

Impact of Acupuncture on Sleep and Comorbid Symptoms for Chronic Insomnia: A Randomized Clinical Trial

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Study Objectives: To evaluate the efficacy and safety of acupuncture at HT 7 (Shenmen) and KI 7 (Fuliu) on sleep and comorbid symptoms for chronic insomnia.

Methods and Design: A randomized, single-blind, parallel and sham-controlled trial consisted of an acupuncture group (n = 41) and a sham acupuncture group (n = 41). Setting: a tertiary hospital of integrated Chinese and Western medicine. Participants: 82 subjects with chronic insomnia based on the International Classification of Sleep Disorders, Third Edition (ICSD-3). Interventions: a 10-session acupuncture treatment at bilateral HT 7 and KI 7 or sham acupoints with shallow needling was performed over 3 weeks. Measurements: the Pittsburgh sleep quality index (PSQI) and insomnia severity index (ISI) were evaluated at baseline, posttreatment, and at two follow-ups as the primary outcome measures. Polysomnography (PSG) on two consecutive nights, the Beck anxiety inventory (BAI), the Beck depression inventory (BDI) fatigue severity scale (FSS) and the Epworth sleepiness scale (ESS) were evaluated at baseline and posttreatment as the secondary outcome measures.

Results: After the treatments, PSQI scores decreased by 5.04 in the acupuncture group and 2.92 in the sham acupuncture group. ISI scores decreased by 7.65 in the acupuncture group and 5.05 in the sham acupuncture group. The between-group differences in the primary outcome measures posttreatment were statistically significant. However, no differences were found between the two groups during the two follow-ups. Regarding the PSG data, there were significantly lower levels of sleep onset latency (SOL), a lower percentage of sleep stage N1 and a higher percentage of sleep stage N3 in the acupuncture group than in the sham acupuncture group. After treatment, there were lower levels of comorbid symptoms (BAI, BDI, FSS and ESS) in both groups. However, no significant differences were observed between the groups.

Conclusion: Acupuncture at HT 7 and KI 7 is an effective and safe nonpharmacologic intervention option for chronic insomnia.

Clinical Trial Registration: The study was registered at the Chinese Clinical Trial Registry, registration ID: ChiCTR1900023787, China.

Keywords: acupuncture, chronic insomnia, sleep and comorbid symptoms, randomized clinical trial

Plain Language Summary

Acupuncture has been used to treat chronic insomnia for years, but no study has focused on the comprehensive evaluation of acupuncture on sleep (subjective and objective) and comorbid symptoms. This was the first randomized controlled clinical trial to study the

therapeutic effect of acupuncture at a pair of acupoints on insomnia. This randomized controlled clinical study showed that, compared with sham acupuncture, the streamlined and optimized acupuncture programme could improve subjective and objective sleep measurements of subjects with chronic insomnia, but there was no significant improvement in comorbid symptoms. This study led to a more comprehensive understanding of this non-pharmaceutical intervention. However, the optimal plan and mechanism of acupuncture treatment for chronic insomnia need to be further determined.

Introduction

Insomnia is a frequently occurring clinical disease that affects people's lives in our society. The incidence of chronic insomnia has increased year by year.¹ According to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders-4th (DSM-IV), the incidence rate of chronic insomnia in Chinese adults is 19.6%.² Long-term chronic insomnia can cause serious health problems and many other chronic diseases such as diabetes,³ obesity,⁴ cardiovascular disease,⁵ chronic kidney disease,⁶ and hypertension.⁷ The most direct harm is effects on quality of life.⁸ Furthermore, patients with chronic insomnia usually have mood disorders,^{9,10} and chronic insomnia is often accompanied by daytime dysfunction.¹¹ All these factors can deteriorate the severity of chronic insomnia and contribute to the difficulty of treatment, which requires clinical attention and a search for simpler and faster treatment options.

At present, cognitive behavioural therapy for insomnia (CBT-I) and other psychotherapeutic approaches are generally accepted internationally as the primary recommended treatment for chronic insomnia disorder.^{12,13} However, due to its time-intensive nature and because physicians need much professional training to conduct them,¹⁴ these methods are not fully implemented in China. Although pharmacologic treatments have the advantages of being effective and fast, there are many side effects of sedative-hypnotic medicine, such as cognitive impairment, hangover effects, and drug addiction.^{15,16} Therefore, more patients with chronic insomnia seek complementary and alternative therapies, such as acupuncture, especially among Chinese people.¹⁷ Studies have shown that acupuncture can improve sleep quality and psychological health.^{18,19} An earlier Cochrane review showed that, when compared with untreated subjects and those receiving placebo acupuncture, acupuncture can significantly improve sleep quality among subjects with insomnia.²⁰ Our previous study also indicated that

acupuncture has better clinical efficacy and safety in perimenopausal insomnia than sham acupuncture.²¹

However, most of the previous studies on acupuncture for insomnia have some general disadvantages, such as an unreasonable control group, no randomization, no blinding method, and no objective indicators for sleep evaluation.^{22–24} In addition, the existing studies generally lack the guidance of traditional Chinese medicine (TCM) theory,^{25,26} and the selection of acupoints is highly variable,²⁷ which increases the difficulty of implementation and increases subject pain. Most of the studies on acupuncture for insomnia did not use comprehensive indicators to evaluate sleep and related symptoms. However, the Recommendations for a Standard Research Assessment of Insomnia highlight that evaluating and reporting the diagnosis of insomnia and its comorbid symptoms, sleep symptoms, and waking correlates and consequences of insomnia (ie, fatigue, depression, anxiety, quality of life and function) are the basic elements for treatment efficacy and effectiveness studies.²⁸ More studies are needed to investigate the subjective and objective indicators of acupuncture for improving sleep and explore the secondary benefits of treating insomnia, such as reductions in depression, anxiety, fatigue, and daytime sleepiness.

According to TCM theory, the main causes of chronic insomnia are Yin deficiency leading to heart fire and dysregulated coordination between the heart and the kidney.²⁹ Therefore, we chose acupoints based on disease differentiation and special acupoint combinations to nourish Yin, calm the mind, and regulate mental activity. HT 7 (Shenmen) and KI 7 (Fuliu) are adopted as the points to nourish Yin, and they are especially used to nourish Yin of the liver and kidney and decrease heart fire.^{30,31} According to the theory of TCM, acupuncture at this pair of acupoints can solve sleep problems and related symptoms of insomnia. There are no reports on the treatment of insomnia through these two acupoints in the existing literature. This was the first randomized controlled clinical trial to study the therapeutic effect of acupuncture at HT 7 and KI 7 on insomnia. The objective was to explore the efficacy and safety of acupuncture at HT 7 and KI 7 on sleep and comorbid symptoms for chronic insomnia in sham-controlled, subject- and assessor-blind, randomized controlled trials.

