Journal of Psychiatric Research 47 (2013) 726–732

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

A 6-week randomized controlled trial with 4-week follow-up of acupuncture combined with paroxetine in patients with major depressive disorder

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ARTICLE INFO

Article history:
Received 22 November 2012
Received in revised form
5 February 2013
Accepted 5 February 2013

Keywords:
Acupuncture
Paroxetine
Major depressive disorder
Clinical trial
Follow-up

ABSTRACT

Acupuncture possesses the antidepressant potential. In this 6-week randomized controlled trial with 4-week follow-up, 160 patients with major depressive disorder (MDD) were randomly assigned to paroxetine (PRX) alone ($n = 48$) or combined with 18 sessions of manual acupuncture (MA, $n = 54$) or electrical acupuncture (EA, $n = 58$). Treatment outcomes were measured mainly using the 17-item Hamilton Depression Rating Scale (HAMD-17), Self-rating Depression Scale (SDS), clinical response and remission rates. Average PRX dose taken and proportion of patients who required an increased PRX dose due to symptom aggravation were also obtained. Both additional MA and EA produced a significantly greater reduction from baseline in score on HAMD-17 and SDS at most measure points from week 1 through week 6 compared to PRX alone. The clinical response was markedly greater in MA (69.8%) and EA (69.6%) groups than the group treated with PRX alone (41.7%, $P = 0.004$). The proportion of patients who required an increase dose of PRX due to symptom aggravation was significantly lower with MA (5.7%) and EA (8.9%) than PRX alone (22.9%, $P = 0.019$). At 4 weeks follow-up after completion of acupuncture treatment, patients with EA, but not MA, continued to show significantly greater clinical improvement. Incidence of adverse events was not different in the three groups. Our study indicates that acupuncture can accelerate the clinical response to selective serotonin reuptake inhibitors (SSRIs) and prevent the aggravation of depression. Electrical acupuncture may have a long-lasting enhancement of the antidepressant effects (Trial Registration: ChiCTR-TRC-08000278).

1. Introduction

Depression is a serious mental illness that affects 8–20% of the worldwide population (Ferrari et al., 2012). Although selective serotonin reuptake inhibitors (SSRIs), such as paroxetine (PRX) and fluoxetine (FLX), are a first-line pharmacotherapy for various depressive disorders, there still remains a large portion of depressed patients who do not make a full response and experience relapse and adverse effects of treatment (Arroll et al., 2005). The delay in the onset of the action of SSRIs further prolongs the suffering of patients and exposes them to a substantial risk of suicide (Adell et al., 2005). A high incidence of side effects also has hampered the clinical use of SSRIs (Arroll et al., 2005). These limitations of treatment with SSRIs are thought to be due to the multisystem pathogenesis of depressive disorders (Ward and Irazoqui, 2010). For example, it is well documented that, in addition to a central serotonin (5-HT) deficiency, depressive disorders are associated with hypothalamic–pituitary–adrenal axis dysfunction and abnormalities in the brain regions associated with stress and emotion processing (Rigucci et al., 2010; Ward and Irazoqui, 2010).

As an ancient therapeutic technique, acupuncture has been well confirmed to be a generally safe and well tolerated therapy for neuropsychiatric disorders (He et al., 2012; Lao et al., 2003; Zhang et al., 2010). It has been increasingly introduced into the treatment of various depressive disorders (Manber et al., 2010; Smith et al., 2010; Wu et al., 2012; Zhang et al., 2010). Both manual and electrical acupuncture stimulation considerably enhances the release of 5-HT from the brainstem raphe nuclei, the principal source of 5-HT neuronal bodies sending axons to cortical and subcortical regions

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0022-3956/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jpsychires.2013.02.004

(Kwon et al., 2000; Lee et al., 2004; Li et al., 2007; Zhao, 2008). It robustly modulates neuroendocrine functions, in particular the hypothalamic–pituitary–adrenal axis; it reduces stress-induced behavior, and targets brain regions involved in emotion processing (Zhang et al., 2012a). These observations suggest that acupuncture may have an antidepressant potential. Indeed, numerous clinical studies and observations have shown the therapeutic benefits of acupuncture in treating depressed patients (Zhang et al., 2010). Acupuncture is also beneficial in alleviating pain, autonomic, sleep, and other mood symptoms (Zhang et al., 2012a). On the other hand, many studies have shown superior effects of electroacupuncture (EA) compared to manual acupuncture (MA) in alleviating tinnitus (Wang et al., 2010), pain (Sator-Katzenschlager et al., 2003, 2004; Schliessbach et al., 2011; Tsui and Leung, 2002), and modulating rat neuroendocrine function (Feng et al., 2012). Most recently, we have demonstrated that EA has an immediate and short-term effect in enhancing the efficacy in the early phase of FLX treatment of patients with major depressive disorder (MDD) (Zhang et al., 2012b) and potential benefit in patients with postpartum depression (Chung et al., 2012). Hence we hypothesize that adjuvant acupuncture, and in particular EA, may provide a long-lasting enhancement of the antidepressant efficacy of SSRIs.

