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Clinical Study

Efficacy and safety of electroacupuncture for perimenopausal insomnia: a randomized controlled trial

电针干预围绝经期失眠的疗效与安全性随机对照研究

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Abstract

Objective: To observe the effectiveness and safety of electroacupuncture (EA) plus Luohua Anshen oral liquid for patients with perimenopausal insomnia.

Methods: A total of 66 participants who met the inclusion criteria were enrolled in the randomized controlled trial and allocated to a treatment group and a control group at a ratio of 1:1, with 33 cases in each group. Both groups were given Luohua Anshen oral liquid as a basic treatment. The treatment group was additionally given EA every other day, three times a week. Both groups were treated for four weeks and a four-week follow-up was conducted. The scores of Pittsburgh sleep quality index (PSQI), Kupperman index (KI) and traditional Chinese medicine sleep syndrome scale (TCMSSS) were recorded at pre- and post-treatment, and at the follow-up. Meanwhile, adverse effects were monitored and recorded.

Results: After four-week treatment, the global scores of PSQI, KI and TCMSSS in both groups declined significantly (all $P<0.05$), and the decreases in the treatment group were more significant than those in the control group (all $P<0.05$). The global scores of PSQI, KI and TCMSSS in both groups at the follow-up visit were significantly different from the corresponding baseline (all $P<0.05$), while insignificantly different from those assessed at post-treatment (all $P>0.05$). The total effective rate was 93.9% in the treatment group, significantly higher than 72.2% in the control group ($P<0.05$). No significant adverse event was reported in this trial excepted one patient experienced slight dizziness in the first acupuncture treatment.

Conclusion: EA plus Luohua Anshen oral liquid is safe for perimenopausal insomnia with satisfactory short- and long-term effectiveness, and it shows certain advantage compared with using Luohua Anshen oral liquid alone.

Keywords: Acupuncture Therapy; Electroacupuncture; Insomnia; Perimenopause; Climacteric; Acupuncture Medication Combined; Randomized Controlled Trial

【摘要】目的：观察电针结合落花安神口服液干预围绝经期失眠症的有效性及安全性。**方法**：将符合纳入标准的66例受试者按1:1的比例随机分为治疗组和对照组，每组33例。落花安神口服液作为两组的基础治疗。治疗组在此基础上加电针疗法，隔日1次，每周3次。两组均连续治疗4周，治疗结束4周后随访。治疗前、治疗后及随访时，采用匹兹堡睡眠质量指数(PSQI)、Kupperman指数(KI)及中医睡眠证候量表(TCMSSS)评估。同时观察并记录不良反应事件。**结果**：治疗4周后，对照组与治疗组PSQI、KI及TCMSSS总分均明显下降，治疗前后评分差异具有统计学意义(均$P<0.05$)，且治疗组评分下降比对照组更显著(均$P<0.05$)。随访时，两组PSQI、KI及TCMSSS总分与本组治疗前差异均具有统计学意义(均$P<0.05$)，但与治疗后评分无统计学差异(均$P>0.05$)。治疗组总有效率为93.9%，对照组总有效率为72.7%，两组差异具有统计学意义($P<0.05$)。研究过程中，除1例患者在初次接受电针治疗时出现轻微晕针外，未发生其他严重不良反应事件。**结论**：电针结合落花安神口服液治疗围绝经期失眠症有效、安全，近期、远期疗效佳；与单纯使用落花安神口服液相比具有一定优势。

【关键词】针刺疗法；电针；失眠症；围绝经期；更年期；针药结合；随机对照试验

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Perimenopause refers to a special period around the menopause in most women's life. It is a transitional period in which the ovarian function gradually declines. Perimenopausal women may experience a series of problems, including autonomic dysfunction, vasomotor dysfunction, urogenital dysfunction, and metabolic disorders, due to activity decrease in sex hormones. The manifestations may include irritability, flush face, hot flashes, palpitations, insomnia, night sweats and/or frequent daily sweating, dizziness, tinnitus, pruritus, algopareunia, soreness and weakness of the low back and knees, frequent urination, or even incontinence[1]. Among them, insomnia affects as high as 53% of perimenopausal women[2], and the incidence of insomnia may increase with age[3-4].

