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RESEARCH ARTICLE

Evaluation of Acupuncture in the Treatment of Restless Legs Syndrome: A Randomized Controlled Trial

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Abstract
The aim of this study was to examine the additive effect of medical acupuncture on controlling the symptoms of restless legs syndrome (RLS). A total of 46 randomly allocated patients diagnosed with RLS were assigned to receive either 10 sessions of acupuncture plus gabapentin (300 mg/d), or gabapentin (300 mg/d) alone (23 patients in each group) over 4 weeks in a single-blind study. The symptoms of patients were assessed by the Visual Analogue Scale (VAS), the International Restless Legs Syndrome Rating Scale (IRLSRS), and the Pittsburgh Sleep Quality Index (PSQI) at baseline, just after the therapeutic course and 8 weeks later. For all outcome measures, there was a significant time-group interaction, showing that the behavior of groups differed regarding changes in VAS, IRLSRS, and PSQI in favor of the experimental group. After therapeutic course termination and in 8 weeks follow up, VAS and IRLSRS had a significant improvement in both the experimental group and the control group, but PSQI improved significantly just in the experimental group. Based on the findings of the present study, acupuncture plus a low dose of gabapentin (300 mg/d) is clinically useful in the treatment of RLS during 8 weeks follow up, and also has an additive therapeutic effect over gabapentin alone in patients with RLS.

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1. Introduction

Restless legs syndrome (RLS) is a neurological disorder characterized by an uncomfortable and unpleasant sensation in the legs that appears at rest, which induces an irresistible urge to move the legs. RLS symptoms are more prominent in the evening and at bedtime and usually disrupt patient sleep [1]. RLS is a common syndrome. Adult prevalence is reported to range from 2% to 5% up to 10—15%. The incidence of this disease worsens with age and the incidence is twice as high in females [2]. A genetic basis for the primary form has been hypothesized. Underlying pathophysiology of RLS is still not fully understood. The most accredited hypothesis recognizes an involvement of the diencephalic A11 dopaminergic neurons [3,4]. Three main causative reasons of the secondary type of this disease are pregnancy, iron deficiency anemia, and renal failure. In secondary types, if diagnosed immediately or causative factors are restricted, the symptoms might remitted [1,5].

Nocturnal legs cramps, paresthesia correlated to peripheral neuropathy, radiculopathy, and venous disorders are some of the differential diagnoses that have been defined for this syndrome [3].

Different drugs have been used for treating RLS, all of which seemingly alleviate the symptoms instead of curing the syndrome. The most effective drug treatment for RLS is dopamine agonists, which possess some side effects [1]. Other drugs used in the treatment of RLS include opioids, benzodiazepines, levodopa, anti-anxiety drugs, baclofen, tramadol, clonidine, and anticonvulsant medications such as carbamazepine, pregabalin, and gabapentin [6].

Many nonpharmaceutical methods have been applied to cure RLS, some of which have been effective in ameliorating the symptoms. These include: exercise and massage therapy through raising blood circulation and releasing endorphin and dopamine; near-infrared light and pneumatic compressed through raising blood circulation; injecting 1—2 mL lidocaine 25%; and pharmaceutical plant injection in trigger points. Decreased use of caffeine, alcohol, and tobacco, and maintaining a regular sleep pattern might also provide some relief for patients with RLS. Probably, the lack of treatment for this syndrome is attributed to the lack of adequate pathophysiology precipitation of the disease. Initial studies on the curing effect of medical acupuncture on RLS symptoms achieved hopeful results [7,8]. In Chinese medical acupuncture methods, selected points showed considerable influence on treatment of RLS. In Chinese medical acupuncture, the theory for the cause of RLS is disclosed as reduction in the legs blood Yin and Xue which is responsible for body and brain relaxation. Particularly, the lack of liver Xue and Yin which controls activity of legs at night is the main cause of RLS [9].

RLS is considered as a preclinical symptom of Parkinson's disease and can be considered as an initial step of neuron degradation disease [10]. According to functional magnetic resonance imaging data and clinical evidence of the influence of medical acupuncture on those parts of brain which are associated to Parkinson's disease such as the substantia nigra, putamen, caudate nucleus, and thalamus, and dopaminergic pathways correlated to the RLS pathophysiology, it can be conclusively said that stimulating the mentioned points can also induce similar curing influences in RLS [11,12]. Based on the above theories, the combination of Chinese traditional science and Western medical science were used in this study to choose the points of medical acupuncture.

