PHQ-9	8.13±4.58	5.63±3.93	5.38±3.70	8.18±4.26	6.91±3.94	6.18±4.17	0.008	0.034	0.046	0.199	0.978
GAD-7	2.00 (11.00)	0.50 (6.75)	1.50 (4.25)	4.00 (9.00)	5.00 (4.00)	2.00 (6.00)	0.052	0.097	0.500	0.534	0.881
HAMD-17	8.88±2.42	6.25±3.62	4.63±2.67	8.00±3.90	6.91±3.67	5.81±4.49	0.013	0.004	0.140	0.117	0.583
HAMA	7.50 (3.25)	6.00 (4.00)	4.00 (3.50)	6.00 (6.00)	5.00 (3.00)	4.00 (6.00)	0.003	0.001	0.557	0.222	0.792

P1, comparison at different scales between pretreatment and 2 weeks in the intervention group; P2, comparison of pretreatment and 4 weeks in the intervention group at different scales; P3, comparison at different scales between pretreatment and 2 weeks in the control group; P4, comparison at different scales between pretreatment and 4 weeks in the control group; P5, comparison of pretreatment at different scales between the intervention group and the control group; P1, comparison at different scales between pretreatment and 2 weeks in the intervention group; P2, comparison of pretreatment and 4 weeks in the intervention group at different scales; P3, comparison at different scales between pretreatment and 2 weeks in the control group; P4, comparison at different scales between pretreatment and 4 weeks in the control group; P5, comparison of pretreatment at different scales between the intervention group and the control group;

Abbreviations: PSQI, Pittsburgh Sleep Quality Scale; ISI, Insomnia Severity Index; PHQ-9, 9-item patient health Questionnaire; Gad-7, 7 generalized anxiety disorder; HAMD-17, 17 Item Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale.

3.2.2. Polysomnography (PSG) evaluation

After 4 weeks of treatment, the PSG indexes of the control group changed significantly (**Figure 3** and **Table 3**; $p > 0.05$). As shown by design expectations, several PSG indexes were significantly higher in the intervention group, including total sleep time, stage 2 sleep time, deep sleep time, REM sleep time, and sleep efficiency; additionally, REM sleep delay was shortened significantly ($p = 0.021$).

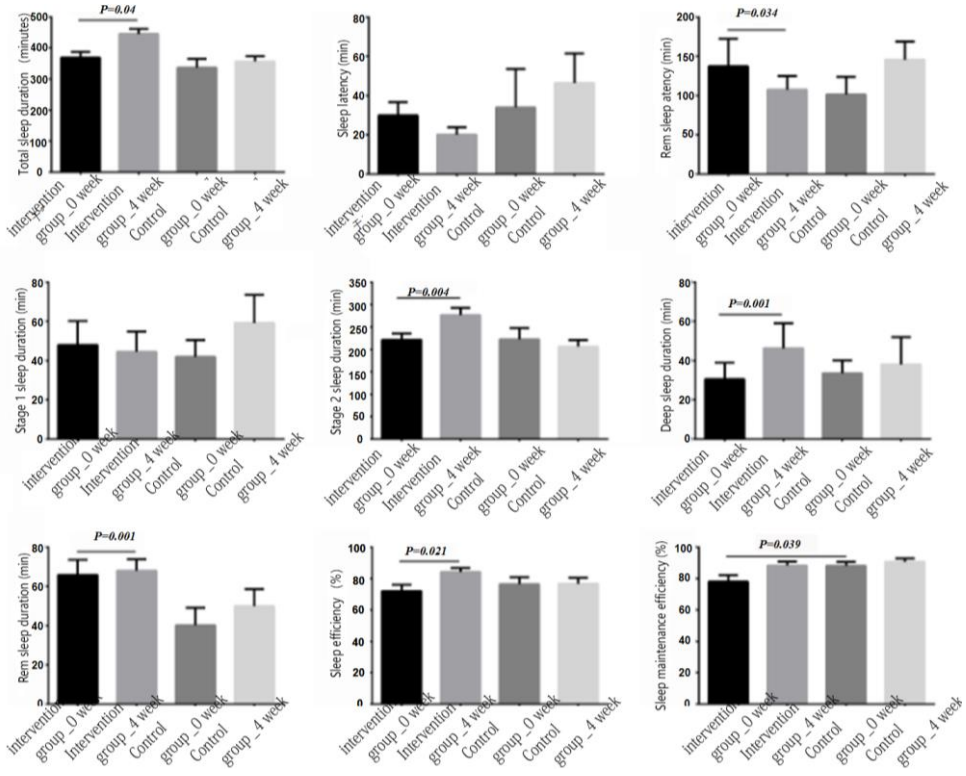

Figure 3. PSG indexed of the intervention group and control group before and after treatment (PSG indexes include total sleep time, sleep latency, REM sleep latency, stage 1 sleep time, stage 2 sleep time, deep sleep time, REM sleep time, sleep efficiency, and sleep maintenance efficiency)