Methods

Study Design

This was a randomized, single-blind, parallel and sham-controlled trial. This study followed the Consolidated

Standards of Reporting Trials (CONSORT)³² and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)³³ guidelines for designing and reporting controlled trials. The trial was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (Shanghai, China).

Participants

The participants were patients with chronic insomnia who came from the outpatient department of the Department of Acupuncture and Moxibustion, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, from June 2019 to January 2020. In addition, the study recruited subjects through community lectures and recruitment advertisements. This study followed the principle of voluntary participation and required the signing of an informed consent document before enrolment. All those who wanted to participate in the study called the study coordinator, and we conducted a preliminary clinical interview.

The diagnosis of chronic insomnia was made with clinical interviews according to the American Academy of Sleep Medicine International Classification of Sleep Disorders, Third Edition (ICSD-3).³⁴ The inclusion criteria were as follows: (1) 18 to 75 years old. (2) In compliance with the diagnostic criteria for chronic insomnia in ICSD-3. (3) In compliance with the TCM diagnostic criteria for insomnia, TCM syndrome of dysregulated coordination between the heart and the kidney. (4) Consistent administration of sedative-hypnotic drugs for more than 3 months before entering the study or not taking such drugs. (5) A total score higher than five on the Pittsburgh Sleep Quality Index (PSQI) questionnaire.³⁵ (6) Patients voluntarily participated in the study and signed informed consent forms.

All subjects who wanted to participate were given an outpatient interview to determine whether they met the inclusion criteria. The interviews were conducted by experienced clinicians in the form of semistructured interview questionnaires. The interview questionnaire included the cause of insomnia, the onset process, the main sleep complaints at the current time, the treatment process, the state before going to bed, the sleep-wake cycle, other sleep-related symptoms, mental states, and daytime symptoms.³⁶ Individuals on stable doses of sedative-hypnotic medications were allowed to remain on them during the study. In addition, all subjects

completed a one-week sleep diary to establish sleep patterns before the clinical interview.³⁷

The exclusion criteria were as follows: (1) severe hepatic or renal function damage, haematological disease, respiratory disease, or diagnosis of one or more mental disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).³⁸ (2) semistructured interviews determined that subjects had sleep disorders other than chronic insomnia. (3) Infectious diseases such as infectious hepatitis, tuberculosis, AIDS and syphilis. (4) Severe digestive system diseases or severe malnutrition. (5) Pregnant or lactating. (6) Severe trauma with no cure or other contraindications to acupuncture, such as allergic constitution or severe dermatosis. (7) An Apnoea-Hypopnea Index >10 or periodic limb movements index during sleep associated with >15 arousals per hour on diagnostic PSG.^{21,39} (8) Participation in other clinical trials in the last 3 months.

Intervention

The acupuncturist had received a master's degree in acupuncture and tui na, had a doctor qualification certificate, and had more than 3 years of acupuncture clinical work experience. All the research assistants received 3 days of training before the start of the study.

Subjects in the acupuncture group were placed in a supine position. The acupuncturist selected two acupoints, HT 7 and KI 7. These acupoints were selected based on a previous systematic review^{40,41} and our clinical experience summary and because the use of only two points can streamline the treatment and alleviate patient pain. The needles used were disposable, sterile, stainless-steel acupuncture needles with a length of 40 mm and a diameter of 0.25 mm (Andy, Guizhou, China). The acupuncturist treated each acupoint bilaterally, and the depth of insertion was 10–20 mm. The acupuncturist selected the depth according to the subject's body type (high, short, fat and thin). After penetration, the acupuncturist lifted and twisted the needles to induce the subject's sensation of "De qi", and the needle was left for 20 minutes.⁴² "De qi" refers to manipulation of the needle by the acupuncturist (extract, intercalate, twist, and rotate) after the needle has been inserted into the acupoints to a certain depth so that the acupoints can be induced by the meridians. The patient has a conscious response, such as soreness, numbness, or tenderness. According to TCM, this is the key to the curative effect of acupuncture.⁴³

Subjects in the sham acupuncture group were treated with shallow needling of sham acupoints. Due to its convenience, this control group setting method has been widely used in acupuncture clinical research, especially for the purpose of exploring acupoint-specific effects among the Chinese population.^{44,45} Sham HT 7 was 2 cun (≈ 40 mm) lateral to HT 7, and sham KI 7 was 2 cun (≈ 40 mm) lateral to KI 7 (Figure 1). The purpose of choosing the sham points in this way is explained in previous similar clinical studies;⁴⁵ this approach avoids the true acupoints and meridian routes. Choosing sham points close to the true acupoints was conducive to blinding. The acupuncturist took the sham points on both sides and performed needling at a depth of 2–4 mm, sufficient only to penetrate the skin. The acupuncturist did not manipulate the needles and did not cause “De qi”. The parameters of the acupuncture needles were identical to those used in the acupuncture group. Subjects in the two groups received the same treatment, which included 3 times a week for a total of 10 treatments. Each subject experienced screening, treatment, and a follow-up period of approximately 8 weeks, and the treatment phase lasted approximately 3.5 weeks. All subjects were treated equally to prevent them from perceiving differences. They were told about the methods of acupuncture as follows:

In our study, different types of acupuncture treatments will be compared. One is ordinary acupuncture, and the other is related to the positive results in previous clinical studies.⁴⁶

Measures

Primary Outcome Measures

Pittsburgh Sleep Quality Index (PSQI): The PSQI contains 19 self-assessed items and 5 other-rated items. The self-assessed items evaluate duration of sleep, sleep onset latency, sleep efficiency, sleep disturbance, need for medications to sleep, daytime dysfunction, and overall sleep quality. The total score is 0–21. A higher score indicates a worse quality of sleep.³⁵ The PSQI is widely used to evaluate sleep dysfunction,⁴⁷ and it is more inclined to evaluate the subject’s sleep state during the workday.⁴⁸ A total score >5 indicates that the subjects have poor sleep quality and has significance for clinical treatment.⁴⁹ The Chinese version of the PSQI has high reliability and validity for the Chinese population and has been used as an effective tool for sleep screening in clinical and scientific research.^{50,51} This study evaluated the PSQI at baseline, posttreatment, one-week follow-up and one-month follow-up.