Few randomized clinical trials have shown the benefits of acupuncture on the treatment of patients with RLS. The purpose of this study is to examine the additive effect of medical acupuncture on controlling the symptoms of RLS in a single-blind, randomized, controlled study.

2. Material and methods

2.1. Study setting

This single-blind, randomized, controlled trial was conducted at the Physical Medicine and Rehabilitation Department of Firoozgar Hospital in Tehran, Iran from March 2014 to October 2015.

2.2. Participants

Eligible participants in this study were 46 patients (27 women and 19 men) aged between 21 and 81 years (mean age 48.39 years) diagnosed with RLS based on quadratic identification criteria [2] by an academic physical medicine and rehabilitation specialist. The symptoms had to have been expressed in the patient for 6 months, with a score of at least 20 on the International Restless Legs Syndrome Rating Scale (IRLSRS) (corresponding to severe RLS). Patients suffering from secondary RLS (renal failure, anemia with iron deficiency, pregnancy, rheumatoid arthritis, recent anesthesia, fracture, or clinical myelopathy and peripheral neuropathy), other sleep disorders, other movement disorders, various psychiatric and organic disorders, cognitive impairment, or bleeding disorders, or who are on anticoagulant therapy, were excluded from the study. Patients also were excluded if they were taking any sleeping or sedative medication.

All patients underwent a complete musculoskeletal and neurologic examination as well as routine blood tests (including serum iron, ferritin, and B12 vitamin concentrations) before entering the study.

The local ethics committee at the Iran University of Medical Sciences approved the study protocol and it was performed in accordance with the ethical standards of the Helsinki Declaration. Written informed consent was signed by all patients before participation in the study. The trial is registered at the Iranian Registry of Clinical Trials (IRCT) with the reference IRCT201510272474N1.

2.3. Intervention

Using block randomization, patients were allocated into two groups: the control group (with low dose gabapentin: 300 mg/d) and the experimental group (with gabapentin 300 mg/d and medical acupuncture) for 8 weeks, in a single-blind, controlled study.

Acupuncture for patients in the experimental group was performed for 10 sessions, three times per week during 4 weeks. A total of 13 bilateral acupoints including Shenshu (BL23), Ganshu (BL 18), Chengjin (BL 56), Chenshan(BL57), Jinggu(BL 64), Zusanli (ST 36), Liangqiu (ST34), Shangqiu(SP5), Xuehai (Sp10), Shanyijiao (SP 6), Taixi (Ki3), Yanglingquan (GB 34), and Xuanzhong (GB 39) were selected based on previous studies [9,11–13]. Dong Bang disposable 0.25 × 40 mm (diameter × length) sterile steel needles were used. Puncture depth was 15–30 mm. In a quiet and comfortable room, acupuncture was done with the patient lying in the supine and then the prone position based on the location of the acupoints. At each acupoint, the skin was wiped with alcohol. After insertion, the acupuncture needles were manipulated (lifting and thrusting, twirling or rotating) for about 1 minute to develop de qi sensation (de qi sensation: numbness, soreness or radiating sensation) and then the needles were held in place for 30 minutes. Manipulation was repeated every 10 minutes. The duration of each session was about 1 hour. Acupuncture was performed by the same experienced acupuncturist in all patients.

Patients were assessed by a resident of physical medicine and rehabilitation at baseline and just after 10 sessions of acupuncture and 8 weeks later.

2.4. Outcome measures

The IRLSRS [14], a validated Persian version of the Pittsburgh Sleep Quality Index (PSQI) [15], together with, the visual analogue scale (VAS) were used to evaluate the effectiveness of presented treatment at baseline, just after treatments, and 8 weeks later. Patients were randomized to receive one of two treatments in a 1:1 ratio using a computer-generated code. Throughout the study, the rater was blind to the assignment.

2.5. Statistical analysis

Statistical data was collected by Windows SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA). At first, the Kolmogorov–Smirnov test was conducted which represented the normal distribution of data, so parametric tests were used. Descriptive statistics were extracted, and "mixed design analysis of variance" was used to explore the main and interaction effects of time and group on outcomes. Significant difference was defined at $p < 0.05$. Greenhouse-Geisser correction was used for sphericity violation. Independent sample t test and Chi-square test were used for analysis of baseline characteristics.

3. Results

A total of 79 patients were evaluated; 50 patients were enrolled in the study based on inclusion and exclusion criteria and allocated randomly into two groups (25 in each group). Two patients in the control group dropped out of the study because of drowsiness caused by gabapentin. In the experimental group, two patients did not end up the study; one due to accidental fracture and the other due to pain of acupuncture. A total of 46 patients (23 in each group) who completed the study were analyzed. Baseline demographic and clinical characteristics of the two groups including age, gender, duration of pain, VAS, IRLSRS, and PSQI are shown in Table 1.