Hormone replacement therapy (HRT) is the first-line treatment for climacteric syndrome in Western medicine, including perimenopausal insomnia (PMI). Though the expected effects might be achieved immediately, HRT was reported to increase the risk for endometrial cancer, ovarian cancer, breast cancer, and cardiovascular accidents[3,5]. Besides, sedatives and hypnotics including benzodiazepine receptor agonists are currently recommended for PMI with satisfactory short-term efficacy[6]. However, certain potential residual symptoms such as excessive sedation, tolerance, addiction and neurological toxicity might be caused by long-term use[7], which is also the key reason why more interests have emerged in seeking traditional Chinese medicine (TCM) approaches in recent years.

PMI belongs to the category of Bu Mei (sleepless), Zang Zao (hysteria) or perimenopausal symptoms in TCM theory. For its cause of hyperactivity of liver-yang and deficiency of kidney-yin, restraining liver-yang plus tonifying kidney-yin is usually considered as the main treatment principle. Luohua Anshen oral liquid has shown satisfactory clinical efficacy for various insomnia conditions[8]. The purpose of this study was mainly to investigate if electroacupuncture (EA) plus this medicinal liquid can achieve a better result.

1 Clinical Materials

1.1 Diagnostic criteria

1.1.1 Diagnostic criteria of TCM

Diagnostic criteria of perimenopausal syndrome referred to the *Guiding Principles for Clinical Study of New Chinese Medicines*[9]: females aged 45 to 55 years old; in addition to menstrual disorders or menopause, accompanied by hot flashes, sweating, fatigue, weak limbs, heel pain, forgetfulness, low back pain, frequent urination, or incontinence.

Diagnosis of insomnia is based on the *Internal Medicine of Traditional Chinese Medicine*[10] and the *Guiding Principles for Clinical Study of New Chinese Medicines*[9]: persistent difficulty initiating and maintaining sleep, frequent sleep disruptions, dreaminess, poor sleep quality, or waking up earlier than desired; these symptoms occurred at least three times per week for more than 4 weeks; with a significant loss of memory, difficulty concentrating, fatigue, dizziness, headache, palpitations, or chest tightness.

The patients were all diagnosed as the pattern of hyperactivity of liver-yang and deficiency of kidney-yin.

1.1.2 Diagnostic criteria of Western medicine

It was based on the 10th edition of *International Classification of Diseases* (ICD-10)[11], the 5th revision of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V)[12], *Gynecology and Obstetrics of Traditional Chinese Medicine*[13] and *Obstetrics and Gynecology*[14]: females aged 45 to 55 years old; insomnia was the primary complaint and was experienced at least three times per week for more than 4 weeks; the insomnia did not occur in the presence of another sleep disease, mental disorder, or as the direct physiological result of a substance or medical condition; in addition to insomnia, patients experienced climacteric syndrome as well.

1.2 Inclusion criteria

Considering that many females aged between 55 and 60 years old still suffer from significant symptoms of climacteric syndrome, the maximum age was increased to 60 years old, so the range of age was set between 45 and 60 years old; conforming to the above diagnostic criteria for both TCM and Western medicine; global scores of Pittsburgh sleep quality index (PSQI) ≥6 points, Kupperman index (KI) ≥15 points, traditional Chinese medicine sleep syndrome scale (TCMSSS) ≥10 points; not taking sedative and other psychoactive drugs, or had terminated for more than two weeks; signed informed consent, voluntarily participated in this clinical trial, and promised to cooperate with follow-up visits.