Insomnia Severity Scale (ISI): The ISI mainly evaluates the nature and severity of insomnia and its impact on daytime function. The scale consists of 7 evaluation items, and the total score ranges from 0–28 points. A higher score indicates more severe insomnia.⁵² The ISI is mainly used to screen for insomnia and to evaluate treatment effects in clinical research.⁵³ A total score of 8–14 indicates subclinical insomnia, and a total score >14 indicates

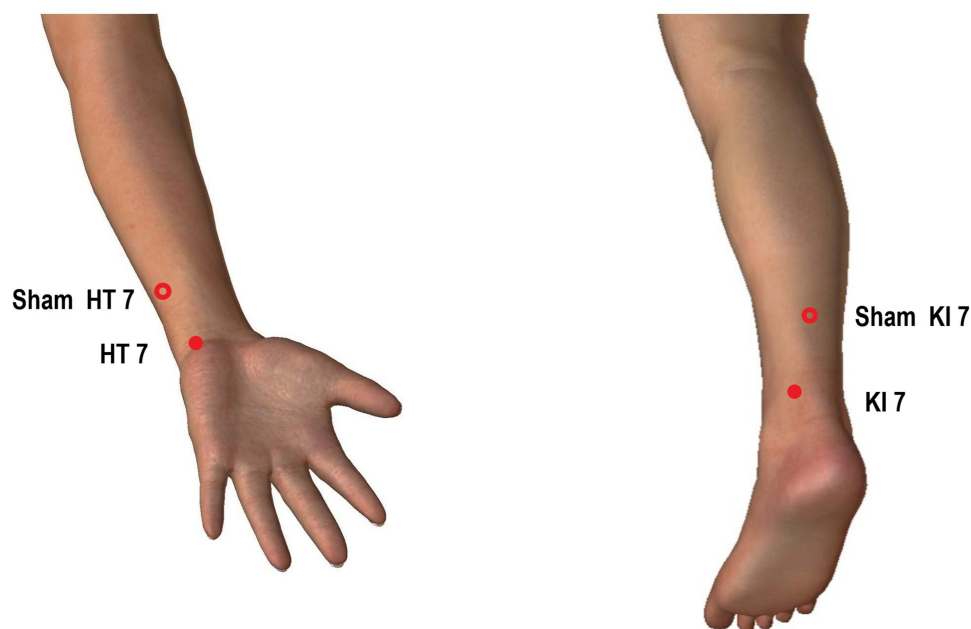


Figure 1 Acupoints for the acupuncture and sham acupuncture groups.

clinically significant insomnia. A reduction in the ISI score by 8 points or more reflects a significant treatment effect in clinical evaluations. ISI has good reliability and validity.⁵⁴ The Chinese version has high reliability and validity for evaluating insomnia among the Chinese population.⁵⁵ This study evaluated ISI at baseline, posttreatment, one-week follow-up and one-month follow-up.

Secondary Outcome Measures

Polysomnography (PSG): PSG was used as the objective sleep evaluation index. The PSG (NIHON KOHDEN, Japan) used in this study was composed of multiple quantitative parameters. The collection indicators included electroencephalogram (EEG), mentalis electromyography (EMG), bilateral electrooculography (ECOG), oral/nasal airflow, and bilateral anterior tibial EMG. In this study, PSG was used for two consecutive nights to eliminate the “first night effect”.⁵⁶ PSG monitoring started from the usual bedtime to the next morning, and a total of 8.0 hours were recorded. The efficacy evaluation of this study was based on EEG. The sleep stages and parameters were manually scored based on the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events.⁵⁷ The objective sleep evaluation parameters used in this study included the following: total sleep duration (TST); sleep onset latency (lights out to first epoch of any sleep, SOL); REM sleep latency (REM-sl); wake after sleep onset (WASO, SOL minus TST); sleep efficiency (SE, TST/total recording time \times 100%); arousal index (Arl; number of arousals \times 60/TST); and percent time in each stage (length of each sleep stage/TST \times 100%). In this study, during the screening period and at posttreatment, two consecutive monitorings were performed, but only the second result for each time-point was used as the efficacy evaluation index.

Beck Anxiety Inventory (BAI): The BAI was developed by Beck et al in 1988⁵⁸ and contains a total of 21 anxiety symptom items. It has been used as an evaluation index to evaluate the anxiety state of the subject within the past week. Higher scores correspond to more serious anxiety. Generally, BAI \geq 45 is used as the criterion to indicate anxiety. The scale is simple in content, easy to administer, and easily understood. The Chinese version has good reliability and validity and is commonly used for the evaluation of anxiety symptoms in China.^{59,60} This study evaluated it at baseline and posttreatment.

Beck Depression Inventory (BDI): The BDI was developed by Beck et al according to the diagnostic criteria for

depression in the DSM-IV.⁶¹ Beck et al formulated the first version of the BDI in 1961 and restructured it for the second version, which is now generally used. The BDI has a total of 21 self-evaluated depression-related items that can evaluate depression in the past 7 days. The higher the total score, the more severe the depression. A total score of 0–13 indicates no depression, 14–19 indicates mild depression, and 20–63 indicates severe depression. The Chinese version of the BDI has good validity and reliability.^{62,63} This study evaluated it at baseline and posttreatment.

Fatigue Severity Scale (FSS): FSS was proposed and formulated by Krupp et al in 1989.⁶⁴ The FSS scale is simple and clear. It consists of only 9 self-evaluation items. Subjects scored themselves on the corresponding symptoms. Higher total scores indicate more fatigue. Studies have shown that the FSS score of patients with insomnia is higher than 5.5, which means that there is a high level of daytime fatigue among patients with insomnia.⁶⁵ The Chinese version of the FSS has good validity and reliability.⁶⁶ This study evaluated the FSS at baseline and posttreatment.

Epworth Sleepiness Scale (ESS): The ESS is a relatively simple and internationally recognized sleepiness assessment scale.⁶⁷ It has a total score of 24 points. The higher the score is, the more severe the daytime sleepiness. This scale is generally used to screen and evaluate the hypopnea status of patients with obstructive sleep apnoea-hypopnea syndrome (OSAHS), but studies have shown that the ESS scale can be used to screen and diagnose other sleep disorders.⁶⁸ The Chinese version of the ESS has good validity and reliability.⁶⁹ This study used the ESS to assess the daytime sleepiness of subjects at baseline and posttreatment.

Safety Assessments

Two types of safety assessments were performed: evaluation of changes in routine blood tests, liver function, and kidney function after the 10 intervention sessions and records of adverse events during the entire study. The record of adverse events in this study was conducted using the Adverse Event Record Form. Subjects were required to fill in the list of adverse events during the study, including the time point, severity, measures taken, whether the event was related to the treatment and prognosis. During the assessment phase, researchers assessed the possible relationship between adverse events and the study treatment, as well as medications taken concurrently. Adverse events include all adverse reactions that are

definitely related to treatment, most likely related to treatment, and likely related to treatment.

