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Clinical Study

Auricular acupressure as assistant in primary insomnia management: a randomized single-blind controlled clinical trial

耳穴按压辅助治疗原发性失眠的随机单盲临床对照试验

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Abstract

Objective: To observe the efficacy and safety of dexzopiclone plus auricular acupressure in intervening primary insomnia.

Methods: A total of 72 participants who met the inclusion criteria were enrolled in a randomized controlled trial, with 36 cases allocated to a treatment group and 36 cases allocated to a control group. Both groups were given dexzopiclone as the routine treatment. Patients in the treatment group were given auricular acupressure with *Wang Bu Liu Xing* (*Semen Vaccariae*) seeds at the auricular acupoints related to sleep and emotion based on meridian theory, whereas for patients in the control group, the medical plasters with *Wang Bu Liu Xing* (*Semen Vaccariae*) seeds were only gently stuck to acupoints unrelated to sleep without stimulation. Patients in both groups were required to visit the hospital once a week for replacing the seeds and plasters. The course of intervention lasted for 8 weeks and the patients were followed up for another 4 weeks. Pittsburgh sleep quality index (PSQI) and Karolinska sleep diary (KSD) were used to evaluate the outcomes. Meanwhile, adverse effects were monitored and recorded.

Results: In the enrolled 72 cases, 4 patients (one in the treatment group and three in the control group) reported thirst and a bitter taste, and one case in the control group reported nausea and vomiting. At last, 3 cases in the control group dropped out for adverse reactions, and 69 cases completed the clinical trial. After 8 weeks of treatment, the global scores of PSQI in both treatment and control groups decreased significantly compared with the baseline (both $P<0.001$). Furthermore, the global score of PSQI in the treatment group was lower than that in the control group ($P<0.01$). The global scores of PSQI in both groups at the follow-up were significantly different from the baseline (both $P<0.001$), but insignificantly different compared with the post-treatment results (both $P>0.05$). According to KSD, both treatment protocols could prolong the total sleep time, shorten sleep-onset latency, improve sleep efficacy and sleep quality significantly, and the changes in the treatment group were more significant. The total effective rate was 88.9% in the treatment group, higher than 81.8% in the control group, though the difference was statistically insignificant ($P>0.05$).

Conclusion: Dexzopiclone plus auricular acupressure is effective and safe for patients with primary insomnia both in short and long terms, and it is more effective than monotherapy of dexzopiclone.

Keywords: Acupuncture-moxibustion Therapy; Acupoint Therapy; Auricular Point Sticking; Insomnia; Dexzopiclone

【摘要】目的：观察右佐匹克隆联合耳穴按压干预原发性失眠症的有效性及安全性。**方法：**将符合入组标准的72例受试者随机分为两组，治疗组36例，对照组各36例。两组均接受右佐匹克隆作为基础治疗。治疗组在此基础上根据经络理论选用与睡眠、情绪相关的耳穴以王不留行籽按压，对照组则只在与睡眠无关的耳穴上轻轻贴上王不留行籽，不予以按压。所有患者被要求1周来院更换1次耳贴。治疗共持续8周，随访4周。采用匹兹堡睡眠质量指数(PSQI)和卡罗林斯卡睡眠日志(KSD)评价临床疗效，同时观察并记录不良反应。**结果：**招募的72例受试者中，4例(治疗组1例，对照组3例)报告口干、口苦，1例(对照组)报告恶心呕吐。最终，对照组3例因不良反应退出临床试验，共69例完成临床研究。经8周治疗，对照组与治疗组PSQI评分均明显下降，治疗前后评分均具有统计学差异(均$P<0.001$)，且治疗组PSQI总分下降较对照组更明显($P<0.01$)。随访时与治疗前相比，两组PSQI总分均有统计学

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差异(均P＜0.001)，但与治疗刚结束时相比，差异均无统计学意义(均P＞0.05)。根据KSD，提示两种治疗方案均能显著延长睡眠总时间，缩短睡眠潜伏期和提高睡眠质量及睡眠效率，且治疗组效果更显著。治疗组总有效率88.9%，高于对照组的81.8%，但组间差异无统计学意义(P＞0.05)。**结论：**耳穴按压联合右佐匹克隆是治疗原发性失眠的有效、安全方法，近期、远期疗效佳，且疗效优于单独应用右佐匹克隆。