1.3 Exclusion criteria

Aged <45 or >60 years old; those with cancer, premature ovarian failure or bilateral oophorectomy due to other diseases, severe hepatic and renal insufficiency, primary diseases involving hematopoietic system or endocrine system; received cardiac pacemakers or cardiac stenting before; those with mental disorders that may affect cooperation, or those used sedatives within two weeks before the commencement of this study; Hamilton anxiety scale ≥14 points, and/or Hamilton depression scale ≥18 points; secondary insomnia induced by anxiety and/or depression disorders, obsessive-compulsive disorder, or phobia, or due to occupational factors (including sleep disorders induced by work shift), jet lag syndrome, or obstructive sleep apnea-hypopnea syndrome; those allergic to Luohua Anshen oral liquid used in this study; those with a tendency of skin infections or bleeding; those had been treated with sex

hormones or participated in other clinical trials within the previous one month.

1.4 Withdrawal and dropout criteria

Serious adverse event occurred; participant asked to withdraw from the trial for any reason at any time; the treatment had to be interrupted due to unforeseen reasons; participant accepted other treatment during this trial or failed to cooperate with the researcher; participant failed to revisit on time.

1.5 Participants and recruitment

A total of 66 eligible patients were recruited by hospital-based advertisements from the outpatient clinic and the WeChat of TCM Sleep Research Institute, Shanghai Municipal Hospital of TCM Affiliated to Shanghai University of Traditional Chinese Medicine between July 2015 and November 2016. This trial had been approved by the Ethics Committee of Shanghai Municipal Hospital of TCM Affiliated to Shanghai University of Traditional Chinese Medicine (number: 2015SHL-KY-17).

2 Research Methods

2.1 Randomization and allocation

The 66 participants were numbered according to the order of visit, and random numbers were generated by SPSS version 21.0 statistical software (random code was set as: 123456). The patients were randomly assigned to a treatment group or a control group according to the random number at a ratio of 1:1, thus with 33 cases in each group.

2.2 Single blind

In order to ensure the objectivity, this study was conducted in light of the principle of single-blind design (separate system of evaluator and therapist), i.e. the evaluator was not involved in the treatment process, including providing the medicinal liquid and acupuncture treatment, but was in charge of scoring the scales at pre- and post-treatment, and the statistical analysis and inference. The rater had been trained for Psychiatry Scale Identity Score by Shanghai Mental Health Center before the commencement of this clinical trial. The therapist did not participate in case screening, data processing, and score rating (The therapist had no access to the patients' baseline, scale scores, and symptom improvement or deterioration after each treatment), but only provided corresponding treatments. The purpose of this single-blind design was to prevent therapist from possible bias, thereby affecting the objectivity of the results.

2.3 Interventions

All the patients were provided with regular health education at the first visit, including a handbook of *Rehabilitation and Prevention Lectures on Insomnia* compiled by the TCM Sleep Research Institute. At the same time, the patients were asked to complete sleep diary everyday by themselves or supervised and helped by their family members.

2.3.1 Treatment group

The treatment group received EA plus Luohua Anshen oral liquid.

Major acupoints: Tousanshen points [Sishencong (EX-HN 1), Shenting (GV 24), and bilateral Benshen (GB 13)].

Adjunct acupoints: Baihui (GV 20), bilateral Shenmai (BL 62) and Zhaohai (KI 6).

Method: Patient was asked to lie in a supine position and relax the body naturally. Skin around acupoints was sterilized by 75% alcohol. Sterilized disposable needles (0.25 mm in diameter and 25 mm in length) were inserted subcutaneously into Sishencong (EX-HN 1), Baihui (GV 20), Shenting (GV 24) and Benshen (GB 13), while Shenmai (BL 62) and Zhaohai (KI 6) were inserted perpendicularly. After needling sensation was achieved through twisting or thrusting the needles, the needles at Baihui (GV 20) and Shenting (GV 24) were connected to an EA instrument with sparse-dense wave, and the intensity was set according to the patient's tolerance. All of the needles were retained for 30 min. The EA treatment was performed once every other day and three days a week. A total of 4-week treatment was given.