Table 3. Pretreatment and post-treatment sleep monitoring records of the intervention group and control group

Variable	Intervention group (n = 80)		Control group (n = 110)		P_1	P_2	P_3
	Pretreatment	Post-processing	Pretreatment	Post-processing			
The total sleep time, min	368.88±18.65	445.31±16.31	336.64±28.27	356.73±16.87	0.040	0.081	0.496
Sleep latency, min	27.70 (27.70)	20.05 (21.23)	33.90 (85.10)	46.30 (78.40)	0.111	0.073	0.239
Rem sleep latency, min	104.50 (135.63)	89.50 (61.13)	79.00 (49.00)	131.00 (59.50)	0.034	0.199	0.474
Stage 1 sleep, min	33.75 (23.75)	47.00 (42.25)	33.00 (40.00)	53.00 (57.50)	0.097	0.534	0.678
Stage 2 sleep, min	221.31±13.95	276.38±16.26	222.36±25.37	205.86±14.88	0.004	0.117	0.972
Deep sleep, min	30.50 (15.00)	46.25 (48.63)	33.50 (31.00)	38.00 (31.00)	0.001	0.222	0.882
Rem sleep, min	60.25 (20.25)	64.75 (10.25)	34.5 (43.50)	43.50 (43.00)	0.010	0.130	0.053
Sleep efficiency, %	74.40 (16.93)	85.60 (12.23)	84.90 (19.90)	75.00 (22.70)	0.021	0.937	0.495
	78.04±4.11	88.30±2.50	88.15±2.45	90.58±2.22	0.056	0.158	0.039

P1. Different lead more sleep monitoring index in the intervention group under the condition of pretreatment and post-treatment of different: P2, different lead more sleep monitoring index in the control group under the condition of pretreatment and post-treatment of different: P3, before the treatment, intervention group and control group in the comparison of different lead more sleep monitoring

3.2.3. Evaluation of anxiety and depression

Figure 4 and **Table 2** show the changes of emotion-related evaluation indexes of patients in the intervention group and control group. Compared with the control group, the scores of PHQ-9, HAMD-17, and HAMA significantly decreased after two and four weeks of intervention with Shexian bupleurum ($p < 0.05$). However, in the control group, only the PHQ-9 score significantly decreased after two weeks of treatment compared with the baseline ($p = 0.046$). In addition, there was no significant difference in the GAD-7 score between the intervention group and the control group during the 2-week and 4-week test cycle ($p > 0.05$).

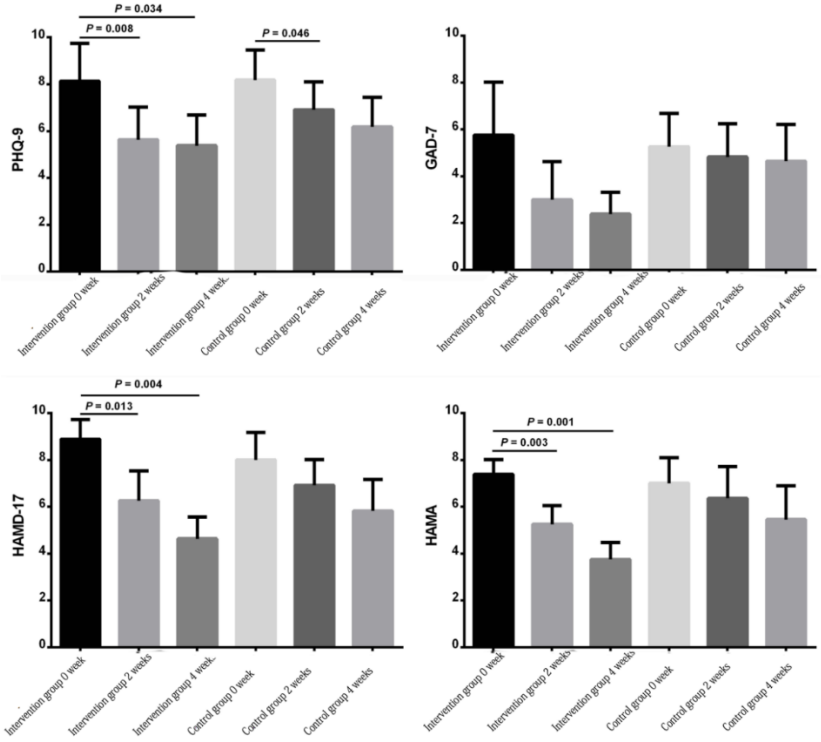

Figure 4. PHQ-9, GAD-7, HAMD-17, and HAMA scores of the intervention group and control group before and after treatment

3.2.4. Adverse reactions

All the patients in the intervention group and control group showed no adverse reactions during the clinical trial. The grounds for the withdrawal of the 70 subjects from the clinical trial were not related to the occurrence of adverse reactions.