【关键词】针灸疗法；穴位疗法；耳穴贴压；失眠；右佐匹克隆

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With a prevalence of 30%-49%, insomnia is one of the most common health complaints[1]. Previous epidemiological surveys showed that the prevalence of insomnia in Chinese adults was approximately 38.2%, which was higher than that in many Western countries. Among all types of insomnia, primary insomnia (PI) accounted for about 25%[2]. PI is defined by an inability to initiate and/or maintain sleep for a sufficient amount of time during regular sleeping hours, accompanied by significant daytime consequences or even impairments, and is not attributed to another sleep disorder, a mental and psychopathic illness, or as the direct effect of a substance use[3]. As a global public health issue, PI not only affects the patient's physical and mental health, but also aggravates the medical burden of the whole society[4]. Present treatment for PI falls into three main categories, pharmacotherapy, psychotherapy and complementary and alternative medicine (CAM) therapy. Although satisfactory treatment results for PI could be immediately achieved through pharmacotherapy, long-term use of hypnotics or sedatives is deemed to be associated with dependence, cognitive impairment, residual daytime sedation, traffic accidents, and so forth[5-7]. Psychotherapy, especially cognitive behavior therapy (CBT) is a first-line treatment of PI as well, but limited to its high cost[8-9]. Therefore, more and more insomniacs seek CAM therapy, particularly acupuncture, for another possible option[10]. Auricular acupressure (AA) is a non-invasive variant of acupuncture by attaching small magnetic beads or *Wang Bu Liu Xing* (*Semen Vaccariae*) seeds to the outer ear to stimulate specific areas based on meridian theories in traditional Chinese medicine (TCM)[11-12].

Numerous studies of AA plus Western medication for PI seem far less convincing due to some crucial limitations, including lack of sham AA as a control[13] and proper sleep assessment items[14]. To address the design defects mentioned above, in this study, a randomized, single-blind, sham-controlled clinical trial was conducted to evaluate the clinical efficacy and safety of AA plus dexzopiclone for the treatment of PI. Different from previous relevant research, Pittsburgh sleep quality index (PSQI) was used at three assessment time points including follow-up. In addition, Karolinska sleep diary (KSD)[15] was introduced as a high-quality self-reported outcome measure instead of general sleep diary at pre- and post-treatment evaluation. The treatment period was extended to 8 weeks, and another 4 weeks were taken for follow-up. The report is given as follows.

1 Clinical Materials

1.1 Diagnostic criteria

The diagnostic criteria were based on the 10th revision of *International Statistical Classification of Diseases and Related Health Problems* (ICD-10)[16], 5th edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V)[17], 3rd edition of *Chinese Classification of Mental Disorders* (CCMD-3)[18], and *Internal Medicine of Traditional Chinese Medicine*[19]: a type of sleep disorder with main symptoms of sleep latency or wakening after sleep onset >30 min, and difficulty initiating and maintaining sleep, frequent sleep disruptions, dreaminess, poor quality of sleep, or early waking up; the sleep disorder mentioned above occurred at least 3 times per week for more than 4 weeks; patient usually had a significant loss of memory, difficulty concentrating, fatigue, dizziness, headache, palpitation, or chest tightness due to sleep disorders; insomnia was the primary complaint and it did not occur in the presence of another sleep disease, mental disorder, or as the direct physiological effect of a substance or medical condition.

1.2 Inclusion criteria

Aged 18-65 years old; conformed to the above diagnostic criteria; global score of PSQI ≥6 points; not taking any sedative or psychoactive drug except dexzopiclone; signed informed consent, voluntarily participated in this clinical trial, and pledged to cooperate with follow-up visit.