Sample Size

The required sample size was estimated based on the change in PSQI scores. According to previous research by our team,²¹ sham acupuncture can reduce the PSQI to 14.76 after 10 interventions, with an SD of 3.35. This study hypothesized that acupuncture at HT 7 and KI 7 for insomnia would reduce the PSQI by 2.70 points more than sham acupuncture. According to the needs of this study, we made $\alpha=0.05$ and $1-\beta=0.90$, according to the formula:⁷⁰

$$n = 2 \left[\frac{(u_{\alpha} + u_{\beta})}{\delta/\sigma} \right]^2 + \frac{1}{4} u_{\alpha}^2$$

A two-sided test was performed. Through the query, $u_{0.05/2}=1.96$, $u_{0.1}=1.282$, and calculated $n=33.32 \approx 34$. In addition, considering the loss factor (according to a 20% loss rate), the final sample size was 41 subjects in each group, for 82 subjects in total.

Randomization and Blinding

Specialized statisticians who were independent of the research group generated 82 random numbers in SPSS 25.0 and then arranged these numbers in order from small to large. Numbers 1–41 were artificially specified as the acupuncture group, and 42–82 were specified as the sham acupuncture group. The random numbers are reproducible (random seed number: 20190520). Subjects entered the acupuncture group or the sham acupuncture group according to randomly assigned numbers at a ratio of 1:1 after signing the informed consent form. The random number and treatment plan corresponding to each subject were printed on a card and stored in an opaque envelope. Each subject who signed the informed consent form was given an envelope with their name, which was handed over to the acupuncturist during the treatment. The acupuncturist checked the envelope and removed the treatment card to view the treatment plan.

During the study, the generation of the random numbers list, subject recruitment, acupuncture treatment, outcome measure assessment and follow-up were performed independently by different researchers. Only the outside assistant and the acupuncturist were aware of the allocation. Participants and other relevant researchers were blinded to the allocation.

Statistical Analysis

The statistics and analysis of all data were performed by two analytical researchers independent of the trial. Intention-to-treat (ITT) was used as the evaluation method to evaluate the results of the study. Statistical analysis of the data was performed using SPSS 25.0. The measurement data conformed to a normal distribution, and homogeneous variances were determined using the mean \pm standard deviation to describe the central tendency and the degree of dispersion. The primary outcome assessments were analysed using a mixed-effect model for repeated measures (MMRM) with patients as a random-effect factor, treatment group, age, gender, time and comorbidities as the fixed variable, patients as the random variable, random effects including intercept, baseline as a covariable, age*group, gender*group, time*group and comorbidities*group as interaction effect using a first-order ante dependence covariance matrix. The comparison between groups used the independent sample *t* test, and the comparison of multiple time points within groups used repeated measurement data combined with multivariate variance analysis. For measurement data that did not conform to the normal distribution, the median, minimum, and maximum were given. The between-group comparisons used the Mann–Whitney *U*-test, and the within-group comparisons used the Friedman (F) test. Enumeration data were expressed as frequency and composition rate. For binary or multicategory nonranked data, comparisons between groups were performed by the χ^2 test. If the data were ranked as ordinal data, the comparison between groups was performed by the Mann–Whitney *U*-test.

All statistical analyses used two-sided tests, and *P* values of ≤ 0.05 were considered statistically significant.

Results

Subject Characteristics

A total of 91 subjects were recruited, of whom 9 were excluded during screening. Eighty-two subjects with chronic insomnia meeting the criteria were included in this study and were randomly assigned to the acupuncture group or the sham acupuncture group. Among the subjects, 4 withdrew for personal reasons; 1 withdrew due to poor results; 1 withdrew due to adverse reactions; and 1 completed the treatment but did not undergo posttreatment evaluation. Therefore, a total of 75 eligible subjects completed the treatment and follow-up stage, including 37 in

the acupuncture group and 38 in the sham acupuncture group (Figure 2).

Table 1 presents the demographic characteristics of the subjects. Subjects' ages ranged from 25 to 73 (median 58 years), 23 (28.0%) were male, and 59 (72.0%) were female. The majority of the subjects were normal weight ($n = 68$, 82.9%). The subjects had a longer course of insomnia (median 9.5 years). Approximately 53.7% of the subjects were taking sedative-hypnotic drugs. There were no differences in the demographics between the two groups. Baseline clinical characteristics were also balanced between the two groups (Tables 2 and 3).

Efficacy

Primary Outcome Assessments

The mixed-effect model analysis revealed that there were significant effects for the time \times treatment interaction on the PSQI ($F=4.756$, $P=0.004$) (Table 2 and Figure 3), which means that the change trend of the PSQI over time was different due to the different groups. The mixed-effect model analysis also showed significant effects for the time \times treatment interaction on the ISI ($F=4.130$,

$P=0.008$) (Table 2 and Figure 4), which means that the change trend of the ISI over time was different due to different groups. There were improvements in PSQI and ISI scores after either acupuncture or sham acupuncture treatment (Table 3). PSQI scores decreased from 14.78 to 9.74 in the acupuncture group and from 14.61 to 11.69 in the sham acupuncture group. After treatment, the difference between groups was statistically significant ($F=-2.537$, $P=0.013$). ISI scores at baseline were 18.78 for the acupuncture group and 20.49 for the sham acupuncture group. The scores decreased to 11.13 for the acupuncture group and 15.44 for the sham acupuncture group. After treatment, the difference between groups was statistically significant ($F=-3.796$, $P<0.001$). Although the PSQI and ISI scores were lower than at baseline at the one-week follow-up and one-month follow-up, no differences were observed between groups ($P>0.05$ for all comparisons).

Secondary Outcome Assessments

PSG Assessments

The results of PSG measurements are summarized in Table 4. After treatment, there were significantly lower levels of SOL [15.5 (10.0, 18.5) vs 18.5 (11.5, 31.0), $P = 0.039$] in the

