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Original Article

Response to placebo acupuncture in insomnia: a secondary analysis of three randomized controlled trials

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ABSTRACT

Objective: To determine the patient characteristics that are associated with a response to noninvasive placebo acupuncture for insomnia.
Methods: We performed a secondary analysis of three randomized, double-blind, placebo-controlled trials of acupuncture for primary insomnia and residual insomnia associated with major depression. A total of 86 participants were randomized to receive placebo acupuncture three times per week for three consecutive weeks. Outcome was assessed at 1-week posttreatment. Response was defined as an Insomnia Severity Index (ISI) score improved by eight points or more from baseline to 1-week posttreatment. Sociodemographic, clinical, and baseline characteristics including sleep diary-derived and actigraph-derived sleep parameters as predictors of placebo response were examined using univariate and multivariate logistic regression.
Results: The effect size of placebo acupuncture was estimated at 0.18 for total sleep time, 0.08 for sleep efficiency, and 0.92 for ISI score. Eighteen (20.9%) of the 86 participants were responders. Responders had a higher ISI score ($p = 0.03$), higher sleep diary–derived total sleep time ($p = 0.02$), less discrepancy between sleep diary–derived and actigraph-derived total sleep time ($p = 0.03$), and higher expectation toward acupuncture ($p = 0.03$) at baseline compared to nonresponders. Multivariate regression analysis found that only ISI score remained significant (odds ratio = 1.23, 95% confidence interval = 1.02–1.50, $p = 0.03$).
Conclusions: Baseline sleep parameters and perceived effectiveness were shown to predict the placebo response of acupuncture for insomnia. Although the study was limited by a small sample size, our findings highlighted the potential implication of sleep duration and sleep-state misperception in the treatment of insomnia.

1. Introduction

The placebo effect is commonly observed in clinical trials of insomnia [1]. The episodic nature of insomnia and the positive reinforcement in response to intervention may account for the response to placebo [2]. A recent meta-analysis has shown that a placebo pill produces a small to moderate effect in both subjective and polysomnographic sleep parameters [1]. Another meta-analysis has revealed that significant clinical improvement in insomnia is found in pharmacological but not psychological placebo [3]. The placebo effect is beneficial in clinical practice; however, it can obscure the difference between an intervention and a placebo and contributes to negative results in some placebo-controlled trials. Better understanding of the patient factors that are associated with the placebo effect has significant clinical and research implications.

A placebo-controlled study design has been used to divide an intervention into specific and placebo elements [4]. The specific elements can be referred to as the therapeutic actions or strategies that are theoretically derived, unique to a specific treatment, and believed to be causally responsible for the outcome. The placebo elements are not only restricted to an imitation of an intervention but also a combination of patient expectations, hope, intensive monitoring, diagnostic procedures, patient–practitioner interaction, conditioning, anxiety reduction, and reporting bias. In addition to regression to the mean and the natural course of illness, all of these placebo elements contribute to the improvement with a placebo as well [5,6]. An exploratory analysis has been performed to examine the impact of regression to the mean, expectancy, and social desirability on the response to a placebo pill in insomnia. The authors found that all three factors were related to placebo response but that their relationship with improvement was different; for example, regression to the mean was observed in Insomnia Severity Index (ISI), whereas social desirability was related to improvement in total sleep time (TST) [3].

Acupuncture is one of the most popular and safest complementary and alternative medicine therapies for the treatment of insomnia

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[7,8], but acupuncture is well known to have a significant placebo effect [9,10]. Across different medical conditions, the effect size associated with acupuncture when compared to placebo acupuncture is usually small, in the range of 0.15–0.25. When compared to waitlist, standard care, or no treatment, the effect size of acupuncture is moderate, around 0.50, meaning that a large part of the acupuncture effect is due to placebo elements. Previous studies have found that the placebo effect is stronger with a device, such as acupuncture, than a pill [9]. However, no studies have been conducted on the placebo effect of acupuncture in insomnia.

In a randomized, placebo-controlled, cross-over trial comparing real and noninvasive placebo acupuncture in patients with low back pain, Wasan et al. [11] found that greater expectancy predicted greater response to both real and placebo acupuncture, whereas psychiatric comorbidity was not a significant predictor of response and had no relationship with expectancy toward acupuncture. Noninvasive placebo acupuncture is often administered using the Streitberger placebo needles [12]. The placebo needles have a blunt tip and movable copper handle. A pricking sensation is felt by subjects when the placebo needle touches the skin. The needle is moved inside the copper handle and appears shortened. Previous studies showed that placebo needles have high credibility, particularly in acupuncture-naive subjects [13]. In our previous randomized controlled trials (RCTs) of acupuncture for insomnia, noninvasive placebo acupuncture was associated with a significant reduction in insomnia severity, but the difference between real and placebo acupuncture was small [14–16]. To minimize the masking of acupuncture–placebo differences, it may be important to control the factors that are associated with placebo response in future clinical trials of acupuncture for insomnia. Although factors such as patient expectations and psychiatric comorbidity have been examined in a previous study of acupuncture for pain, predictive factors of the placebo effect in insomnia have not yet been examined. We conducted a post-hoc analysis of three randomized, double-blind, placebo-controlled trials of acupuncture for primary insomnia and residual insomnia in depressed patients. The aim of the exploratory analysis is to determine patient characteristics that are predictive of a response to noninvasive placebo acupuncture for insomnia.