During the period of receiving EA treatment, patients were also given one dose of Luohua Anshen oral liquid (prepared by Shanghai Municipal Hospital of TCM Affiliated to Shanghai University of Traditional Chinese Medicine, lot number: Z05190756, 10 mL/dose] 30 min after breakfast and dinner, respectively, and two doses of it 30 min prior to sleep per night, for 4 weeks in total.

2.3.2 Control group

Patients in the control group were only provided with Luohua Anshen oral liquid, following the same dosage and course as those in the treatment group.

2.4 Evaluation methods and indicators

PSQI, KI, and TCMSSS were assessed at pre-treatment (baseline), post-treatment, and at 4-week follow-up. Total effective rate evaluation was performed at post-treatment. Observation and record of adverse event (including causing factors, solutions and results) were also required during the whole trial.

2.4.1 PSQI

As a standardized, subjective and self-report questionnaire, PSQI includes seven domains, namely sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each domain has a set weight between 0 and 3 that produces one global score ranging from 0 to 21. A total score higher than 5 points indicates a poor sleep quality, and the higher the PSQI global score, the more severe the insomnia[15].

2.4.2 KI

The severity of menopausal symptoms was assessed using KI. KI is a numerical index that scores 13 menopausal symptoms (hot flashes, paresthesia, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia or myalgia, headache, palpitations, formication, algopareunia and frequent urination) from 0 to 3 points (a greater score shows a higher frequency of the symptom). A score ranging from 15 to 39 points is considered to indicate mild to severe symptoms[3,16].

2.4.3 TCMSSS

The scale was designed by our Sleep Research Institute and has been used to assess more than one thousand patients with insomnia. The preliminary reliability and validity analysis has proven that this scale can not only fully record insomniac's sleep condition and accompanied symptoms, but also can serve as a reliable tool for evaluating the efficacy of various TCM interventions for insomnia. The scale contains 38 items, each scored from 0 to 3: 0 point for no obvious symptoms, 1 point for mild symptoms, 2 points for moderate symptoms, and 3 points for severe symptoms. In addition to assessing the severity of insomnia, rater can also use this scale to determine the TCM syndrome of insomnia, because these 38 items have already covered the four diagnostic contents of TCM[17].

2.4.4 Total effective rate

Efficacy rating indicator was based on the reduction rate of PSQI score = (Pre-treatment score − Post-treatment score) ÷ Pre-treatment score × 100%.

Clinically recovered: The reduction rate of PSQI score ≥80%.

Markedly effective: The reduction rate of PSQI score ranged from 50% to 79%.

Effective: The reduction rate of PSQI score ranged from 30% to 49%.

Invalid: The reduction rate of PSQI score <30%.

2.5 Statistical methods

The SPSS 21.0 statistical software was used for statistical description and inference after the original data were input through Excel 2010. Measurement data in normal distribution were expressed as mean ± standard deviation ($\bar{x}$ ±*s*) and analyzed by paired *t*-test or two dependent samples *t*-test for both inter-group and intra-group comparisons. 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.

3 Observation of Treatment Results

3.1 Baseline data

The baseline data, including demographic and clinical characteristics of the participants (such as age and duration of disease) and scores of PSQI, KI and TCMSSS were examined. As shown in Table 1 and Table 2, there were no statistically significant differences in age, duration of disease, global scores of PSQI, KI, and TCMSSS and sleep features between the two groups (all *P*>0.05), suggesting the comparability between the two groups and the objectivity of the trial (Table 1-Table 3).

Table 1. Comparison of age and disease duration between the two groups ($\bar{x}$ ±*s*)

Group	*n*	Average age (year)	Average disease duration (month)
Treatment	33	52.1±4.1	13.2±6.0
Control	33	51.9±3.9	13.0±6.2
t-value		−0.185	−0.161
P-value		0.854	0.872

Table 2. Comparison of global scores of PSQI, KI and TCMSSS at baseline ($\bar{x}$ ±*s*, point)

Group	*n*	PSQI	KI	TCMSSS
Treatment	33	12.12±3.59	28.85±7.16	35.18±10.32
Control	33	11.97±3.26	30.52±5.71	36.06±9.06
F-value		0.572	1.813	0.316
P-value		0.858	0.300	0.714