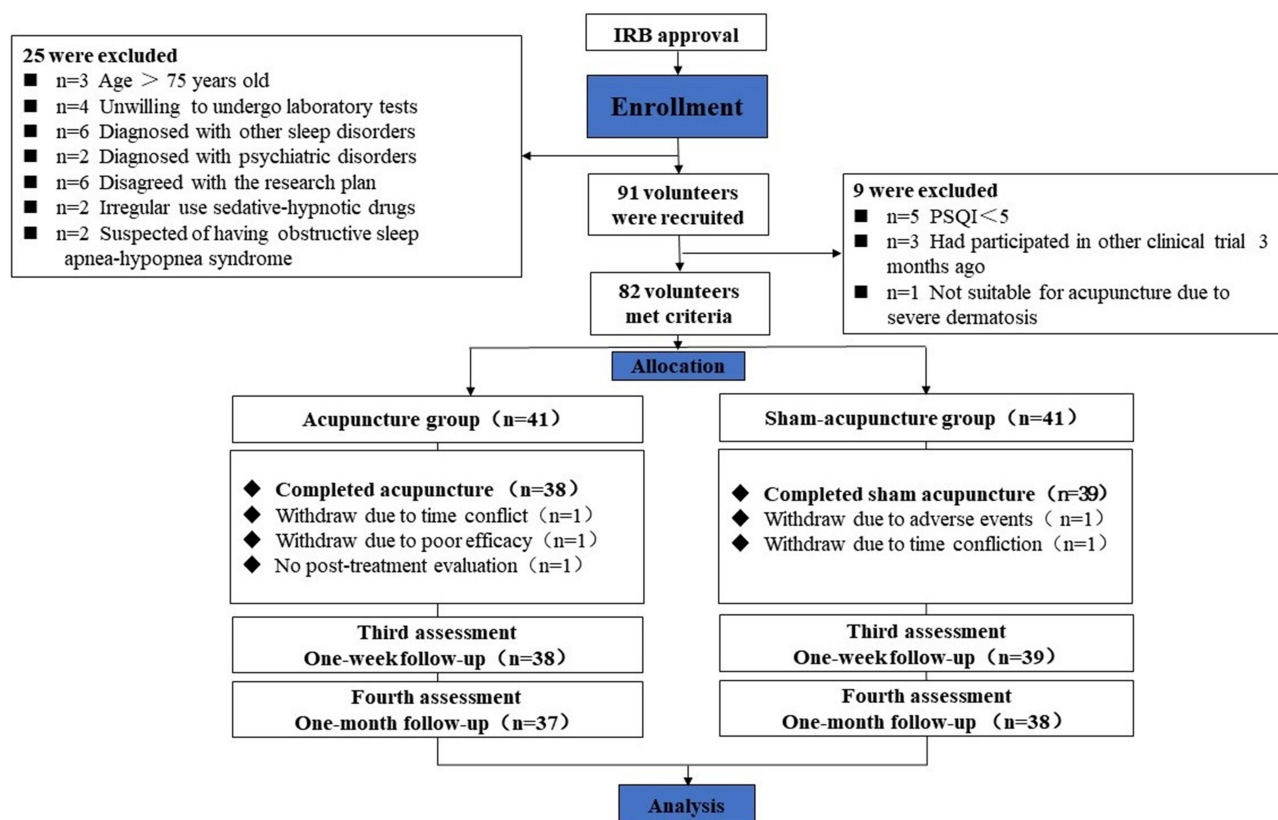


Figure 2 Flow of subjects randomized to acupuncture or sham acupuncture.

Table 1 Demographic Characteristics of Subjects

Variable	Total Sample (n = 82)	Acupuncture (n = 41)	Sham Acupuncture (n = 41)	Z/ χ^2 Value ^a	P
Age, y	58(25, 73)	57(25, 72)	58(25, 73)	-0.264	0.791
Gender	–	–	–	0.544	0.461
Male	23(28.0%)	13(31.7%)	10(24.4%)		
Female	59(72.0%)	28(69.3%)	31(75.6%)		
BMI, kg/m ²	–	–	–	-1.106	0.269
Under weight	2(2.4%)	1(2.4%)	1(2.4%)		
Normal weight	68(82.9%)	36(87.8%)	32(78.0%)		
Overweight	10(12.3%)	3(7.4%)	7(17.2%)		
Obesity	2(2.4%)	1(2.4%)	1(2.4%)		
Education	–	–	–	1.352	0.853
Primary school	3(3.8%)	1(2.4%)	2(4.9%)		
Junior high school	11(13.6%)	7(17.1%)	4(9.8%)		
High school	20(24.4%)	9(21.9%)	11(27.1%)		
College degree	40(48.4%)	20(48.8%)	20(48.4%)		
Graduate degree	8(9.8%)	4(9.8%)	4(9.8%)		
Insomnia duration, y	9.5(0.3, 40.0)	6.0(0.3, 40.0)	10.0(0.5, 40.0)	-1.297	0.195
Concomitant diseases	35(42.7%)	18(43.9%)	17(41.5%)	0.050	0.823
Drug allergy	20(24.4%)	12(29.3%)	8(19.5%)	1.058	0.304
Current hypnotics	–	–	–	-0.603	0.546
Never	38(46.3%)	18(43.9%)	20(48.8%)		
Taking one or more	44(53.7%)	23(56.1%)	21(51.2%)		

Notes: Data are presented as either M (Min, Max) or number (%). ^aThe measurement data did not conform to normality after the Shapiro–Wilk test. Comparison between the acupuncture and sham acupuncture groups by Mann–Whitney U-test or χ^2 test.

Table 2 The Mixed Effect Model Analysis of Primary Outcome Measures

	Group	Age	Gender	Time	Comorbidity	Age Group*	Gender Group*	Time Group *	Comorbidity Group*
PSQI									
F	2.129	20.486	0.031	71.178	0.261	0.832	1.406	4.756	1.058
P	0.145	<0.001	0.860	<0.001	0.609	0.362	0.236	0.004	0.304
ISI									
F	0.440	4.222	6.264	59.901	0.005	0.038	1.682	4.130	0.534
P	0.507	0.040	0.012	<0.001	0.946	0.845	0.195	0.008	0.465

Notes: Data were analyzed using a mixed-effect model for repeated measures (MMRM). *Interaction.

Abbreviations: PSQI, Pittsburgh sleep quality index; ISI, insomnia severity index.

acupuncture group than in the sham acupuncture group. In terms of sleep architecture, the percentage of sleep stage N1 (19.65±5.06% vs 24.99±4.60%, $P = 0.015$) was decreased and that of stage N3 (25.22±5.31 vs 17.88±4.84, $P = 0.002$) was increased significantly in the acupuncture group compared with the sham acupuncture group. However, no

significant differences in the percentage of stages N2 or R were noted between the groups ($P > 0.05$).

Assessment of Comorbid Symptoms

The results of comorbid symptom assessments are summarized in Table 5. After treatment, there were lower

Table 3 Primary Outcome Measures from Baseline to 4-Week Follow-Up

Assessments	Group		Baseline	Post-Treatment	Follow-Up 1	Follow-Up 2	F	P
PSQI score	Acupuncture (n=41)	$\bar{x} \pm s$	14.78±2.71	9.74±3.08	10.66±3.43	10.51±3.60	41.694	<0.001
	Sham-acupuncture (n=41)	$\bar{x} \pm s$	14.61±3.11	11.69±3.65	11.03±3.40	10.59±3.95	32.217	<0.001
	Between-group	F	0.265	-2.537	-0.472	-0.075	–	–
		P	0.791	0.013	0.638	0.940	–	–
ISI score	Acupuncture (n=41)	$\bar{x} \pm s$	18.78±4.68	11.13±3.74	12.05±5.60	12.14±5.03	43.048	<0.001
	Sham-acupuncture (n=41)	$\bar{x} \pm s$	20.49±4.65	15.44±5.98	14.49±7.45	13.42±6.58	34.019	<0.001
	Between-group	F	-1.657	-3.796	-1.624	-0.949	–	–
		P	0.101	<0.001	0.109	0.346	–	–

Notes: Data are presented as the mean \pm SD. Comparison within-group and between-group by repeated-measures ANOVA.

