

Acupuncture in Migraine Prevention

A Randomized Sham Controlled Study With 6-months Posttreatment Follow-up

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Objective: To assess the efficacy of acupuncture in migraine prophylaxis.

Methods: Thirty-seven patients with migraine were enrolled in a randomized control trial at the Headache clinic located in a University Hospital. Real and sham acupuncture groups received 16 acupuncture sessions over 3 months. Treatment was individualized in the real acupuncture group and minimal acupuncture was used in the sham group. The primary end point was the percentage of patients with a $\geq 50\%$ reduction in their migraine attack frequency in the second, third, fourth, fifth, and sixth (months) compared with the first one (baseline period). Primary and secondary end points were measured comparing headache diaries.

Results: Real acupuncture group showed improvement with significant differences compared with the sham acupuncture group in the primary efficacy end point ($P = 0.021$) at the second month of the treatment. Differences also appeared in 2 secondary end points: number of days with migraine per month ($P = 0.007$) in the second month and the percentage of patients with $\geq 40\%$ reduction in migraine attack frequency in the first ($P = 0.044$) and second months ($P = 0.004$) of the treatment. These differences disappeared in the third (last) month of the treatment as a consequence of the high improvement of the sham acupuncture group. Comparisons within each group showed that several migraine parameters evaluated improved significantly in both groups.

Conclusions: Individualized treatment based on traditional Chinese medicine plays a role in preventing migraine attacks.

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Nevertheless, sham acupuncture had similar effects. Major conclusions were limited by the small sample sizes however the observed trends may contribute to design future trials.

Key Words: acupuncture, migraine, prophylaxis, randomized controlled trial, headache, efficacy, effectiveness

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The history of acupuncture shows the very old relationship between this medical approach and the treatment of pain.¹ In the western world, acupuncture is widely used and accepted for controlling chronic pain.^{2,3} Up to now, according to the Evidenced Based Medicine, acupuncture has only showed uncontested effectiveness in pain in 2 areas: chronic low back pain and postoperative dental pain.^{4–6}

The prevalence of migraine in the United States is about 18% for females and 5% for males.⁷ These rates like to be lower in Asian Americans population as well as in Asian and African countries.^{8–10} Migraine is not recognized as a specific disease in the theory of traditional Chinese medicine (TCM).¹¹ Nevertheless, acupuncture has been largely used for people with migraine in western countries.¹² In the last 30 years, several trials were performed to test acupuncture efficacy to control migraine.^{2,13–22} However, a series of methodological problems make it impossible to reach definitive conclusions.^{23–25} Recently published trials have noted that acupuncture plays a role in migraine^{26–28} and tension-type headache,²⁹ but they showed no statistically significant differences between acupuncture based on principles of TCM and the sham acupuncture. The aims of the present study were to assess the direction and magnitude of acupuncture effects in migraine prophylaxis.

STUDY DESIGN

Patients and Methods

This study was conducted between December 2001 and June 2003 in the State University of Campinas (UNICAMP), Brazil. The Institutional Ethics Committee approved it in June 2000 in accordance with the

Declaration of Helsinki. Patients were recruited via an advertising campaign in the media. The protocol was structured according to the Guidelines for Controlled Trials of Drugs in Migraine³⁰ and the Guidelines for Clinical Research on Acupuncture.³¹

Thirty-seven consecutive patients with migraine with or without aura for at least 1 year diagnosed according to the International Headache Society³² criteria were included. Major inclusion criteria were age between 18 and 50; 2 to 6 migraine attacks per month (baseline period) and having not used prophylactic migraine drugs or acupuncture in the last 3 months. The principal exclusion criteria were diagnoses of any other pain syndrome including other associated headache type; having used any migraine prophylactic drugs in the 3 months before inclusion; having used analgesics for more than 10 days a month.

