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Original article

Treatment of moderate obstructive sleep apnea syndrome with acupuncture: A randomised, placebo-controlled pilot trial ☆

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Abstract

Background and purpose: To investigate the efficacy of acupuncture in the treatment of moderate obstructive sleep apnea syndrome (OSAS), assessed by polysomnography (PSG) and questionnaires of functional quality of life (SF-36) and excessive daytime sleepiness (Epworth).
Patients and methods: We performed a randomised, placebo-controlled, single-blinded study, with blinded evaluation on 36 patients presenting an apnea/hypopnea index (AHI) of 15–30/h, assessed by PSG. The study took place at the Public Hospital of the Universidade Federal de São Paulo, Brazil, in the Division of Sleep Disorders of the Department of Psychobiology, between January, 2002 and August, 2004. Patients were randomly assigned to three groups: the acupuncture group ($n = 12$); the *sham* group, submitted to needle insertion in non-acupoints ($n = 12$); and the control group, receiving no treatment ($n = 12$). Patients received acupuncture or *sham* acupuncture once a week for 10 weeks.
Results: Twenty-six patients completed the study. The AHI ($P = 0.005$), the apnea index (AI) ($P = 0.008$) and the number of respiratory events ($P = 0.005$) decreased significantly in the acupuncture group but not in the *sham* group. On the other hand, the control group displayed significant deterioration in some of the polysomnographic parameters, with a significant increase in the number of respiratory events ($P = 0.025$). Acupuncture treatment significantly improved (before vs. after treatment) several dimensions of the SF-36 and Epworth questionnaires. There was no significant association between changes in the body mass index (BMI) and AHI.
Conclusions: Acupuncture is more effective than *sham* acupuncture in ameliorating the respiratory events of patients presenting with moderate OSAS.

Keywords: Acupuncture; Obstructive sleep apnea syndrome; Polysomnography; Quality of life; Excessive daytime sleepiness

1. Introduction

Obstructive sleep apnea syndrome (OSAS) has recently been accepted as a major public health issue because of its high prevalence and serious associated consequences, including daytime symptoms of excessive sleepiness, neuropsychiatric effects such as depression and cognitive dysfunction, and cardiovascular diseases such as hypertension, arrhythmias, heart failure and stroke [1]. In addition to these consequences, the economic effects of sleep disorders was estimated in 1990 to be at $15.9 billion in the United States only for direct costs [2].

Nasal continuous positive airway pressure (nCPAP) therapy is the standard treatment for the management

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of clinically significant OSAS [3]. Proper use of nCPAP manages apneas and hypopneas, eliminates hypoxia, restores normal sleep architecture and significantly improves subjective and objective measures of wakefulness as well as averts cardiovascular consequences [4]. Despite the efficacy of this treatment, there is evidence that CPAP compliance is not ideal [5].

There is considerable evidence that the effects of acupuncture include the release of serotonin from caudal raphe nucleus [6] and endogenous opioids systems (e.g. endorphins/enkephalins) [7] and also the involvement of sympathetic nervous mechanisms [8]. It is also shown in the literature that acupuncture suppresses inflammation by activating the hypothalamus–pituitary–adrenal axis (HPA) [9].

Several recent investigations have highlighted evidence for sensory nerve damage in the upper airways of patients with OSA [10], and for a reduction of the excitatory drive from the caudal raphe serotonergic neurons which are responsible for exciting upper airway muscles, leading to the aggravation of pharyngeal collapse [11].

Rather than directly testing this hypothesis, which poses a great level of difficulty, we decided to address the therapeutic effectiveness of acupuncture for the treatment of OSAS.

2. Materials and methods

2.1. Study design and subjects

Between January, 2002 and August, 2004, we screened patients who attended the out-patient clinic for sleep disorders in the São Paulo Hospital of the Universidade Federal de São Paulo for inclusion in this research. Eligible patients ($n = 36$) had obstructive sleep apnea confirmed by a full polysomnographic (PSG) study with an apnea/hypopnea index (AHI) > 15/hour and < 30/hour (moderate OSAS) and were acupuncture-naïve. From the total of 38 eligible patients approached to participate in the study, 36 agreed to participate. There were only two subjects whom upon being asked were not interested in participating. Patients with a high alcohol intake (> 80 g/day), morbid obesity, significant lung disease, neurological disease, intellectual deficits, skeletal facial framework problems, or central apnea, or who were taking any hypnotic drugs, had undergone oropharyngeal surgeries or had been treated with CPAP or oral devices were excluded. Randomisation was done by a blinded independent researcher and was conducted by selecting a closed piece of paper out of a box, with a treatment order written on it. Only the physician applying the treatments (acupuncture/*sham* acupuncture) was aware of which group each patient had been assigned to and did not participate in any phase of the subsequent evaluation. Patients underwent an interview, during which they answered a health-related questionnaire-SF 36 and a specific questionnaire (Epworth); they also had their neck and abdominal circumferences and body mass index (BMI) measured.