Table 3. Comparison of sleep features (each item of PSQI) between the two groups at baseline ($\bar{x}$ ±*s*, point)

Group	*n*	Sleep quality	Sleep latency	Sleep duration	Sleep efficiency	Sleep disturbances	Daytime dysfunction
Treatment	33	1.76±1.00	2.58±0.50	2.67±0.54	2.21±0.74	1.12±0.82	1.79±1.34
Control	33	1.70±0.95	2.55±0.62	2.67±0.48	2.18±0.81	1.27±0.67	1.61±1.27
F-value		0.429	1.753	0.143	0.581	0.084	0.436
P-value		0.802	0.827	1.000	0.874	0.415	0.574

3.2 Treatment outcomes

3.2.1 Total effective rate

The total effective rate of the treatment group was significantly higher than that of the control group (*P*<0.05), indicating that the treatment group produced a more significant efficacy than the control group (Table 4).

Table 4. Comparison of the total effective rate (case)

Group	*n*	Clinically recovered	Markedly effective	Effective	Invalid	Total effective rate (%)
Treatment	33	4	24	3	2	93.9[1)]
Control	33	0	13	11	9	72.7

Note: Compared with the control group, 1) $P<0.05$

3.2.2 PSQI

Global scores of PSQI decreased significantly in both groups at post-treatment (both $P<0.05$) and remained till the 4-week follow-up (both $P<0.05$), though there were no significant differences between post-treatment and follow-up ($P>0.05$). Moreover, the decline in the treatment group was more significant than that in the control group ($P<0.05$). It can be concluded that both therapies can improve insomnia in perimenopausal women with satisfactory short- and long-term effects, and the effect of the combo therapy should be better than that of Luohua Anshen oral liquid (Table 5).

3.2.3 KI

Compared with pre-treatment, global scores of KI in both groups showed significant differences at post-treatment (both $P<0.05$) and at the follow-up (both $P<0.05$). The decrease in the treatment group was more significant ($P<0.05$). No statistical inner-group differences were shown in the two groups between post-treatment and follow-up (both $P>0.05$). It is suggested that both therapies could mitigate the symptoms of climacteric syndrome, and the effect could maintain for at least 4 weeks. Moreover, the effect of the combo therapy was more significant than that of using Luohua Anshen oral liquid alone in improving climacteric syndrome (Table 5).

3.2.4 TCMSSS

Compared with baseline data, global scores of TCMSSS in both groups declined significantly after treatment (both $P<0.05$) and the effect remained till the 4-week follow-up (both $P<0.05$). The decrease in the treatment group was more significant ($P<0.05$). It is indicated that both therapies could improve the insomnia-related symptoms, and the combo therapy displayed a better effect than using Luohua Anshen oral liquid alone (Table 5).

Table 5. Comparison of global scores of PSQI, KI and TCMSSS ($\bar{x}$ ±*s*, point)

Item	Treatment group (*n*=33)			Control group (*n*=33)		
	Pre-treatment	Post-treatment	Follow-up	Pre-treatment	Post-treatment	Follow-up
PSQI	12.12±3.59	4.67±2.92[1)2)]	4.55±2.77[1)2)]	11.97±3.26	7.42±3.09[1)]	8.36±3.54[1)]
KI	28.85±7.16	23.67±7.27[1)2)]	23.55±7.14[1)2)]	30.52±5.71	27.79±5.07[1)]	27.88±5.49[1)]
TCMSSS	35.18±10.32	27.30±10.50[1)2)]	27.09±9.97[1)2)]	36.06±9.06	31.27±8.07[1)]	31.61±8.78[1)]

Note: Compared with pre-treatment in the same group, 1) $P<0.05$; compared with the control group at the same time point, 2) $P<0.05$