Patients were analyzed retrospectively on the basis of their clinical history and prospectively through headache diaries and visits by an experienced neurologist. Clinical and demographic data are shown in Table 1. At the first neurologist visit selected patients were informed (orally and through a print-out) about the study, risks, and their right to withdraw at any time without specifying reasons. A group meeting allowed learning how to keep a headache diary. The diary required considerable amount of details about the daily behavior of migraine throughout the month, including the intensity in the morning, afternoon, and night, duration, medication intake (type and doses), nausea, vomiting, and menstruation. Patients spent a month (baseline period) keeping their diary and were scheduled for a second neurologist's visit. Data from baseline period allowed for checking inclusion and exclusion criteria. Selected patients provided written informed consent. Before the acupuncture treatment, patients were evaluated by an acupuncture specialist physician who recorded the clinical history and physical evaluation on the basis of the principles of TCM. It was followed by an active acupuncture treatment period.

Randomization

Patients were randomly assigned to sham or real acupuncture groups through opaque numbered and sealed envelopes. The random digits list³³ was used to determine different letters sequence in 7 blocks. Each block contained 3 letters C and 3 letters D. Each letter

signed one of the 2 acupuncture groups. Only the medical acupuncturist knew the meaning (group) of each letter.

Blinding

Both groups were treated with 16 acupuncture sessions. The neurologist and the medical acupuncturist were prohibited from commenting on any treatment details with patients. The medical acupuncturist adopted a uniform, neutral attitude toward the patients so as not to disrupt the blind design of the trial.

At the end of the study, patients were invited to complete a questionnaire that evaluated the treatment they received and to state their impression about which treatment group they thought they had been included.

Outcome Measurement

Patients were instructed to complete diaries for 6 months: baseline period (1 mo), acupuncture treatment period (3 mo), early follow-up (first month after the last acupuncture session), and late follow-up (sixth month after the last acupuncture session). Posttreatment follow-up periods were designed to test the long-lasting effects.

The Acupuncture Treatment

There were several common approaches in both groups including: bilateral points; usage of disposable, sterile steel needles (0.25 mm × 40 mm); skin disinfection with 70% alcohol; needles in place for 30 minutes and no moxa or electrical stimulation. Treatment could be altered from session to session, as it happens when acupuncturists treat patients in their offices.

Real acupuncture treatment was individualized based on the principles of TCM. Each treatment was defined for at least 2 experienced physicians specialized in acupuncture for more than 11 years. A maximum of 20 needles were inserted. However, the central principle of the treatment was followed. The needles were manipulated by rotation methods to produce a characteristic sensation known as De Qi, which was explained to the patients of this group in the first session.

Sham acupuncture treatment was minimal acupuncture and consisted of a very superficial insertion in acupuncture points with needles almost falling out. The number of needles varied from 10 to 15. No manipulation was done. The points were selected after an extensive consultation of the Chinese acupuncture literature with no references to effects on headaches.^{34–39} Some sham points were localized in the head to preserve the patients blinding.

Parameters and Statistics

The primary end point was the percentage of patients with ≥ 50% reduction in migraine attack frequency each month compared with the baseline period. A new attack was recorded when the patient had been free of headaches for 48 hours before the pain returning. Secondary efficacy parameters included the percentage of patients with ≥ 40% reduction in migraine attack frequency, the number of attacks per month, the number of days with migraine per month, the total duration of

TABLE 1. Clinical Details of the Population Studied

	Real Acupuncture (n = 19)	Sham Acupuncture (n = 17)	P
Mean age (y)	36.7 ± 9.2	33.2 ± 9.2	ns
Sex (F/M)	17/2	15/2	ns
Schooling (y)	13.5 ± 3.5	13.6 ± 3.5	ns
Duration of disease (y)	20.6 ± 10.8	14.5 ± 7.6	ns
No. attacks (baseline period)	4.5 ± 0.9	4.7 ± 1.0	ns
Nausea	18 (94.7%)	17 (100%)	ns
Migraine without aura	17 (89.5%)	9 (52.9%)	ns
Migraine with aura	2 (10.5%)	8 (47.1%)	0.025

migraine pain in hours per month, the mean total duration of each migraine attack, the mean headache severity in each attack, the amount and the type of rescue medication used per month, nausea frequency (number of days with nausea per total of migraine days per month), and vomiting frequency (total of vomiting episodes per total of migraine days per month). All of these parameters were compared within and between groups, with the reference point being the baseline period in each group. The severity of headache was evaluated on a 4-point scale (0—no headache, 1—mild headache = migraine not interfering with daily activities, 2—moderate headache = migraine interfering with daily activities, and