The patients signed an informed consent form, which described that we were testing acupuncture in comparison to a *sham* acupuncture procedure. Patients were also informed that they would not know to which group they were allocated. Finally, patients were informed that at the end of the study all patients allocated to the *sham* acupuncture group would receive 10 sessions of acupuncture treatment if they so wanted. Patients assigned to the control group were offered weight reduction advice if overweight and sleep hygiene counseling. Given the usual waiting list for nCPAP at our service, which is about 6 months, the waiting time was not a matter of ethical concern. Patients were also informed about the possible risks of acupuncture treatment such as infection, fainting, and haematoma, including death in case of improper handling of the needle [12]. After the interview, the patients were instructed as follows: the acupuncture group and the *sham* acupuncture group were to come once a week during the afternoon for 10 consecutive weeks to receive the proposed treatments. The control group had a re-evaluation scheduled for within 3 months (Fig. 1) and was not seen meanwhile. The Ethical Committee of the Universidade Federal de São Paulo approved the study protocol (number 786/01).

2.2. Treatment applied

2.2.1. Needle type: real and sham acupuncture

We used single-use, sterile, cooper-handle, pre-packed needles with guide tubes, 40×0.25 mm (Dongbang Acupuncture Needle, Boryeong City, South Korea). All points were disinfected with ethanol before the needles were inserted. The set of acupuncture points used (Fig. 2) [13] was decided before the treatment and was the same for all individuals in accordance with other studies cited in the literature [13]. The choice of acupoints was based on their specific characteristics, such as points that 'tonify the whole "energy" of the subject,' are specific for the treatment of somnolence, are specific for the treatment of throat diseases, are specific to treat rhinitis, and are 'specific to move the "stagnations" in the whole body.' The location and depth of insertions was as described in traditional texts [13]. The points used were P 6 (Neiguan) 2 *cun* (*cun* is similar to 1 in; measurement used to localize the points corresponds to the size of the thumb of the patient) above the wrist crease, between the tendons of palmaris longus and flexor carpi radialis; Lu 7 (Lieque) 1.5 *cun* above the wrist crease, superior to the styloid process of the radius; Li 4 (Hegu) in the middle of the second metacarpal bone on the radial side; Li20 (Yingxiang) in the nasolabial groove, level with the midpoint of the lateral border of the ala nasi; Gv20 (Bahui) 5 *cun* posterior to the anterior head line; Ren 23 (Lianquan) at the upper

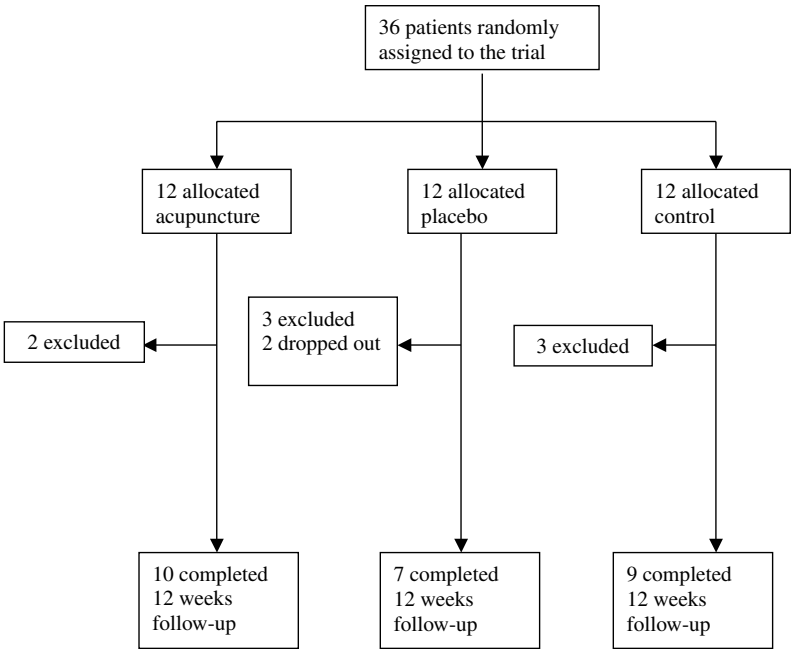

Fig. 1. Trial profile.