1.3 Exclusion criteria

Individuals aged <18 or >65 years old; those with cancer, severe hepatic or renal insufficiency, hematopoietic system and endocrine system primary diseases; those had mental diseases, or used any sedative and psychoactive drugs besides dexzopiclone within two weeks before the commencement of this study; Hamilton anxiety scale ≥14 points, and/or Hamilton depression scale ≥18 points; secondary insomnia (insomnia induced by anxiety or depression disorders, obsessive-compulsive disorder, or phobia), insomnia due to occupational factors (including sleep disorders induced by shift work), jet lag syndrome, and obstructive sleep apnea-hypopnea syndrome; patients who were allergic to *Wang Bu Liu Xing* (*Semen Vaccariae*) seeds or medical adhesive plaster used in

this study; those participated in other clinical trials within the last 1 month.

1.4 Discontinuation, elimination and dropout criteria

1.4.1 Discontinuation and elimination criteria

The treatment had to be ceased due to unforeseen reasons; serious adverse events that occurred during the intervention; participants who accepted other treatments during the intervention or did not cooperate with the researcher.

1.4.2 Dropout criteria

Participants who failed to return to hospital on time besides the reasons mentioned in the discontinuation and elimination criteria; participants who were not willing to accept further treatment since the expected therapeutic effect had been achieved; participants who were not willing to accept further treatment since the treatment result was far from expected.

1.5 Statistical methods

The SPSS statistical software version 21.0 was used for statistical description and analysis after the original data were input via Excel 2010. Measurement data in normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$) and analyzed by paired *t*-test or two dependent samples *t*-test. The measurement data in abnormal distribution were analyzed by Wilcoxon rank-sum test. The enumeration data were expressed by ratio and processed by Chi-square test. Ranked data were analyzed by non-parametric test. The significance level was set at 0.05.

1.6 Clinical data

This was a randomized patient-blinded parallel-group trial with a 1:1 ratio between the treatment and control groups. Before the commencement of recruitment, the random numbers were generated by SPSS statistical software version 21.0, and these random numbers were placed inside 72 opaque envelopes. A total of 72 patients who met the inclusion criteria were recruited by hospital-based advertisements from the outpatient and the Wechat of TCM Sleep Research Institute of Shanghai Municipal Hospital of Traditional Chinese Medicine from March 2015 till June 2016. These patients were randomly allocated by simple envelope method. Outcome assessments were performed at baseline, post-treatment and 4-week follow-up. The trial was approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine.

However, three patients in the control group failed to complete the 8-week treatment, so their assessment data were not included in the statistical analysis. Therefore, 69 cases with valid data were evaluated eventually, including 36 cases in the treatment group and 33 cases in the control group. There were no significant differences in neither age nor disease duration between the two groups (all $P>0.05$), indicating the comparability after grouping (Table 1).

Table 1. Comparison of the general data ($\bar{x} \pm s$)

Group	*n*	Average age (year)	Average duration (month)
Treatment	36	43.3±15.4	13.5±6.3
Control	33	40.7±16.1	12.7±5.9

2 Methods

2.1 Intervention methods

All patients were provided with regular health education at the first visit, including a handbook of *Rehabilitation and Prevention Lectures for Insomnia* compiled by TCM Sleep Research Institute of Shanghai Municipal Hospital of Traditional Chinese Medicine. At the same time, patients and their family members were taught how to use KSD for a sleep record. Patients were asked to record KSD every day and bring it to the doctor for check at each subsequent visit.

2.1.1 Treatment group

Patients in the treatment group received dexzopiclone and real AA.

Real AA: Shenmen (TF_4), Subcortex (AT_4), Occiput (AT_3), Heart (CO_{15}), Stomach (CO_4), and Heart of Posterior Surface (P_1) were selected as auricular acupoints according to *Nomenclature and Location of Auricular Points* (GB/T 13734-2008). After sterilization by 75% alcohol swab, the auricular acupoints were applied with *Wang Bu Liu Xing* (*Semen Vaccariae*) seeds tightly using medical adhesive plasters by a certified acupuncturist. These seeds were left in place and replaced each week by the acupuncturist. Three acupoints were chosen from one ear, and the rest three acupoints were chosen from the other ear. One week later, the two groups of acupoints were switched. The participants were asked to press the seeds four times a day, respectively after breakfast, lunch and dinner, and 30 min prior to sleep, for a total of 8 weeks. Each acupoint should be pressed for 2 min each time, and the pressure should be stable and induce a mild tingling sensation or a slight sense of discomfort.