2. Methods

2.1. Subjects

We pooled the data of three RCTs (ClinicalTrials.gov identifier: #NCT00839592, #NCT00838994, #NCT01707706) [14–16]. A total of 288 participants were randomized to receive traditional acupuncture, minimal acupuncture, or noninvasive placebo acupuncture. Two of the RCTs included persons with residual insomnia associated with major depressive disorder [15,16], and one RCT was in individuals with primary insomnia [14]. Participants were recruited from the community and at psychiatric outpatient clinics in Hong Kong. This secondary analysis involved 86 participants who received placebo acupuncture. The complete list of inclusion and exclusion criteria is available from the clinicaltrials.gov registry. In brief, participants had to be ethnic Chinese, aged 18–70 years, who fulfilled the insomnia symptoms and impairment criteria of the DSM-IV-TR diagnosis of primary insomnia [17], had been suffering from insomnia ≥3 nights per week for at least three months, had an Insomnia Severity Index (ISI) score of ≥15, had no specific sleep disorders (including parasomnia, circadian rhythm sleep–wake disorder, sleep apnea, or periodic limb movement disorder as assessed by interview or overnight polysomnography), and had not received any acupuncture in the past 12 months; for the participants with past episodes of major depressive disorder, the episodes had to fulfill the diagnostic criteria of the DSM-IV-TR.

2.2. Study design and intervention

All procedures used in the studies were reviewed and approved by the local institutional review board. Subjects underwent telephone screening, face-to-face interview, and laboratory-based overnight polysomnography. Eligible subjects completed 1-week sleep diary and a 3-day [14] or 7-day [15,16] actigraphy recording in the week before a scheduled baseline visit. They received their first treatment on the day of the baseline visit. The explanation was provided to the subjects that different types of acupuncture would be compared, and that placebo acupuncture was a procedure which mimicked the real acupuncture procedure. Streitberger placebo needles were placed [12] one inch beside the acupuncture points used in the traditional acupuncture group to avoid a therapeutic effect. The acupuncture points used were the same in our two RCTs [14,15], including Yintang (EX-HN3) and Baihui (GV20), and bilateral Ear Shenmen, Sishencong (EX-HN1), and Anmian (EX). In the most recent RCT [16], additional points, including Neiguan (PC6), Shenmen (HT7), and Sanyinjiao (SP6), were used. The placebo needle was connected to an electric stimulator but with zero frequency and amplitude so as to mimic real acupuncture. Subjects were told that the electric stimulation was set at a fixed level and were advised to inform the acupuncturist if the impulse was too strong. Acupuncture treatment was performed by the same acupuncturist with at least three years of clinical experience of providing acupuncture treatment three times per week for three consecutive weeks. Participants were assessed at baseline and one week posttreatment.

2.3. Sleep diary, ISI, PSQI, actigraph, and CTRS

The outcomes used included the ISI [18], the Pittsburgh Sleep Quality Index (PSQI) [19], sleep parameters derived from sleep diary and actigraphy, and the Credibility of Treatment Rating Scale (CTRS). The ISI is a scale assessing the perceived severity of insomnia symptoms and the associated functional impairment, with scores ranging from 0 to 28. The PSQI is designed to measure general sleep disturbances, with scores ranging from 0 to 21 [20]. The 1-week daily sleep diary [21] inquired about bedtime and rising time, from which total time in bed (TIB) was calculated. Subjects were also advised to estimate sleep onset latency, wake after sleep onset, the number of wakenings, early morning awakening, and TST. Sleep efficiency (SE) was calculated as (TST/TIB × 100%). Actigraphs (Model Actiwatch-2; Respironics Inc; Murrysville, PA; Octagonal Basic Motionlogger, Ambulatory Monitoring, Inc., Ardsley, NY) are watch-like devices that record individuals' physical movements by means of an accelerometer–microprocessor link. Wrist actigraphy is considered as a valid objective measure of sleep because movement is related to wakefulness and lack of movement to sleep [22]. Actigraphs were worn on the nondominant wrist every day for three days [14] or one week [15,16] before each study visit. The recording length of epoch was set at one minute. The data recorded were analyzed with Actiware software (Version 5, Respironics Inc) or Action-W software (Version 2.0, Ambulatory Monitoring, Inc.). The CTRS was used to assess subjects' "confidence in the treatment to alleviate their complaint," "confidence in recommending the treatment to their friends who have similar complaints," "perceived logic of the treatment," and "likelihood that the treatment would alleviate their other complaints" [23]. The questionnaires and sleep diaries were presented in the Chinese language. The Chinese-language ISI and PSQI have been shown to have adequate validity and reliability [24,25].

2.4. Classification of responders/nonresponders

In line with a previous study [26], participants with ISI scores improved by eight points or more from baseline to 1-week