3.2.5 Comparison of sleep features

Compared with baseline, both groups showed significant decline in sleep latency, total sleep duration, sleep efficiency, and improvement of daytime dysfunction after treatment (all $P<0.05$). In the domain of sleep quality, there was no significant change in the control group between pre- and post-treatment ($P>0.05$), whereas the treatment group showed a significant difference ($P<0.05$). Meanwhile, both therapies were found effective in shortening sleep latency, increasing total sleep duration, improving sleep efficiency, relieving sleep disturbances and mitigating daytime dysfunction among patients with PMI. Between-group comparisons showed significant differences in the scores of sleep quality, sleep latency, and sleep efficiency (all $P<0.05$), suggesting that the treatment group was significantly better than the control group in improving the three sleep features. However, there were no significant differences between the two groups in improving total sleep duration, sleep disturbances, and daytime dysfunction (all $P>0.05$), (Table 6).

3.3 Safety assessment

There were no serious adverse events occurred in this trial. Only one patient from the treatment group had a slight dizziness due to nervousness and having missed breakfast at her first EA treatment. The treatment stopped and the needles were removed immediately. Meanwhile, the patient was given warm sweet water and explanation about EA treatment. Her condition was recorded in details in the Case Report Form for future reference. In the following treatments, this patient took the therapist's advice, and no adverse reactions occurred again until the end of the treatment.

Table 6. Comparison of sleep features between the two groups ($\bar{x}$ ±*s*, point)

Item	Treatment group (*n*=33)		Control group (*n*=33)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Sleep quality	1.76±1.00	0.61±0.83[1)2)]	1.70±0.95	1.58±0.90
Sleep latency	2.58±0.50	0.97±0.92[1)2)]	2.55±0.62	1.64±0.65[1)]
Sleep duration	2.67±0.54	1.12±0.70[1)]	2.67±0.48	1.48±0.80[1)]
Sleep efficiency	2.21±0.74	0.85±0.80[1)2)]	2.18±0.81	1.39±0.79[1)]
Sleep disturbances	1.12±0.82	0.64±0.60[1)]	1.27±0.67	0.64±0.70[1)]
Daytime dysfunction	1.79±1.34	0.48±0.67[1)]	1.61±1.27	0.70±0.88[1)]

Note: Compared with pre-treatment in the same group, 1) $P<0.05$; compared with the control group, 2) $P<0.05$

4 Discussion

Epidemiological investigation in Western countries shows that 33% to 51% of perimenopausal women have sleep disturbances[18-19]. As the population in China is larger, the incidence of insomnia in Chinese perimenopausal women is much higher than that in the West, which has already been proved by the large-sample epidemiological survey conducted in China[20-21]. Previous studies also confirmed that women with PMI were more likely to be affected by depression, anxiety, or other mental illnesses such as stress, anxiety and irritability. Vice versa, anxiety, depression, bipolar disorder and other mental disorders would in turn further aggravate PM-I, and thus form a vicious circle in the end[3,22-23]. In addition to mental and psychological problems, long-term PMI is also deemed to cause or aggravate patient's somatic diseases[24]. For instance, the incidence of hypertension might increase by 2 times and the risk of acute myocardial infarction and stroke might increase by 6.08 times if insomnia could not be effectively managed in the long run[25]. Fortunately, attention to PMI has been increased with continuous improvement of women's social status and education level in recent years.

In the management of PMI, satisfactory effects might be achieved by short-term use of HRT or sedatives, while the serious side effects due to long-term use of these drugs cannot be ignored[3]. Therefore, more individuals turn to seek help from TCM, especially acupuncture. Furthermore, EA therapy has been proved to significantly improve various types of perimenopausal discomforts, including insomnia, through the regulation of hypothalamic-pituitary-ovarian axis [3,26].