3—severe headache = migraine making normal daily activities impossible) following International Headache Society recommendations.³⁰

Statistical comparisons were made using univariate analysis with the χ^2 test and Fisher exact test. Comparisons within each group were made using the nonparametric Mann-Whitney test and differences were estimated using the Wilcoxon Signed Rank test. The significant level used was $P < 0.05$.

RESULTS

Thirty-seven patients with and without aura were randomly assigned to the real or sham acupuncture

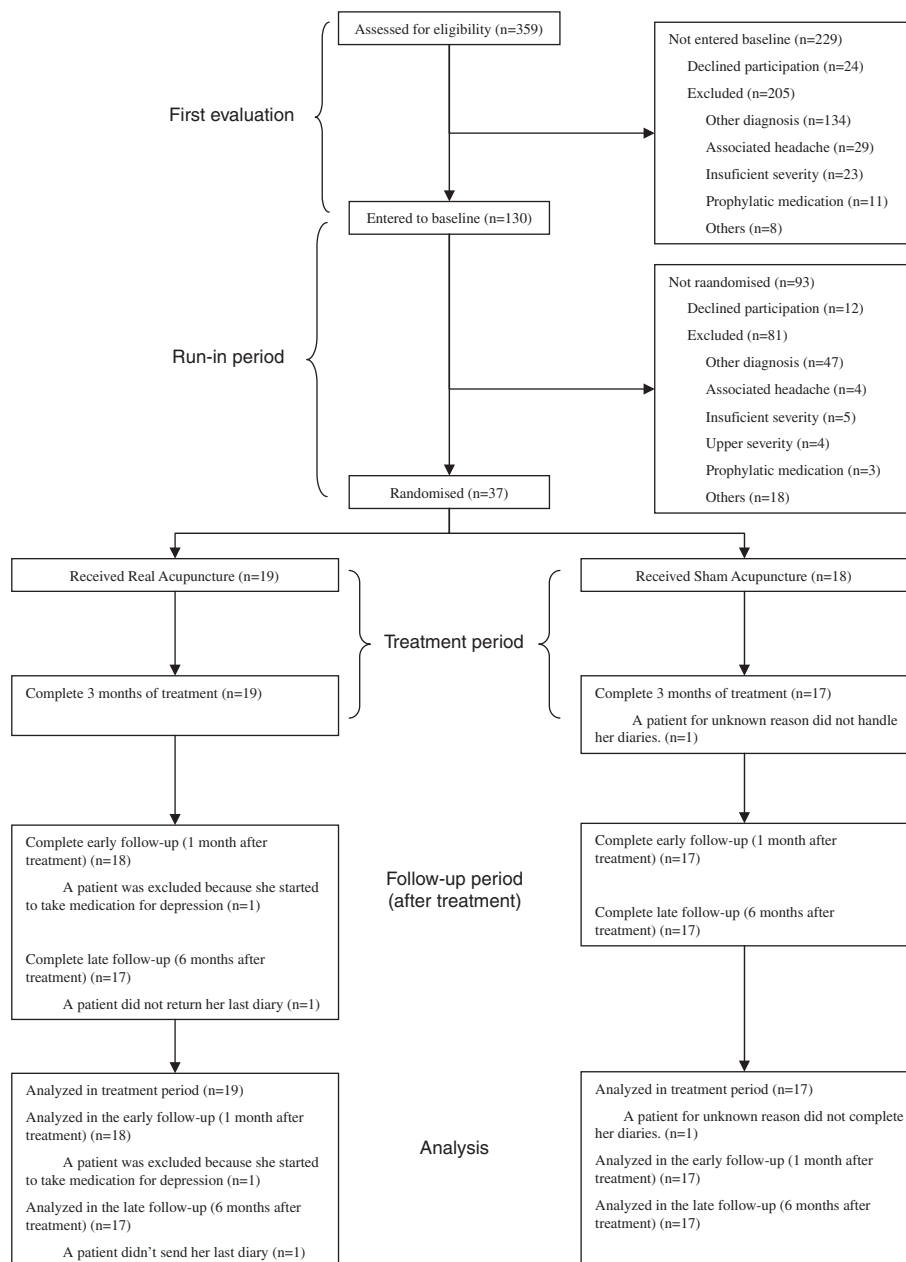


FIGURE 1. Flow of participants through the trial.

groups. Thirty-six patients were included in the statistical analysis (Fig. 1). For unknown reasons, a patient of the sham acupuncture group did not complete her diary. As shown in Table 1, both groups were homogeneous in almost all of the characteristics. An exception was in the type of migraine where migraine patients with aura were significantly more numerous in the sham group.

A patient from the real acupuncture group was excluded in the early posttreatment follow-up period, because she started to take amitriptyline for depression. There was an additional dropout in the late posttreatment follow-up from the real acupuncture group. The patient moved to another city and did not send in her last diary.

Efficacy

In the first and second months of acupuncture therapy, the frequency of migraine attacks fell by $\geq 50\%$ in greater proportion in the real acupuncture group, and statistical significant differences appeared in the second month of the treatment ($P=0.021$). In the third and last treatment month, the frequency of migraine attacks declined in both groups, especially in the sham group. As a result, the significant difference seen between groups in the previous months was no longer detected ($P=0.332$). During the posttreatment follow-up periods, when the end points were analyzed, no statistically significant differences were observed between groups (Fig. 2).