Dexzopiclone: In addition to real AA, patients in the treatment group were also prescribed with oral administration of dexzopiclone, one tablet each time, 30 min prior to sleep each night (batch number: H20100074, Chengdu Kanghong Pharmaceutical Group Co., Ltd., China, 3 mg/tablet), for a total of 8 weeks.

2.1.2 Control group

Patients in the control group received dexzopiclone plus sham AA.

Sham AA: Six auricular acupoints unrelated to the treatment of insomnia, including Tooth (LO_1), Sciatic Nerve (AH_6), Rectum (HX_2), Finger (SF_1), External Nose ($TG_{1,2i}$) and Pelvis (TF_5) were selected to conduct sham AA. *Wang Bu Liu Xing* (*Semen Vaccariae*) seeds were gently fixed to each acupoint. However, the patients

were informed that it's unnecessary to press these points since it could be effective as long as the seeds existed. The patients were only required to keep the adhesive plasters dry and visit the hospital once a week to replace the seeds and plasters. The intervention also lasted for a total of 8 weeks.

Dexzopiclone: The use of dexzopiclone in the control group was consistent with that in the treatment group.

A 4-week follow-up study was conducted for both groups.

2.2 Evaluation methods and indicators

2.2.1 PSQI

PSQI is a self-report questionnaire that assesses sleep quality over a period of one month. The measure consists of 19 individual items, creating 7 components that produce one global score. Each item is weighed on a scale of 0-3 points. The global PSQI score is calculated by totaling the seven component scores, providing an overall score ranging from 0 to 21, where a lower score denotes a healthier sleep quality. A total score >5 points indicates low sleep quality, and the higher the PSQI global score, the severer the insomnia[20].

2.2.2 KSD

KSD consists of 12 items, including total sleep time, sleep efficiency, sleep-onset latency, sleep quality index, sleep quality, feeling refreshed after awakening, ease of falling asleep, calmness of sleep, slept throughout the allotted time, repeated awakenings, sufficient sleep, and easy awakening. Each item has a set weight between 1 (very badly) and 5 (very well)[15, 21-22].

2.2.3 Clinical efficacy

The clinical efficacy was determined based on the reduction rate of PSQI score. Reduction rate of PSQI score = (Pre-treatment score – Post-treatment score) ÷ Pre-treatment score × 100%.

Clinically recovered: Reduction rate of PSQI score was ≥80%.

Markedly effective: Reduction rate of PSQI score was ≥50%, but <80%.

Effective: Reduction rate of PSQI score was ≥30%, but <50%.

Invalid: Reduction rate of PSQI score was <30%.

3 Results

3.1 Comparison of PSQI score

There was no significant difference in the global score of PSQI between the two groups at baseline (P>0.05), suggesting the comparability (Table 2). The global score of PSQI showed a significant difference in both groups after 8-week treatment (P<0.001), which was remained at the follow-up (P<0.001). Although the between-group differences were statistically insignificant at post-treatment and follow-up (both P>0.05), the decreases in the global score at the two time points compared with the pre-treatment value in the treatment group were more significant than those in the control group (P<0.01, P<0.001). The result indicated that both therapies could improve sleep quality in patients with PI and the efficacy showed consistency, and the combo therapy of real AA and dexzopiclone can produce more significant efficacy. Besides, the global score of PSQI showed a tendency to increase in the control group at the follow-up, suggesting that there might be a rebound in the control group in the long run. The detail is shown in Table 2.