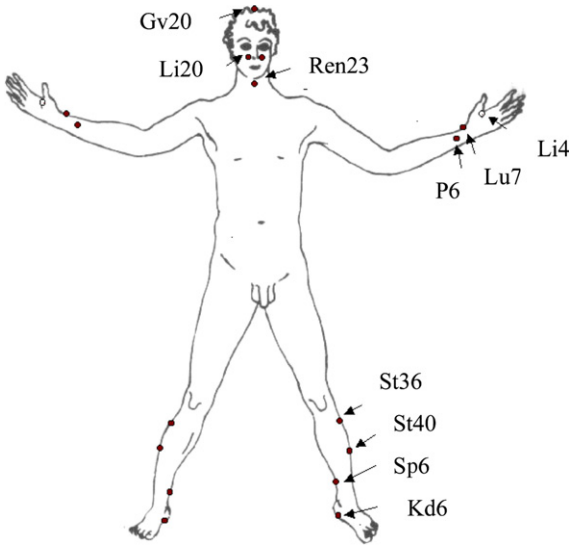

Fig. 2. Selection of the acupoints.

border of hyoid bone; St 36 (Zusanli) four fingers' breadth below the lateral depression of the patella, one-finger width lateral from the anterior border of the tibia; St 40 (Fenglong) 8 *cun* below the inferior border of the knee and two finger widths lateral to the anterior border of the tibia; Sp 6 (Sanyinjiao) 3 *cun* directly above the tip of the medial malleoulus on the posterior border of the tibia; Kd 6 (Zhaohai) in a depression below the tip of the medial malleolus.

The sham acupuncture group was stimulated with the same number of needles as the acupuncture group, and the points were localized 1 cun from the real point, in a region not related to any acupoints or meridians and was done following the standards of minimal acupuncture [14]. For the sham acupuncture group, the needles were inserted and no manipulation was done. In the acupuncture group, the needles were correctly inserted and manually stimulated by lifting and rotating until the 'de qi' sensation of heaviness and numbness were elicited [13]. All acupuncture procedures, as well as sham acupuncture, were performed by an experienced physician, who was a specialist in acupuncture, according to traditional Chinese acupuncture methods. All procedures were performed in the afternoon between 3 p.m. and 6 p.m. Body needles were left in situ for 30 min. No adverse events occurred during the trial.

2.2.2. Evaluation of general health/functional status and subjective sleepiness

General health and functional status were assessed with the Medical Outcome Study 36-item short-form health survey (SF-36) [15], self-administered by each subject on the day of the first evaluation and of the reevaluation, together with the Epworth sleepiness scale (ESS) [16], which evaluates the degree of sleepiness in eight different daily conditions. ESS scores vary from 0 to 24, with increasing scores indicating greater sleepiness. The SF-36 questionnaire yields summary scores for each of eight health concepts. Four are considered 'functional status' measures (physical functioning, social functioning, role limitation due to physical problems and role limitation due to emotional problems), three are considered measures of well-being (mental health, energy/fatigue and pain), and one is a measure of overall health. As recommended [15], raw scores for each subscale are transformed to scores that range from 0 to 100. In all instances, a higher score is consistent with a more positive health status.

2.2.3. Polysomnography procedures

Every subject went to bed in the laboratory at their usual bedtime and had a minimum of 7 h of PSG recordings. The following sleep variables were collected and stored using amplifiers and pre-amplifiers (Meditron™) and a computerized 32-channel sleep system (Sonolab® Meditron, São Paulo, Brazil). A total of four electroencephalogram (EEG) leads, two electro-oculogram (EOG) channels, two electromyogram (EMG) channels (chin and both legs), and one electrocardiogram (ECG) channel were recorded. Respiration was monitored as follows: (a) nasal cannula with flow measured using a pressure transducer; (b) mouth thermocouple to monitor mouth flow; (c) two channels for chest and abdominal efforts with calibrated inductive respiratory plethysmography; and pulse oximetry was obtained using a Nellcor™oximeter.