In this study, Tousanshen points, including Sishencong (EX-HN 1), Shenting (GV 24), and Benshen (GB 13), were selected as the major acupoints in combination with Baihui (GV 20), Shenmai (BL 62), and Zhaohai (KI 6) as the adjunct acupoints. Among the Tousanshen points, Shenting (GV 24) is a crossing acupoint of the Governor Vessel, Bladder Meridian and Stomach Meridian. Since the Governor Vessel links the three yang meridians of hand and the three yang meridians of foot to brain, Shenting (GV 24) can be viewed as the gathering spot of qi and blood in the Governor Vessel. Meanwhile, the Bladder Meridian administrates the activities of mind and brain. Therefore, qi and blood in meridians will be regulated and delivered to brain through puncturing Shenting (GV 24). Sishencong (EX-HN 1) belongs to extraordinary acupoint. Tonifying kidney-yin may be achieved through puncturing Sishencong (EX-HN 1) because its anterior and posterior points belong to the Governor Vessel and link heart and kidney, and its bilateral points are next to the Bladder Meridian and link kidney as well. Benshen (GB 13) is where qi originates in the Gallbladder Meridian, and is also the pivot that manages the opening and closing of the three yang meridians. Acupuncture at Benshen (GB 13) may achieve the purpose of restraining liver yang. To sum up, puncturing Tousanshen points can calm the heart and mind, soothe the liver, and tonify the kidney. Meanwhile, the connection between Zang-fu organs and brain can also be further strengthened. That's why many other symptoms involving multiple Zang-fu organs such as hot flashes, frequent urination, forgetfulness, and dizziness could be improved simultaneously, in addition to insomnia. Baihui (GV 20) is not only passed by the Governor Vessel, but also is the convergence of various meridians. Regulation of yin and yang in Zang-fu organs may be achieved by puncturing Baihui (GV 20). Shenmai (BL 62) and Zhaohai (KI 6) are two points from the Eight Confluent acupoints, linking the Yang Heel Vessel and the Yin Heel Vessel, respectively. They are able to regulate the opening and closing of eyes according to *Huang Di Nei Jing* (*Yellow Emperor's Classic of Internal Medicine*). They are often used in the management of insomnia in clinic as well.

It is found that the improvement of sleep quality in patients with PMI is mainly achieved through the regulation of neurological substances in brain[27], estrogen levels[28] and sleep patterns[29] by acupuncture therapy. Furthermore, electrical stimulation can enhance the effects. EA can not only produce repetitive mechanical movements of the needles and improve the work efficiency of acupuncturist, but also objectively control the amount of stimulation and further improve the standardization of acupuncture operations instead of the subjectivity of manual acupuncture. Sparse-dense wave was chosen in this study because it can overcome the electrical adaptation generated by single waveforms. Moreover, application of sparse-dense wave to head acupoints has been proved to improve brain blood circulation and tissue metabolism to a certain extent, and promote sleep-wake cycle as well[30].

The curative effect of Luohua Anshen oral liquid is positive, and has been widely used as a Chinese patent drug in clinic[8]. However, the current study found that the effectiveness of EA plus Luohua Anshen oral liquid was proven to be obviously better for patients with PMI than monotherapy of Luohua Anshen oral liquid. Therefore, the combo protocol is worthy of clinical promotion.

5 Limitations

One of the limitations of our trial was the absence of placebo-acupuncture in the control group, which may result in the statistical bias in outcome assessment. In a few high-quality studies targeting at exploring the effectiveness of acupuncture conducted in Western countries, acupuncture was proven to have only caused a 'placebo' effect and viewed as a 'mega-placebo'[31-33]. Therefore, whether the effect of EA in improving PMI is only a mental placebo or not, can only be proved through setting a placebo-acupuncture for control. In addition, another bias to outcome measures might also be caused by the small sample size in this trial. The relatively short intervention and follow-up period in this study was another limitation. For further research, conducting a multi-center, randomized, single-blind, placebo-controlled clinical trial with a larger sample and long-term observation of effects of acupuncture is warranted. Polysomnography (PSG) is also expected to be included as the objective outcome measure, combined with self-reported outcome such as sleep diary and scales, to provide more practical and stricter clinical research modals in sleep-related clinical studies.

In conclusion, EA plus Luohua Anshen oral liquid is an effective and safe method to improve sleep quality and other climacteric symptoms in patients with PMI.

Conflict of Interest

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 included in this study.

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