Table 2. Comparison of the global score of PSQI ($\bar{x}$ ±s, point)

Group	n	Pre-treatment	Post-treatment	Follow-up	D1	D2
Treatment	36	14.97±3.68	6.64±3.38[1)]	6.50±3.26[1)]	8.33±3.95[2)]	8.47±3.91[3)]
Control	33	14.42±3.70	8.36±3.07[1)]	9.30±3.26[1)]	6.06±2.37	5.12±3.01

Note: D1=Difference between pre- and post-treatment values; D2=Difference between the pre-treatment and follow-up values; compared with the pre-treatment value in the same group, 1) P<0.001; compared with the control group, 2) P<0.01, 3) P<0.001

3.2 Comparison of KSD parameters

There was no significant difference in KSD scores between the two groups at baseline (P>0.05), suggesting the comparability. The scores of total sleep time, sleep efficacy, sleep-onset latency, sleep quality index, sleep quality and ease of falling asleep showed a significant difference in both groups after 8-week treatment (P<0.001 or P<0.05). Furthermore, scores in the treatment group increased more significantly in total sleep time, sleep efficacy, sleep-onset latency and sleep quality (P<0.01 or P<0.05) compared with those in the control group. The result revealed that both therapies could improve total sleep time, sleep efficacy, sleep-onset latency, sleep quality index, and sleep quality in patients with PI. Moreover, the combo therapy of real AA plus dexzopiclone could produce more significant efficacy in extending total sleep time, shortening sleep-onset latency, and promoting sleep efficacy and sleep quality. The scores in 'feeling refreshed after awakening' and 'repeated awakenings' elevated significantly after 8-week intervention in the treatment group (P<0.01, P<0.05) but not in the control group, suggesting that the combined therapy could decrease the repeated awakenings in PI patients and

make them feel better after awakening. In addition, patients in both groups reported 'slept enough' after 8-week treatment (P<0.001, P<0.01), and patients in the treatment group felt even better (Table 3).

Table 3. Comparison of KSD parameters ($\bar{x}$ ±s, point)

Item	Treatment group (n=36)		Control group (n=33)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Total sleep time	1.33±0.83	3.53±0.97[3)5)]	1.06±0.79	2.45±0.97[3)]
Sleep efficacy	1.25±0.73	3.42±1.05[3)4)]	1.27±0.67	2.85±0.83[3)]
Sleep-onset latency	1.44±0.73	3.31±0.98[3)5)]	1.15±0.80	2.45±1.03[3)]
Sleep quality index	1.19±0.75	2.50±1.28[3)]	1.18±0.81	2.27±1.33[3)]
Sleep quality	1.22±0.64	2.53±1.16[3)4)]	1.27±0.67	2.09±1.07[3)]
Feeling refreshed after awakening	1.50±0.56	1.83±0.85[2)]	1.48±0.57	1.61±0.75
Ease of falling asleep	1.00±0.53	1.31±0.82[1)]	0.97±0.53	1.21±0.93[1)]
Calmness of sleep	2.94±0.75	2.97±0.97	3.00±0.90	3.09±0.98
Slept throughout the allotted time	2.28±0.61	2.36±0.87	2.45±0.79	2.55±0.87
Repeated awakenings	2.75±0.73	3.08±0.91[1)]	2.72±0.67	2.94±0.66
Sufficient sleep	1.03±0.51	1.53±0.77[3)]	1.24±0.61	1.61±0.83[2)]
Easy awakening	1.22±0.68	1.33±0.76	1.24±0.66	1.30±0.73

Note: Compared with the baseline in the same group, 1) P<0.05, 2) P<0.01, 3) P<0.001; compared with the control group, 4) P<0.05, 5) P<0.01

3.3 Clinical efficacy assessment

The total effective rate of the treatment group was higher than that of the control group, though the difference was statistically insignificant (P>0.05). Besides, six patients in the treatment group achieved clinical recovery after 8-week treatment while no one did in the control group (Table 4).

3.4 Safety assessment

Four patients (one in the treatment group and three in the control group) reported significant thirst and bitter taste in mouth. Among them, two patients in the control group withdrew from the trial at week 4 and week 6, respectively. In addition, one case in the control group withdrew from the trial due to nausea and vomiting. These adverse events were reported and recorded in the case report form (CRF) for future reference.