Sleep recordings were scored according to the criteria of Rechtshaffen and Kales [17]. Arousals were defined as abrupt shifts in EEG frequency lasting ≥ 3 s and < 15 s, according to the criteria published in the 1992 American Sleep Disorders Association (ASDA) report [18]; the arousal index (AI) was calculated as the number of arousals per hour of sleep. Apneas were defined as complete cessation of oronasal airflow for at least 10 s and hypopneas as any reduction in airflow compared to baseline, associated with a $\geq 3\%$ desaturation or a microarousal lasting 10 s or more [19]. The AHI was defined as the number of apneas–hypopneas per hour of sleep. Lowest and mean values of oxygen saturation (SaO_2) were also recorded. All of the PSG recordings were assessed by two experienced sleep physicians (S.M. Togeiro and F.S.Chrispin), who were blind to the groups to which the patients had been assigned. A total of 40 PSGs were scored by both readers before the commencement of the trial for calculation of interobserver agreement (IOA). The post-treatment PSG recording was obtained 2 weeks after the last application procedure. We did not score inspiratory flow limitation, in order to exclude patients with upper airway resistance syndrome.

No adverse events occurred during the trial.

3. Statistics analysis

As there were no previous studies on this subject, a preliminary power calculation suggested that about 24 patients would need to be randomly assigned for the study to achieve statistical power of 90%, designed to detect a 80% response in the treated group and 20% response in the placebo group, with a probability of type I error of 0.05, and type II error of 0.10. All data were computer-analysed using SPSS 9.0 software. The characteristics of the patients were expressed as median and compared between groups by the Kruskal–Wallis test. Changes as a consequence of treatment were assessed in two ways: compared between, before and after by the Wilcoxon matched pairs signed ranks test and compared between groups by the Kruskal–Wallis test [20]. The Kappa statistic was used in order to measure the IOA, calculating the unweighted κ-value with its 95% confidence intervals. Conventional interpretation of K-values is as follows: 0.00–0.20, poor agreement; 0.21–0.40, regular; 0.41–0.60, moderate; 0.61–0.80, good; 0.81–1.00, very good. Negative values are interpreted as equal to 0.00 [21].

4. Results

A total of 36 patients with a recent PSG yielding a diagnosis of moderate OSAS were eligible for the study (Fig. 1): 20 females (55.6%) and 16 males (44.4%). Patients were randomly assigned to the acupuncture group, sham acupuncture group or control group ($n = 12$ each group). During the study, eight patients were excluded, of which seven justified their withdrawal on the basis of the long-distance they had to travel or the length of the study. One patient from the control group was excluded for starting a separate treatment protocol with acupuncture for another medical condition (e.g. pain). Two patients from the sham acupuncture group stopped the treatment (drop-out). Of the 26 patients who finished the study, 15 were females (57.7%) and 11 were males (42.3%). Baseline characteristics of the three groups were similar (Table 1). There was no statistical difference in any of the clinical parameters measured (BMI, abdominal and neck circumferences) between the patients before and after the study nor between the groups.

4.1. General health/functional status and subjective sleepiness

Table 2 shows changes in the outcomes of questionnaire parameters before and after treatment in the three

Table 1
Baseline characteristics of patients

	Acupuncture group	*Sham* acupuncture group	Control group	*P*
Age (years)	54.0 (51.0–63.0)	53.0 (49.0–63.0)	57.0 (50.0–64.0)	0.89
Body index mass (Kg/m^2)	26.9 (26.6–28.0)	25.7 (25.0–30.0)	28.6 (24.8–28.8)	0.47
Neck circumference (cm)	39.5 (37.0–41.0)	37.0 (34.0–41.0)	38.0 (35.0–40.0)	0.73
Abdominal circumference (cm)	97.0 (94.0–105.0)	94.0 (83.0–102.0)	97.0 (89.0–104.0)	0.97
Apnea–hypopnea index	18.0 (17.0–21.0)	19.0 (18.0–27.2)	19.1 (18.0–21.0)	0.79
Apnea index	8.5 (7.0–11.0)	5.3 (4.0–9.6)	9.0 (2.7–9.0)	0.89
Hyponea index	9.0 (6.4–15.0)	12.0 (9.3–23.2)	14.1 (12.0–18.0)	0.79

Data are median (5th–95th centiles) with range in parentheses. $P < 0.05$.