Baseline parameters that showed a significant difference between the two groups (VAS, PSQI) were entered as covariates in analysis of variance and did not change the results.

With regard to VAS, there was a significant time-group interaction, showing that the behavior of treatment groups differed regarding changes in VAS across time in favor of the experimental group (df = 1.60, F = 18.34, $p < 0.001$). In addition, there was a significant effect of both treatments on VAS between before and just after therapeutic course termination (4 weeks later) ($p < 0.001$ in each group) as well as after 8 weeks follow up ($p < 0.001$ in each group) but there was not a significant change between Week 4 and Week 8.

For IRLSRS, the behavior of the treatment groups was significantly different regarding changes in IRLSRS across time in favor of the experimental group (df = 1.15, F = 13.03, $p < 0.001$). In addition, there was a significant effect of treatment on IRLSRS in both the experimental and control groups between before and just after therapeutic course termination ($p < 0.001$, $p = 0.007$, respectively) as well as after 8 weeks follow up ($p < 0.001$, $p = 0.002$, respectively), but the changes did not significantly differ between just after treatment and at 8 weeks follow up.

With regard to PSQI, there was also a significant time-group interaction, showing that the behavior of treatment groups differed significantly across time in favor of the

Table 1 Baseline characteristics of experimental and control groups.

	Control (n = 16)	experimental (n = 17)	p
Age (y)	47.65 ± 13.93	49.13 ± 15.57	0.83*
Duration of pain (mo)	94.05 ± 101.57	97.78 ± 113.33	0.63*
Gender (N)	11 female	16 female	0.06 †
VAS (mean ± SD)	7.78 ± 2.57	9.13 ± 1.84	0.04*
IRLSRS (mean ± SD)	22.73 ± 11.10	28.52 ± 9.47	0.06*
PSQI (mean ± SD)	6.91 ± 6.30	11.13 ± 6.60	0.03*

IRLSRS = International Restless Legs Syndrome Study Group rating scale; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation; VAS = visual analogue scale.

* Independent samples t test.

† Chi-square test.

experimental group (df = 1.71, F = 6.99, $p = 0.003$). In addition, there was a significant effect of treatment on PSQI just in the experimental group between before and just after therapeutic course termination ($p < 0.001$) as well as after 8 weeks follow up ($p < 0.001$) but not between just after treatment and 8 weeks follow up. PSQI score did not change significantly at any time point in the control group.

Comparisons of outcomes in experimental and control groups are shown in Table 2.

4. Discussion

Patients with a severe form of RLS require a therapeutic approach. Many pharmacological trials on RLS have been performed [4]. Although preliminary studies have shown the benefit of nonpharmacological treatment such as acupuncture, randomized, controlled studies are lacking. The mechanism of acupuncture treatment for RLS is still unclear. According to a traditional Chinese medicine theory, acupuncture restores the balance between Yin and Yang and regulates Qi (the essence) and blood [7]. Acupuncture is especially known for its effectiveness in reducing pain due to triggering a release of analgesic neuropeptides [16]. Previous studies have shown that the neuroprotective effect of acupuncture is mediated through the same common mechanisms as other neuroprotective agents, including antioxidative stress, antiinflammatory, and antiapoptotic pathways at molecular and cellular levels [11]. Shenshu (BL23) improves "Shen Qi" and "Yin" of the waist and legs. Zusanli (St36), Sanyinjiao (Sp6), and Taixi (Ki3) increase both "Yin" and "Xue" (blood) of the body. Xuehai (Sp10) increases "Xue" (blood) of the body [13].

Yanglingquan (GB 34), Xuanzhong (GB 39), Zusanli (ST 36), and Shanyijiao (SP 6) provide neuroprotection of dopaminergic neurons of the substantia nigra [11].

In the present single-blind, randomized clinical trial, although both groups of patients showed significant improvement on VAS and IRLSRS during 8 weeks follow up, the combination of acupuncture with gabapentin had additive therapeutic effects over gabapentin alone. In regard to sleep disturbance, PSQI significantly improved just in the experimental (acupuncture plus gabapentin) group.

The findings of the present study are consistent with a randomized clinical trial on 90 patients with RLS that showed that the combination of dermal needle therapy with Western medications (dipyridamole 50 mg 3 times a day + nicotinic acid 50 mg 3 times a day + inositol 1 g before bedtime) and self-massage of the legs, slightly improved the therapeutic effect on unpleasant sensations in the legs compared to medications and massage administrated alone in 1 month follow up [17].