Table 4. Comparison of the clinical efficacy (case)

Group	n	Clinically recovered	Markedly effective	Effective	Invalid	Total effective rate (%)
Treatment	36	6	18	8	4	88.9
Control	33	0	12	15	6	81.8

4 Discussion

Approximately 35% of adults experience insomnia at least once in their lives[1,23]. In addition to the severe influence on daily life, PI without intervention has been proved to be a high risk factor for impaired function, and other physical and psychological illnesses[24], such as depression, anxiety, hypertension, dementia, cardiovascular accident, and chronic fatigue syndrome[25-27]. In severe cases, it might even lead to suicidal ideation[23]. Among patients with PI, although much more interests have been increased to seek for CAM approaches in recent years[28-29], and non-pharmaceutical therapy is indeed indispensable and effective for most PI sufferers[30], sedatives and hypnotics might not be absolutely given up or completely replaced in a short time for some patients. Therefore, it is necessary to investigate the effectiveness and safety of an integrative therapy, and explore if the combination therapy is superior to monotherapy of Western medication in clinical efficacy, or whether it can minimize the side effects of Western medication. The aim of this preliminary study was to evaluate and assess the validity of AA plus dexzopiclone as an integrative therapy in the management of PI.

Since it is convenient and non-invasive, AA has basically become a popular form of TCM therapies based on the theory that the ear is a microsystem[31-34], which reflects the entire body. Specific points on the auricle correspond to major organs and systems of the

body, so that the function of the target organ or system can be modulated by stimulating corresponding auricular acupoints. In AA, *Wang Bu Liu Xing* (*Semen vaccariae*) seeds or small magnetic beads are usually fixed tightly onto the acupoints with medical adhesive plasters. Although the patients might not be able to locate the acupoints correctly due to lack of professional TCM theory, they could be trained to conduct and manage the treatment themselves through pressing the seeds/beads to exert stimulation at a required strength and frequency after the seeds/beads were fixed to the correct acupoints by the qualified acupuncturists.

In a few high-quality studies aiming to explore the effectiveness of acupuncture conducted in Western countries, acupuncture was proved to have only caused a 'placebo' effect and thus was viewed as a 'mega-placebo'[35-37]. In order to minimize placebo effect as much as possible, in our trial, a sham AA intervention was set up with insomnia-unrelated acupoints and no stimulation. According to the results of PSQI scales, though both therapies were proved to improve sleep in patients with PI, the effectiveness of AA plus dexzopiclone was better than that of monotherapy of dexzopiclone. Similar results were also revealed by the comparison of KSD parameters between the two therapies. To be more specific, AA plus dexzopiclone was significantly better than monotherapy of dexzopiclone in increasing sleep time, shortening sleep latency, and improving sleep quality and efficiency. In addition, AA plus dexzopiclone could significantly reduce awakening times and improve patient's feelings after awakening, whereas there was not enough evidence in this trial to show that monotherapy of dexzopiclone could. Autonomic nervous system regulation by the auriculovagal afferent pathway has been considered a potential explanation for how AA improves PI[38].

It should be noted that, in terms of adverse events, though the sample size was not enough to conduct statistical analysis, the less adverse events occurred in the group of combination therapy than in the group of medication therapy. Hence, further research is expected to investigate if AA can reduce the side effects of hypnotic or sedatives. Based on the result of the present trial, the combo protocol is worthy of clinical promotion.

However, some limitations should be noticed in this trial, including the absence of evaluation based on an objective outcome such as polysomnography (PSG), which might result in statistical bias in outcome assessment. Bias might also be caused by the small sample size, and relatively short intervention and follow-up period. Another weakness was that the participants were all recruited from the Shanghai Municipal Hospital of Traditional Chinese Medicine, which might result in the bias of the results. For further research, conducting a multi-centered randomized single-blind placebo-controlled clinical trial with a large sample size and long-term observation is required. With objective outcome measures such as PSG and actigraphy, and self-report outcome measures such as KSD, we will be able to provide more practical and stricter clinical research modalities in sleep-related clinical studies.

Conflict of Interest

The authors declared that there was no potential conflict of interest in this article.

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Statement of Informed Consent

Informed consent was obtained from all individual participants in this study.

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