Abbreviations: PSQI, Pittsburgh sleep quality index; ISI, insomnia severity index.

levels of comorbid symptoms (BAI, BDI, FSS and ESS) in both the acupuncture group and the sham acupuncture group. However, no significant differences were noted between the groups after treatment ($P > 0.05$).

Safety Assessments

The main observation and recording indicators in this study were WBC, RBC, Hb, and PLT as routine blood tests; AST, ALT, and ALP for liver function; and UREA,

CRE, and UA for kidney function. The blood indicators of the subjects were divided into three levels: normal range, abnormalities with no clinical significance, and abnormalities with clinical significance. The results showed that the blood indicators of the two groups had no abnormal changes from baseline to posttreatment.

During the implementation of this study, one subject in the sham acupuncture group withdrew due to foot swelling. The research leader judged that the relationship with

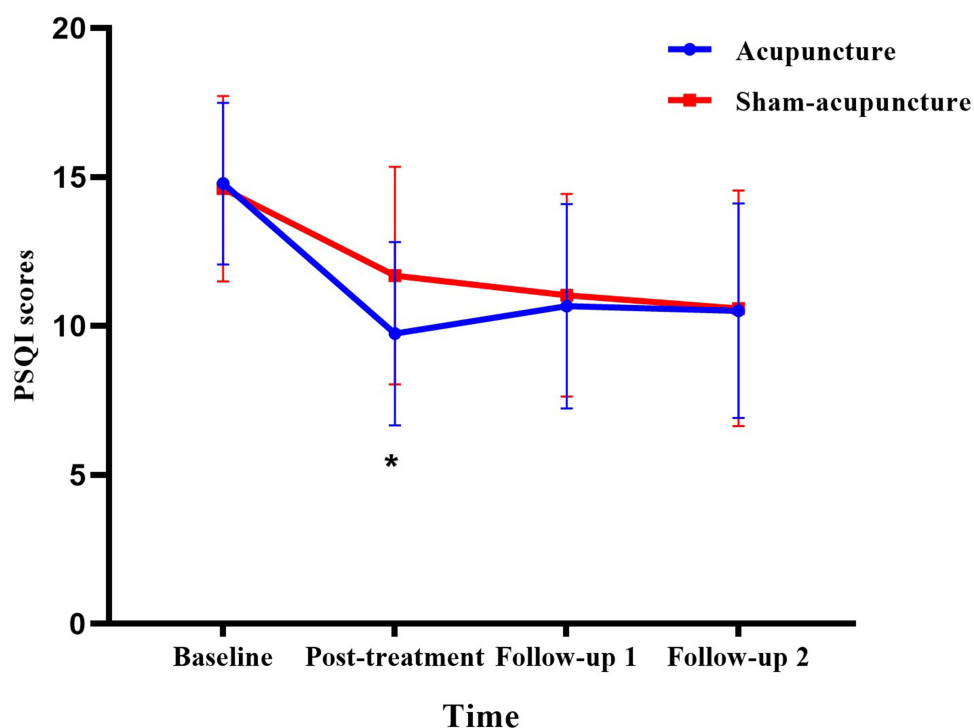


Figure 3 Mean PSQI scores of the two groups during the study period.

Note: * $P < 0.05$ vs sham-acupuncture group.

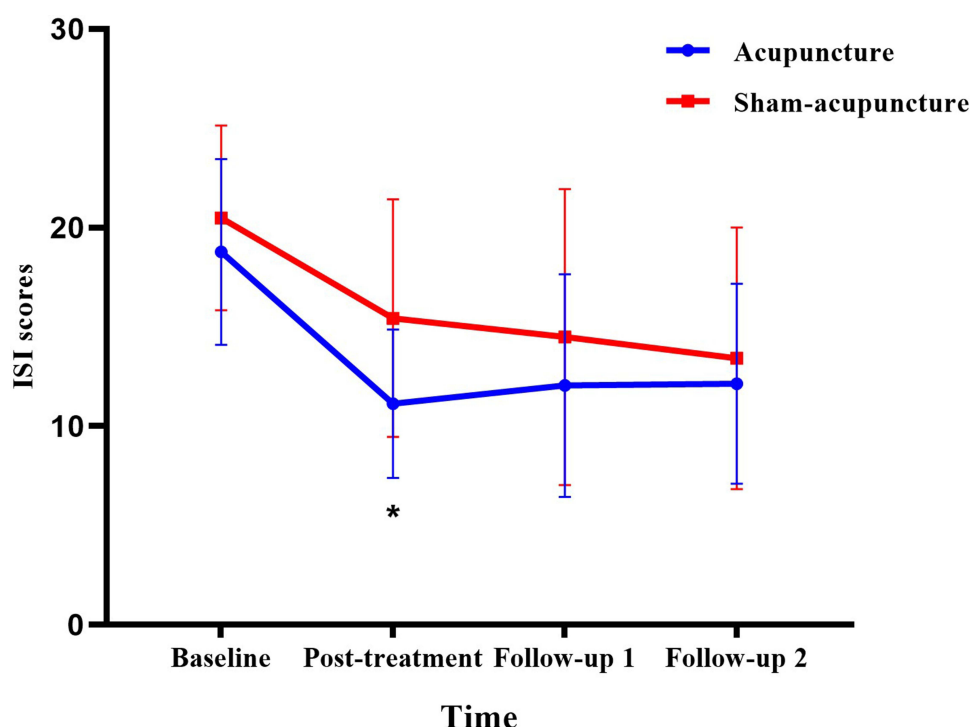


Figure 4 Mean ISI scores of the two groups during the study period.

Note: * $P < 0.05$ vs sham-acupuncture group.

intervention was “may not be relevant”. Some subjects experienced local subcutaneous bleeding symptoms after the needles were removed, but the bleeding time did not exceed 1 minute, and there was no other discomfort. During the study period, no subjects experienced adverse reactions such as needle syncope, needle sticking, or subcutaneous haematoma, and no subjects experienced pain for longer than 30 minutes due to the intervention.