Differences with statistical significance between groups appeared in the second month of the treatment in 3 secondary parameters: number of days with migraine per month ($P=0.006$), the total duration of migraine pain in hours per month ($P=0.025$), and reduction of

$\geq 40\%$ in the frequency of migraine attacks ($P=0.004$). Greater improvement was observed in the real acupuncture group. From the third month of the treatment to the late posttreatment follow-up, the statistical difference between groups disappeared (Figs. 3, 4).

Comparisons within each group showed that all migraine pain parameters evaluated improved significantly in both groups except for headache severity. However, that improvement appeared with statistical significance in the real acupuncture group from the first month of the treatment through the late posttreatment follow-up. In the sham acupuncture group, the improvement started only in the second month of the treatment and then stayed right through. The evolution of the improvement within each group for the total duration of pain in hours is displayed in Figure 5.

Rescue Medication

There was a reduction in the total intake of rescue medications in both groups. However, there were no statistical significant differences between them. The type of rescue medication varied. Most of the patients used more than 2 types of medication that included simple and combined analgesics, nonsteroidal anti-inflammatory drugs, ergots, and triptans.

Associated Symptoms

There were no statistical significant differences between groups in the associated symptoms (nausea and vomiting). In the analysis within each group appeared a significant and progressive reduction in the frequency of nausea during migraine attacks in the real acupuncture group from the first month of acupuncture through to the