Table 2
Changes in the outcomes of the mean psychometric results for the SF-36 and Epworth questionnaires before and after procedures in the studied groups

	Acupuncture			*Sham*			Control			
	Baseline Mean (SD)	12-week Mean (SD)	*P* before/after	Baseline Mean (SD)	12-week Mean (SD)	*P* before/after	Baseline Mean (SD)	12-week Mean (SD)	*P* before/after	*P* comparing groups[a]
Epworth	11.1 (3.3)	7.5 (3.0)	0.029[b]	12.7 (4.3)	13.1 (5.0)	n.s.	11.0 (5.7)	13.3 (7.0)	0.047[b]	n.s.
Physical function	64.5 (26.0)	69.5 (22.0)	n.s.	70.7 (22.0)	71.4 (24.0)	n.s.	52.8 (25.0)	57.8 (23.0)	n.s.	n.s.
Role physical	52.5 (44.8)	72.5 (40.0)	0.033[b]	71.4 (41.9)	75.0 (25.0)	n.s.	38.9 (46.9)	33.3 (41.0)	n.s.	n.s.
General health	50.6 (16.7)	69.9 (21.0)	0.034[b]	69.9 (11.1)	70.0 (20.0)	n.s.	41.4 (22.3)	46.9 (19.0)	n.s.	n.s.
Pain	62.1 (19.7)	71.8 (24.3)	n.s.	73.4 (14.9)	72.4 (16.3)	n.s.	60.6 (18.5)	57.2 (16.0)	n.s.	n.s.
Vitality	36.5 (25.0)	56.5 (25.0)	0.028[b]	58.6 (26.0)	65.0 (18.0)	n.s.	45.0 (17.0)	43.3 (14.0)	n.s.	n.s.
Social functioning	60.0 (29.3)	67.5 (24.0)	n.s.	73.2 (24.4)	75.0 (26.0)	n.s.	62.5 (27.2)	68.1 (23.0)	n.s.	n.s.
Role emotional	53.3 (44.9)	73.3 (34.0)	n.s.	61.9 (40.5)	66.7 (43.0)	n.s.	37.0 (48.4)	44.4 (44.0)	n.s.	n.s.
Mental health	50.4 (23.1)	68.4 (21.0)	0.005[b]	70.3 (15.5)	81.7 (15.0)	0.037[b]	55.6 (17.9)	52.0 (16.0)	0.029[b]	0.001[b]

[a] Comparison between the three groups by Kruskal–Wallis test.
[b] Acupuncture vs. control group. $P < 0.05$. SD, Standard deviation.

groups. After 10 weeks of treatment with acupuncture, there was a significant improvement in the ESS scores ($P = 0.028$) and also in the dimensions of the SF-36 particularly in: role physical ($P = 0.016$), bodily pain ($P = 0.017$), vitality ($P = 0.024$) and mental health ($P = 0.005$). Among the patients treated with sham acupuncture we observed a significant change only in the mental health dimension of the SF-36 ($P = 0.033$). In contrast, in the control group there was deterioration in the mental health ($P = 0.029$) dimension, and the ESS score became significantly worse with an initial mean of 11.0 changing to 13.3 by the time of the reevaluation ($P = 0.047$). The only significant difference encountered between the three groups was the marked improvement in the mental health dimension for the acupuncture group as compared to controls ($P = 0.001$).

4.2. Polysomnographic parameters

Results for IOA show that the average agreements between each observer pair did not differ greatly; global agreement was considered very good ($k = 0.82$). Of the six variables analysed, average agreement between observers was good for two variables: microarousal (0.79) and hypopneas (0.80), and very good for sleep latency (0.86), rapid eye movement (REM) latency (0.85), apneas (0.81) and REM stage (0.85). Table 3 shows the changes in the outcomes of the PSG parameters, depicting the results before and after procedures for the three groups. The acupuncture group showed a marked significant improvement, mainly in respiratory parameters. We observed a significant decrease in the AHI (Fig. 3), AI and number of respiratory events from the baseline of 50.5% ($P = 0.005$), 79% ($P = 0.008$), 43% ($P = 0.005$), respectively. Patients subjected to acupuncture also showed significant improvements in sleep onset (67% shorter latency), in sleep efficiency (8% increase), and in the mean saturation rate (92.8 before to 95.4 after). As for the outcomes of the sham acupuncture group, there was a significant increase only in sleep efficiency (14%). A similarly significant improvement of 12% in sleep efficiency was also seen in the control group. The control group, however, became significantly worse in the number of respiratory events (53% more).