The results of two clinical trials which compared the therapeutic effects of acupuncture with medication on RLS are contradictory. In the study of Wu et al [18], the effect of acupuncture combined with a Teding Diancibo Pu (TDP) lamp was compared with L-dopa on 158 cases with RLS (79 cases in each group) for 30 days. Although both treatments were effective, the total effective rate was significantly higher in the acupuncture group of patients. By contrast, in the trial by Shi et al, 120 cases of RLS were randomly divided into three groups: the treatment group treated by scalp and body acupuncture plus steaming-washing with Chinese herbs, the medicine group treated by Western medicine (oryzanol 20 mg 3 times a day plus diazepam 5 mg before bedtime for 30 days), and the third group treated with body and scalp acupuncture group alone. The effective rates of the three groups were, respectively, 97.5%, 77.5%, and 75.0%, the treatment group being superior to the medicine group and the acupuncture group; however, there were no significant differences between the medicine group and the acupuncture group [19].

The inadequacy of allocation concealment and blindness, using other treatments in combination with acupuncture and administration of different methods, may result in contradictory findings.

A randomized clinical trial in 2005 compared two methods of acupuncture on 81 patients with RLS. Patients were randomly divided into a treatment group treated by an acupoint selection method according to nerve anatomy, positive findings, and neurobiological theory, and a control group treated by a traditional acupoints selection method. Analysis revealed that although both methods were effective, but the first method was significantly more effective than the traditional method [20]. In addition, a single-blind, randomized clinical trial in 2015 which compared standard acupuncture (16 cases) with random acupuncture (15 patients) on RLS using leg actigraph recordings, the IRLSRS, and the Epworth Sleepiness Scale over 6 weeks,

Table 2 Pairwise comparisons of outcomes in experimental and control groups.

		Before treatment	Just after treatment	After 8 wk follow-up	P1	P2	P3
		Mean ± SD	Mean ± SD	Mean ± SD			
IRLSRS	Experimental	28.52 ± 9.47	15.52 ± 9.30	14.26 ± 10.17	<0.001	0.050	<0.001
	Control	22.73 ± 11.10	17.82 ± 11.41	16.78 ± 11.69	0.007	0.136	0.002
VAS	Experimental	9.13 ± 1.84	3.47 ± 2.25	3.21 ± 2.27	<0.001	1/000	<0.001
	Control	7.78 ± 2.57	5.17 ± 3.47	4.73 ± 3.38	<0.001	0/402	<0.001
PSQI	Experimental	11.13 ± 6.60	9.39 ± 5.77	9.43 ± 6.16	<0.001	1/000	<0.001
	Control	6.91 ± 6.30	6.65 ± 6.31	6.86 ± 6.81	1/000	1/000	1/000

P1: p value between before treatment and just after treatment, P2: p value between just after treatment and 8 weeks follow up, P3: p value between before treatment and 8 weeks follow-up.
IRLSRS = International Restless Legs Syndrome Study Group rating scale; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation; VAS = visual analogue scale.

showed that standard but not randomized acupuncture reduced the abnormal leg activity [9].

A case series studied the effect of acupuncture and moxibustion therapy plus herbal injection in Bilateral BL 57 point on 49 cases of RLS. The clinical symptoms of 41 cases disappeared totally within 6 months follow up [21].

A retrospective study of the electroacupuncture effect on 19 patients with RLS either previously treated by dopaminergic drugs (16 patients) or not (3 patients), showed that, although there was a large reduction in symptom score (VAS) in both patient groups in a long duration (6 months), patients not previously treated with dopaminergic drugs demonstrated a greater reduction [22].

In the present study, the PSQI did not change significantly in the medication group. Although covariate analysis showed that the significant difference in PSQI between the two groups at baseline (11.13 in the experiment group vs. 6.91 in the sham group) did not change the result, the low score and mild sleep disturbances in the medication group and also the low dose of gabapentin used in this study may explain this finding. In addition, it should be mentioned that antiepileptic drugs have a variety of effects on sleep architecture [23].

However, considering other limitations of this study, further studies with a greater sample size and longer follow up duration should be conducted. Furthermore, the effect of acupuncture on neuropathophysiology by objective outcome measures such as functional brain magnetic resonance imaging should be a consideration in future studies.

This study tested the additive effect of acupuncture to medication in the treatment of RLS, and due to limited data directly comparing the therapeutic effect of acupuncture to medication alone, it should be targeted in future studies.

Disclosure statement

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