4. Discussion

This is the first randomized, double-blind, placebo-controlled study of PSG to investigate the efficacy of Shexian bupleurum on adult insomnia that we are aware of. According to this research, Shexian bupleurum has better therapeutic effect than placebo and significantly improves the structure of sleep after four weeks of intervention. It is also worth noting that Shexian bupleurum improved the mood of the patients compared to their baseline.

The observed efficacy in the treatment of insomnia may be related to the herbal constituents of Shexian bupleurum, namely, the main ingredient of bupleurum.

Saikosaponin is said to have a calming effect on the heart rate, alleviate depression, and soothe the liver [29]. Recent studies have reported that bupleurum may alleviate insomnia by upregulating the levels of γ-aminobutyric acid in the brain, downregulating the levels of glutamate in the brain, and increasing the protein expression of hippocampal 5-hydroxytryptamine 1A receptor [30]. According to the 2021 Guidelines for the Diagnosis and Treatment of Insomnia for Chinese Adults, improving sleep quality and reducing adverse effects are the fundamental goals of treatment of insomnia [31]. From the sleep monitoring records through PSG, the total sleep time, REM sleep latency, second stage sleep, deep sleep, REM sleep, and sleep efficiency of the patients in the intervention group significantly improved after four weeks of treatment with Shexian bupleurum. Additionally, no adverse events were recorded in this study. As a genuine medicinal material, Shixian bupleurum may be a safe choice to relieve insomnia, depression, and anxiety. It has significant advantages over benzodiazepines, which might result in drug addiction, drug tolerance, reduced sleep quality, and altered sleep structure [32].

This study also found that in addition to sleep improvement, the PHQ-9, HAMD-17, and HAMA scores of the patients in the intervention group were remarkably lower than those in placebo group. This suggests that Shexian bupleurum can improve the anxiety and depression of patients with insomnia. In addition, the results are also supported by a recent study focusing on sleep and emotional disorders caused by COVID-19, which pointed out that saikosaponin can improve depression and anxiety in COVID-19 patients during the recovery phase [33]. In addition, these results are consistent with various other clinical trials. This indicates that the above mechanism of improving emotions may be closely related to saikosaponin. Since the compound have rich tryptophan, which is the precursor of serotonin, this suggests that saikosaponin can effectively increase the level of serotonin in the body and balance the effect of neurotransmitters, thus restoring autonomous sleep and improving depression and anxiety. The highlights of this study are as follows: (1) patients' subjective perceptions were assessed by the use of scales; patients' objective efficacy and actual sleep changes before and after treatment were assessed by the used of PSG, which comprehensively evaluated the efficacy of Shexian bupleurum; (2) patients were randomly treated with either Shexian bupleurum or placebo by the double-blind method, which prevented subjective bias; (3) the study only included patients with insomnia, which was helpful to accurately evaluate the efficacy of Shexian bupleurum with a single diagnosis.

However, this study also has some limitations. The sample size was relatively small due to the strict inclusion criteria and test requirements. The PSG indexes between male and female patients with insomnia were not investigated, since the majority of researchers believe that men are less likely to suffer from insomnia than women. Moreover, since there were no follow-ups after drug discontinuation, it is impossible to verify whether Shexian bupleurum may continue to have other effects after discontinuation. In follow-

up studies, a larger sample can be used, and the patients should be specifically divided into male and female groups; additionally, follow-up records should be compiled after drug discontinuation. All these will be necessary to obtain preliminary results of whether gender has an effect on insomnia.

5. Conclusion

In conclusion, Shexian bupleurum helps in alleviating insomnia after four weeks of treatment. According to subjective scales and objective sleep indexes, it increases total sleep time and deep sleep time, as well as improves sleep efficiency. Anxiety and depression symptoms also dramatically improve with the intervention of Shexian bupleurum. During the 4-week clinical trial, the patients in both the intervention group and the control group tolerated the treatment well. In short, this study proves that Shexian bupleurum not only improves the subjective and objective sleep indexes, but also alleviates accompanying anxiety and depression symptoms of patients with insomnia, with minimal side effects. In the future, a large sample of patients with insomnia should be included to further evaluate the safety and efficacy of Shexian bupleurum in alleviating insomnia and the accompanying symptoms of anxiety and depression.

Disclosure statement

The authors declare no conflict of interest.

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