Table 3
Changes in the outcomes of the polysomnographic parameters before and after procedures in the studied groups

	Acupuncture			*Sham*			Control			
	Baseline Mean (SD)	12-week Mean (SD)	*P* before/after	Baseline Mean (SD)	12-week Mean (SD)	*P* before/after	Baseline Mean (SD)	12-week Mean (SD)	*P* before/after	*P* comparing groups[a]
Sleep onset	13.7 (9.6)	4.4 (3.0)	0.019	19.8 (17.1)	9.0 (6.3)	n.s.	18.8 (26.7)	9.7 (15.0)	n.s.	n.s.
REM onset	122.2 (58.2)	80.6 (59.1)	n.s.	134.3 (97.6)	147.2 (77.3)	n.s.	144.7(63.6)	162.8 (68.9)	0.050	n.s.
Sleep efficiency (%)	79.4 (9.2)	85.7 (11)	0.028	75.9 (5.6)	86.6 (9.0)	0.018	80.3 (12.6)	89.9 (6.2)	0.043	n.s.
REM stage (%)	16.5 (6.6)	20.1 (6.8)	n.s.	16.6 (5.3)	13.8 (4.8)	n.s.	14.9 (4.2)	15.4 (5.0)	n.s.	n.s.
Apnoea–hypopnea index	19.9 (4.1)	10.1 (5.6)	0.005	21.6 (5.3)	24.6 (11.0)	n.s.	20.4 (4.4)	28.2 (18.0)	n.s.	0.002[b,c]
Apnoea index	8.4 (4.4)	1.8 (3.7)	0.008	7.1 (3.3)	9.6 (10.0)	n.s.	6.0 (4.5)	6.0 (7.3)	n.s.	0.018[b]
Hypopnea index	11.7 (7.2)	8.4 (4.4)	n.s.	14.5 (6.7)	15.1 (6.8)	n.s.	14.5 (4.0)	22.4 (15.0)	n.s.	n.s.
Respiratory events	116.1 (22.2)	66.5 (40.0)	0.005	119.1 (19.3)	162.9 (79.0)	n.s.	117.3 (40.0)	180.0 (111.0)	0.025	0.001[b,c]
Microarousal	102.1 (44.6)	85.3 (20.0)	n.s.	140.7 (52.3)	164.7 (89.0)	n.s.	141.7 (76.1)	160.7 (102.0)	n.s.	n.s.
Mean SaO_2 (%)	92.8 (2.1)	95.4 (2.0)	0.011	94.0 (1.3)	94.1 (2.0)	n.s.	94.8 (1.0)	94.2 (2.0)	n.s.	0.005[b]

[a] Comparison between the three groups by Kruskal–Wallis test.
[b] Acupuncture vs. control group.
[c] Aacupuncture vs. *sham* acupuncture group. $P < 0.05$. SD, Standard deviation.