Discussion

This study is consistent with our team’s previous research²¹ and other similar clinical studies of acupuncture for insomnia.^{18,71,72} The current study found that acupuncture can improve subjective and objective sleep indicators in patients with chronic insomnia. To the best of our knowledge, this is the first study to evaluate the efficacy and safety of using acupuncture at HT 7 and KI 7 to improve sleep and comorbid symptoms in chronic insomnia through subjective and objective measurements. On the basis of our previous research,²¹ we reduced the pain of subjects by streamlining the acupoints, improved compliance (drop-out rate 8.54%), introduced more efficacy evaluation indicators, and extended the follow-ups to one month.

This study used the PSQI and ISI as the main outcome measures. We found that in the acupuncture group, PSQI and ISI scores decreased by 5.04 and 7.65 points, respectively, after 10 sessions of acupuncture treatment. Similarly, improvements were also found in other studies of acupuncture for insomnia.^{18,21} Previous research by our team has shown that for patients with perimenopausal insomnia, 10 sessions of acupuncture significantly reduced PSQI and ISI scores by 8.03 and 11.35 points, respectively. This study did not achieve the same effect. The reasons may be as follows: First, the acupoints were simplified in this study, and the effect of the treatment was reduced accordingly. Second, the previous study was aimed at people with perimenopausal insomnia, and appropriate acupoints can reduce perimenopausal symptoms and indirectly improve sleep symptoms. Third, compared with the previous study, the subjects recruited in this study had a lower severity of insomnia at the baseline analysis. In addition, there are some clinical studies on acupuncture for insomnia that have not achieved such a significant effect in subjective measurements. Xua Yin and colleagues¹⁸ found that the ISI score decreased 6.6 points after 4 weeks of acupuncture among subjects with insomnia. The study by Wing-Fai Yeung et al³⁹ found no significant differences between groups in ISI or other outcome measures. The

Table 4 PSG Measures from Baseline to Post-Treatment

PSG Assessments	Acupuncture			Sham-Acupuncture				
	$\bar{x} \pm s / M(\text{Min, Max})$	Z/F ^a	P	$\bar{x} \pm s / M(\text{Min, Max})$	Z/F ^a	P	Z/F ^b	P
SOL(minutes)	–			–				
Baseline	20.0(5.0, 78.0)	2.273	0.132	13.0(5.0, 100.0)	0.333	0.564	–1.141	0.254
Post-treatment	15.5(10.0, 18.5)			18.5(11.5, 31.0)			–2.065	0.039
TST (minutes)	–			–				
Baseline	384.5(226.5, 452.5)	7.364	0.007	353.0(214.5, 443.0)	8.333	0.004	–1.016	0.310
Post-treatment	404.0(318.5, 458.0)			394.0(219.0, 475.0)			–1.046	0.295
WASO (minutes)	–			–				
Baseline	74.5(13.0, 242.5)	7.364	0.007	84.5(12.0, 259.0)	5.333	0.021	–1.037	0.300
Post-treatment	41.5(9.5, 109.0)			76.25(1.5, 258.0)			–1.416	0.157
SE (%)	–			–				
Baseline	73.66±13.63	2.836	0.018	68.82±12.64	3.399	0.006	1.011	0.321
Post-treatment	80.93±9.25			75.70±12.26			1.147	0.264
Arl	–			–				
Baseline	17.38±8.96	–1.789	0.104	16.69±7.72	1.157	0.272	0.224	0.824
Post-treatment	13.38±6.51			18.57±6.03			–1.984	0.060
N1 (%)	–			–				
Baseline	31.61±10.38	–4.737	0.001	28.52±9.68	–1.735	0.111	0.844	0.406
Post-treatment	19.65±5.06			24.99±4.60			–2.654	0.015
N2 (%)	–			–				
Baseline	35.73±10.82	–1.919	0.084	35.96±11.18	–1.695	0.118	–0.056	0.955
Post-treatment	29.13±9.03			32.83±8.14			–1.035	0.312
N3 (%)	–			–				
Baseline	14.37±5.58	6.846	<0.001	17.55±8.34	0.812	0.434	–1.228	0.230
Post-treatment	25.22±5.31			17.88±4.84			3.467	0.002
R (%)	–			–				
Baseline	18.30±5.50	4.856	0.001	17.97±5.16	4.407	0.001	0.168	0.868
Post-treatment	26.01±3.30			24.26±5.51			0.914	0.371

Notes: Data are presented as the mean \pm SD or median (minimum, maximum). ^aComparison within groups by repeated-measures ANOVA or nonparametric test. ^bPost-treatment comparison between groups by repeated-measures ANOVA or nonparametric test.

Abbreviations: PSG, polysomnography; SOL, sleep onset latency; TST, total sleep time; WASO, wake after sleep onset; SE, sleep efficiency; Arl, arousal index; R, rapid eye movement.

inconsistencies may be caused by differences in the choice of acupuncture points (number and attributes), acupuncture manipulation, and study populations. In this study, we provided direct evidence for the benefits of acupuncture at HT 7 and KI 7 in treating chronic insomnia among the Chinese population.

Among the factors that could affect acupuncture treatment for insomnia, the selection of acupoints is the most important. According to TCM theory, the selection for acupoints is based on three main strategies, ie, acupoints of the corresponding meridian, experience points, and special acupoint combinations. Therefore, each clinical study has different acupuncture point selections according to different

TCM theories. In previous studies, acupoints used for insomnia with high frequency were GV20 (Baihui), PC 6 (Neiguan), SP 6 (Sanyinjiao), HT 7 (Shenmen), GV24 (Shenting), and Ex-HN1 (Sishencong),^{41,73} which are experience acupoints for insomnia. Previous studies selected acupoints based on experience but lacked the guidance of TCM theory. We believe that these studies did not fully represent TCM acupoints. The disadvantage of empirical acupoints is that logic suggests that the more acupuncture points are selected for the treatment, the better the effect will be; however, that is not what is observed. Therefore, many studies have used a total of 10 or more acupoints according to the empirical acupoint principle, which not only fails to achieve

Table 5 Comorbid Symptom Measurements from Baseline to Post-Treatment

Comorbid Assessments	Acupuncture			Sham-Acupuncture				
	$\bar{x} \pm s / \mathbf{M}(\mathbf{Min}, \mathbf{Max})$	Z/F^a	P	$\bar{x} \pm s / \mathbf{M}(\mathbf{Min}, \mathbf{Max})$	Z/F^a	P	Z/F^b	P
BAI score	–			–				
Baseline	36 (24, 71)	19.882	<0.001	38 (24, 74)	8.257	0.004	–0.427	0.669
Post-treatment	33 (24, 59)			33 (24, 65)			–0.552	0.581
BDI score	–			–				
Baseline	16 (2, 34)	15.114	<0.001	16 (1, 37)	1.000	0.317	–0.251	0.802
Post-treatment	11.5 (0, 39)			13 (0, 31)			–1.031	0.303
FSS score	–			–				
Baseline	40.59±14.46	0.685	0.497	43.98±13.40	1.414	0.166	–1.101	0.274
Post-treatment	38.13±13.65			41.54±13.16			–1.115	0.269
ESS score	–			–				
Baseline	9 (0, 19)	<0.001	1.000	10 (0, 21)	1.400	0.237	–0.019	0.985
Post-treatment	8.5 (1, 24)			6 (0, 18)			–1.729	0.084

Notes: Data are presented as the mean \pm SD or median (minimum, maximum). ^aComparison within groups by repeated-measures ANOVA or nonparametric test. ^bPost-treatment comparison between groups by repeated-measures ANOVA or nonparametric test.