To test this hypothesis we conducted a 6-week, randomized controlled trial with 4-week follow-up of MA or EA combined with PRX compared to PRX alone in patients with MDD. Adjuvant MA and EA were both studied because a large body of evidence suggests different neural pathways for these two most commonly used stimulation modes (Zhang et al., 2012a). Here, EA is defined as an acupuncture procedure in which inserted needles are manipulated manually at first, followed by electrical stimulation. Paroxetine (PRX) was selected because it is one of the most frequently prescribed SSRIs in China (Fang et al., 2010, 2011) and its pharmacological and therapeutic properties have been well delineated (Gibiino and Serretti, 2012).

2. Methods

2.1. Settings and subjects

This randomized controlled trial was conducted in Outpatient Acupuncture Clinic of Southern Medical University, the First Affiliated Hospital of Jinan University, and Guangdong 999 Brain Hospital between December 2008 and October 2010. The study protocol was approved by Medical Ethical Committee of the First Affiliated Hospital of Jinan University and registered in www.chictr.org (Trial Registration: ChiCTR-TRC-08000278). All participants gave voluntary, written, informed consent before entering the trial.

Outpatients were referred by psychiatrist from the First Affiliated Hospital of Jinan University and Guangdong 999 Brain Hospital. Patients who met the following entry criteria were eligible for the study: (1) either gender aged 18–60 years; (2) had a diagnosis of MDD with the International Classification of Diseases (10th version) (ICD-10); (3) moderate or severe illness, with a score of at least 17 on the 17-item Hamilton Rating Scale for Depression (HAMD-17) (Hamilton, 1960) and at least 4 on the Clinical Global Impression-Severity (CGI-S); and (4) current either PRX or other antidepressant treatment did not exceed one month. Patients who had any of the following conditions were excluded from the study: (1) unstable medical conditions; (2) a history of brain injury or surgery; (3) suicidal attempts or aggressive behavior; (4) a history of manic, hypomanic, or mixed episode illness; (5) comorbid with other neuropsychiatric disorders; (6) a family history of mental illnesses; (7) investigational drug treatment within the previous 6 months; (8) a history of alcohol or drug abuse within the previous 12 months; (9) pregnancy or lactation; (10) currently under cognitive behavioral therapy or other behavioral therapies.

All participants were monitored closely on a daily check-up basis by patient self-report, family member or doctor reports. Those whose conditions developed significant suicidal or aggressive behaviors that were a danger to themselves or others determined by psychiatrists, or had compliance rates with medication or acupuncture regime less than 75% were discontinued from the study and given standard clinical treatment.

2.2. Randomization and group allocation

Patients were randomly assigned to one of three groups: PRX alone or combined with MA or EA. For randomization, simple, complete, non-sequential random numbers were generated in advance by a computer program (SPSS version II) and sealed in envelopes. The group allocation was done in a semi-blind manner, in which random codes were known by only acupuncturists (J.Q.C. and G.L.L.), but blind to other study personnel including the Principal Investigator (Y.H.), the Associate Investigator (Z.J.Z.), psychiatrists (C.H.Z. and S.C.G.), clinical assessors (J.Y.P., Y.C.Z. and C.Q.W.), data collector and analysts (S.S.Q. and Y.R.L.). Clinical assessors and psychiatrists communicated with patients separately and were instructed not acquire information about their treatment conditions.

2.3. Paroxetine treatment

Patients in all three groups received PRX orally for 6 weeks in an open manner. For patients who were not medicated at the time of trial, the PRX dose was initiated at 10 mg/day and escalated to 20 mg/day within one week, based on individual patient response. The FLX dose would be further increased if psychiatrists believed patients' symptom aggravated. The maximum dose was set at 40 mg/day. This PRX dosing regimen has been widely used in Chinese patients (Fang et al., 2010, 2011). Patients who were already taking PRX for less than one month would continue his/her PRX regimen. Those who were taking other antidepressants for less than one month would switch to PRX within one week. During 4 weeks of follow-up after acupuncture ended, patients are asked to continue taking PRX; those whose medications were switched to other antidepressants were excluded from follow-up analysis.

Concomitant use of other psychoactive agents was generally not allowed, but the use of benzodiazepines and non-benzodiazepines (e.g., zopiclone) for insomnia was permitted as long as these were taken no more than 14 days cumulatively, as PRX has least interactions with benzodiazepines and other anti-insomnia agents (Calvo et al., 2004; Sproule et al., 1997).

Treatment outcomes included the average PRX dose taken over 6 weeks of treatment and over 4 weeks of follow-up, and the proportion of patients who required an increase of at least 5 mg/day PRX due to worsening symptoms.

2.4. Acupuncture intervention

Patients allocated to adjuvant MA or EA received 3 sessions per week over 6 consecutive weeks. A brief introduction of acupuncture procedure was given by acupuncturists during first visit. Based on empirical evidence and previous studies (Zhang et al., 2010), the ten commonly used acupoints in the treatment of depressive symptoms were chosen for this study: Baihui (GV20), Yintang (EX-HN3), Fengfu (GV16), Dazhui (GV14), bilateral Fengchi (GB20), bilateral Neiguan (PC6), and bilateral Sanyinjiao (SP6). Disposable acupuncture needles (0.30 mm in diameter and 25–40 mm in length, Hwato) were perpendicularly or obliquely inserted into acupoints at a depth of 10–30 mm. For MA, manual manipulation was conducted and needling sensation was generally achieved within 2 min after the manipulation. After needling sensation was achieved, the needles were retained for 30 min and manipulated