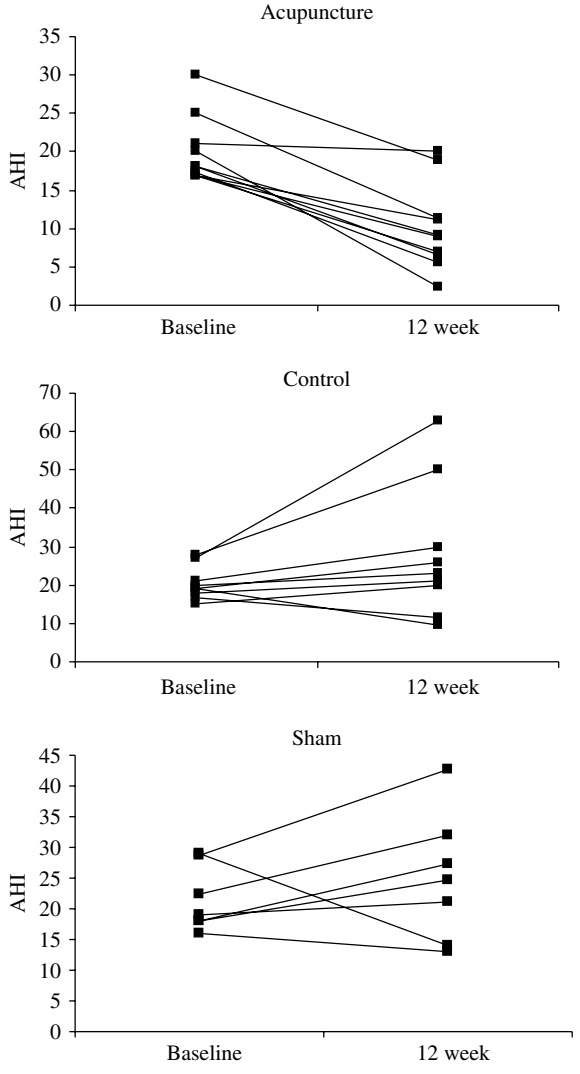

Fig. 3. Changes in the individual apnea hypopnea index (AHI).

Comparison of the three groups after treatment revealed that the acupuncture group significantly differed from both the sham acupuncture and control groups in the AHI ($P = 0.02$) and in the number of respiratory events ($P = 0.001$). The acupuncture group also showed significant changes over the control group (but not over sham) in the AI ($P = 0.018$). Sham-treated subjects did not differ from controls in any of the performed PSG measurements made after the 12-week length of the study (Table 3).

We did not use the intent-to-treat analysis because we could not follow up on these patients. Thus, we do not have data for the patients who dropped out.

5. Discussion

This placebo-controlled pilot study demonstrates that acupuncture is more effective than placebo treatment (*sham* acupuncture) in terms of providing significant changes in the respiratory events assessed by PSG, and in the improvement of the quality of life of patients suffering from OSAS. This is the first study of the effects of acupuncture in the treatment of obstructive sleep apnea; thus, the preliminary results from this study will require validation with additional data.

Bardwell and colleagues [22] showed that CPAP was clearly more effective than placebo (an ineffective CPAP) for reducing the number of apneas and hypopneas and increasing the percentage of REM. In contrast to the CPAP trials that analysed the acute effect of this equipment, our treatment promoted changes in respiratory events during sleep 15 days after the last acupuncture session.

One of the most noticeable changes in PSG parameters in the acupuncture group was the reduction in AHI (Fig. 3). Analysing individual subjects, we observed that six patients of the acupuncture group (60%) had an AI equal to 0 2 weeks after treatment. Widely accepted PSG criteria for treatment to be considered successful is a reduction in AHI to lower than 10, with a 50% reduction from the baseline condition [19]. In our study, 60% of the patients reached these goals, and another 20% reached only the 50% reduction in AHI. In this pilot study, we showed a 50% change in the AHI of the acupuncture group, which is smaller than our original estimation (80%), with standard deviations of 5 and 11 before and after treatment, respectively. On the other hand, we had a negative effect (−) 15% in the sham group (expected 20%). Accordingly, to maintain a significant level of 5% and a statistical power of 90%, we will need a sample size of 25 patients in each group in future studies, Furthermore, the number of respiratory events, as well as the number of microarousals, had diminished in all of the patients in the acupuncture group, 42.7 and 16.5% less than the baseline, respectively. The robustness of this observation was further supported by the fact that no single patient of the *sham* acupuncture and control groups reached an AI of 0. The non-specific improvement in sleep efficiency observed in all groups is likely to be a consequence of the adaptation to the laboratory setting. Another important issue is the possibility of missing other forms of abnormal breathing during sleep, such as periods of increased respiratory effort and parodoxal breathing. Although this protocol did not include esophageal balloon, the gold standard method to detect the respiratory effort, we measured the airflow through the nasal cannula. This measurement provides information about airflow limitation [23], which has been correlated with elevated upper airway resistance and increased esophageal pressure. Since, the PSG scorers did not find any flattened inspiratory airflow associated with microarousals or paradoxal breathing, we could rule out upper airway resistance syndrome (UARS).

Either specific and/or non-specific effects can indicate a treatment has been successful [24]. Acupuncture has

the potential to elicit very powerful placebo effects [25]. Not surprisingly, therefore, almost all patients treated with *sham* acupuncture may respond positively in some manner [26], as we could observe in our study. Although we were careful in the experimental design, many baseline parameters were higher in the *sham* acupuncture group. Even so, the significant improvement in the mental health dimension of the SF-36 among the patients treated with *sham* acupuncture may be associated with the placebo effect mentioned in other acupuncture studies. This speculation may be on the mark, since, we did not observe any objective improvement in that group. Although we did not observe significant deterioration in daytime sleepiness between the groups, the control group as well as the *sham* acupuncture group showed an increase in daytime sleepiness while the acupuncture group showed a significant improvement in this subjective parameter, showing that real acupuncture actually had an effect on the sleep disorder.