Abbreviations: BAI, Beck anxiety inventory; BDI, Beck depression inventory; FSS, fatigue severity scale; ESS, Epworth sleepiness scale.

the expected effect,³⁹ but also increases the subjects' suffering. Therefore, this study abandoned the principle of empirical acupoints and selected acupoints based on TCM and meridian theory. According to the theory of TCM, the comorbidity of the heart and kidney is an important factor in the occurrence of insomnia. Heart belongs to fire, and kidney belongs to water. The relationship between the heart and kidney is one of interaction and restriction. The rise of Yang in the kidney can warm the heart fire, and the heart fire can drop to the kidney, which can nourish the Yin in the kidney. If the functional relationship between the heart and kidney is imbalanced, pathological changes will occur. In addition to insomnia, the symptoms of this imbalance include anxiety, depression and other unhealthy emotions. This study used the theory of harmony between the heart and kidney to treat insomnia. The selected acupoints HT 7 and KI 7 belong to the Hand Shaoyin Heart Meridian and Foot Shaoyin Kidney Meridian, respectively, which satisfy the attributes of meridians and Zang-Fu in the treatment of insomnia according to TCM. The selected points on the meridians with the same name have an appropriate relationship for the mother-son reinforcing-reducing method. The results showed that acupuncture at HT 7 and KI 7 for insomnia had a benign effect based on the theory of harmony between the heart and kidney.

In terms of objective sleep measures, this study found that acupuncture can improve SOL and sleep architecture. Compared with the sham acupuncture group, the

acupuncture group showed a statistically significant decrease in SOL. With respect to sleep architecture, less time in stage N1 and more time in stage N3 were found in the acupuncture group. Other studies on acupuncture for insomnia have rarely explored sleep architecture, although some have used PSG as an objective measure. Some similar studies suggest that acupuncture can improve sleep architecture by increasing the percentage of slow wave sleep (SWS), thereby improving sleep quality,⁷⁴ which was consistent with our study. However, regarding the effects of acupuncture on sleep maintenance and SE, the results of our study are inconsistent with those of similar studies. Studies have suggested that acupuncture can improve TST and SE.^{18,21} This study found that although the acupuncture group showed increases in TST and SE, there was no significant difference between the groups. This may be due to the use of data from only the second consecutive night of PSG monitoring for statistical analysis in this study to exclude the "first night effect". Therefore, this result was more objective than previous studies, but due to the "first night effect", subjects might have been prone to compensatory sleep on the second night; that is, they may have slept better than usual. That is why the baseline analysis of the study showed that the mean TST was >6 hours, and the room for improvement was small. There are different conclusions about the impact of acupuncture for insomnia on objective sleep measures, and it is limited by many factors.

In the future, acupuncture researchers may pay more attention to the recovery and stability of the sleep architecture.

It is worth noting that acupuncture could improve comorbid symptoms, but the difference was not statistically significant compared with sham acupuncture. The reasons may be as follows: First, this study only selected two acupoints (HT 7 and KI 7) to treat insomnia and comorbid symptoms. When selecting the acupoints, we mainly considered that HT 7 and KI 7 can improve insomnia symptoms. Although HT 7 has the effect of improving depression and anxiety symptoms and KI 7 has the effect of improving fatigue symptoms, the effect of a single acupoint may not be sufficient. Second, this study only adopted ten acupuncture treatments. However, chronic insomnia is a long-term disease. Our course of treatment may be relatively short and fail to achieve the expected clinical effect. Finally, this study mainly recruited subjects diagnosed with chronic insomnia and excluded patients with mental illnesses such as anxiety and depression disorders. Although the subjects generally had symptoms of anxiety and depression, they did not meet the relevant diagnostic criteria. Because of the “floor effect”, the indicators improved, but the difference was not significant.

In addition, the results of this study showed that sham acupuncture had a benign effect on subjective and objective measurements. The results were similar to those of other clinical studies, suggesting that sham acupuncture has a certain clinical effect.^{39,40} A possible reason for this discrepancy may be that the participants we recruited had a positive attitude towards acupuncture treatment, and this high expectation might overoptimize the responses. The other reason may be that we used the true needle through, did not manipulate needles, and did not induce “De qi” but rather produced a shallow puncture through the skin.⁷⁵ According to the theory of TCM, this sham acupuncture method belongs to the categories of “burr needling” and “shallow needling” in the Canon of Internal Medicine. It can exert curative effects by stimulating the twelve skin zones (superficial parts of human skin). In future research, we would expand the scope of recruitment and adopt more reasonable sham acupuncture methods.

Overall, acupuncture at HT 7 and KI 7 can significantly improve subjective and objective sleep indicators in subjects with chronic insomnia. While the subjects’ anxiety and depression were reduced, no significant difference compared with sham acupuncture was observed. Acupuncture at HT 7 and KI 7 failed to significantly improve the subjects’ daytime fatigue and sleepiness.

Acupuncture at HT 7 and KI 7 for insomnia had short-term effects, and there was no significant difference between the groups during the follow-ups. This kind of acupuncture method has high safety and no obvious adverse effects and thus has value for further clinical exploration.

Limitations

This study has some limitations. First, the acupuncturist could not be blinded to the treatment group, and the measure of treatment fidelity was not established. Second, due to limited time and insufficient equipment, only some of the subjects were selected for PSG monitoring. The results may be not accurate. Finally, there was no difference between the two groups during the follow-up period. The precise effect duration of acupuncture at HT 7 and KI 7 needs more exploration.

Conclusions

The results of the current trial provide supportive evidence that acupuncture at HT 7 and KI 7 can be an effective, safe, and well-tolerated nonpharmacological intervention for insomnia using both subjective questionnaires and objective sleep measures. However, acupuncture at HT 7 and KI 7 can only provide a short-term effect, and a better combination of acupuncture points needs further exploration.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author (Yun-fei Chen) upon reasonable request. Additionally, the individual deidentified participant data are available after contacting the corresponding author via email (icyf1968@163.com). The data will be available immediately following publication without an end date.

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Disclosure

The authors report no conflicts of interest in this work.

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