Reports of uncontrolled clinical trials with acupuncture abound in the medical literature [27]. Such trials, however, can only give preliminary indications of the general effectiveness of a specific treatment. In the absence of a control group, researchers are unable to ascertain whether changes reported to have occurred during the trial were attributable to the particular method used [28]. Here, we report that several of the measured parameters over the 3 month period that comprised the study became significantly worse in patients in the control group. Possible ethical concerns that could be raised by such study design can readily be dismissed. First, for a country where the minimum wage is approximately US $90 per month, the cost of a CPAP (approximately US $1,000 for the device alone) is inaccessible. Second, the public health system does not have enough funds to cover the treatment of moderate OSAS with CPAP. And third, it is a well-established fact that many patients treated with CPAP have low compliance [5]. Thus, the absence of adequate treatment has catastrophic consequences for the patients.

Asthma and allergic rhinitis are well-known risk factors for OSA. Previous acupuncture trials for asthma [29] and allergic rhinitis [30] found preliminary evidence for its effectiveness. The resolution of OSA in the current study could thus have been secondary to the resolution of asthma and allergic rhinitis. However, only one patient in the acupuncture group had a history of asthma. During the trial, this patient did not develop any crisis. There was a patient in the sham group with controlled allergic rhinitis. We did not observe any changes in this patient during the course of the treatment. Thus, it is unlikely that the current effect is an indirect consequence of the resolution of asthma or allergic rhinitis.

We found no significant change in BMI in all three groups. Therefore, we suggest that the beneficial effects of acupuncture in our study were not due to changes in BMI. Another issue that should be considered is the night-by-night variability of the AHI. Variability of the AHI has been reported when patients without any treatment for OSAS underwent three consecutive PSG recording sessions [31]. Here, in contrast, all patients of the acupuncture group had significant reductions of the AHI, suggesting treatment effectiveness rather than variability of the AHI as the most likely cause for change.

There is strong evidence of the involvement of serotonergic pathways in the responses mediated by acupuncture. Sugai and colleagues [32] showed in rats that treatment with pCPA (para-Chlorophenylalanine), a serotonin inhibitor, blocks the effect of acupuncture over the gastrointestinal system. Similarly, Lee and colleagues showed that a single session of acupuncture stimulation increased serotonin synthesis and tryptophan hydroxylase expression in the dorsal raphe in non-exercised rats [33]. The central mechanism underlying reduction of activity of airway dilator muscles during sleep are not fully elucidated. Nevertheless, it is known that there is a strong projection of caudal raphe serotonergic neurons to upper airway motorneurons, and the firing of caudal raphe neurons declines with sleep particularly during REM sleep, consequently diminishing the airway muscle tonus [34]. As a consequence, the decline of the upper airway motor activity associated with sleep in OSAS patients might result from an impaired serotonin mediated excitatory drive by caudal raphe neurons. Studies have already shown that the administration of L-tryptophan, a serotonin precursor [35] as well as the administration of a serotonin reuptake blocker [36], reduces the number of apneas, in some patients. Taken together, these observations lead us to propose a working hypothesis that the improvement observed in the acupuncture group, mainly in PSG respiratory parameters, might be related to the effects of acupuncture for releasing serotonin from caudal raphe neurons. This speculative hypothesis is currently being tested in our laboratory by a larger trial where we are going to evaluate 5HT levels in platelets for patients submitted to acupuncture treatment.

There is strong evidence that inflammatory cell infiltration and denervation changes affect not only the mucosa but also the upper airway muscles of patients with OSAS [10]. This may have important implications for the ability to generate adequate muscular dilating forces during sleep. We hypothesize that the local effect of acupuncture may also affect this process of inflammation.

The most prominent finding of this study is a major improvement in AHI with active acupuncture. We have found preliminary evidence that acupuncture is effective in the treatment of OSAS. This work, however, must be replicated and the observation period after treatment should be extended in order to evaluate the duration of the improvement obtained and also to establish well defined treatment protocols. If these findings are confirmed, acupuncture treatment may have a role in the management of sleep apnea.

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