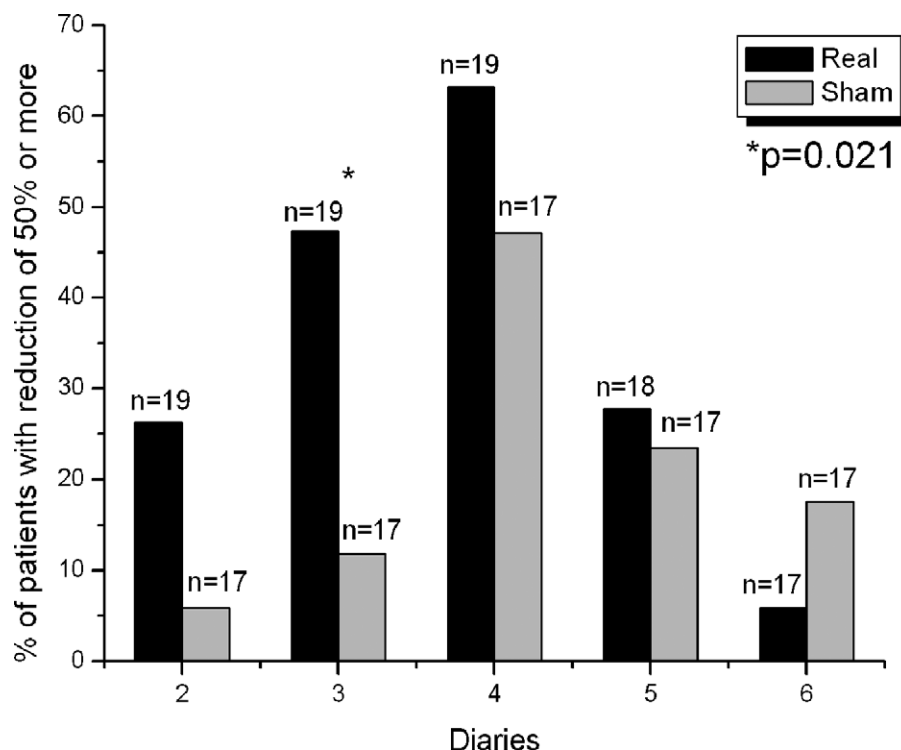


FIGURE 2. Percentage of responders (reduction 50% in migraine attack frequency) in each diary (1 mo) compared with the baseline period (diary 1) in the real and the sham acupuncture groups. Diary 2=first month of the treatment, diary 3=second month of the treatment, diary 4=third month of the treatment, diary 5=first month after the treatment, and diary 6=sixth month after the treatment. In this figure, the P value is referred to the differences between groups.

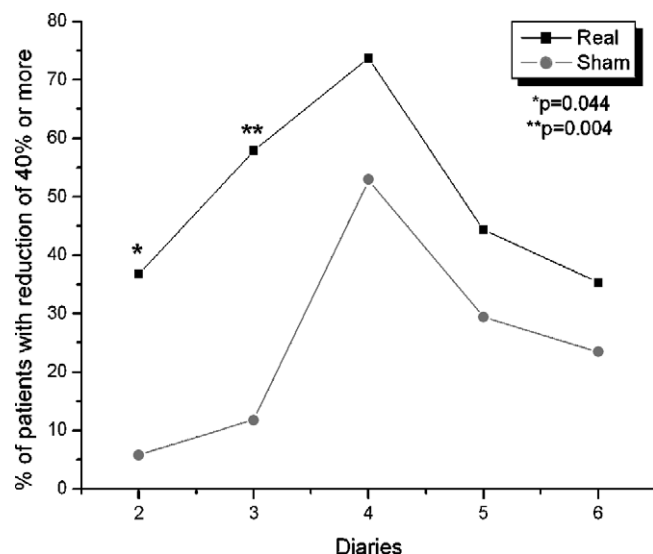


FIGURE 3. Percentage of patients with reduction of 40% or more in migraine attacks frequency in the real and sham acupuncture groups compared with the baseline period. Diary 2=first month of the treatment, diary 3=second month of the treatment, diary 4=third month of the treatment, diary 5=first month after the treatment, and diary 6=sixth month after the treatment. In this figure, the *P* value is referred to the differences between groups.

late posttreatment follow-up. The same was not observed in the sham group.

Adverse Event

The patients were instructed to report all adverse events (AEs) to the medical acupuncturist. No serious

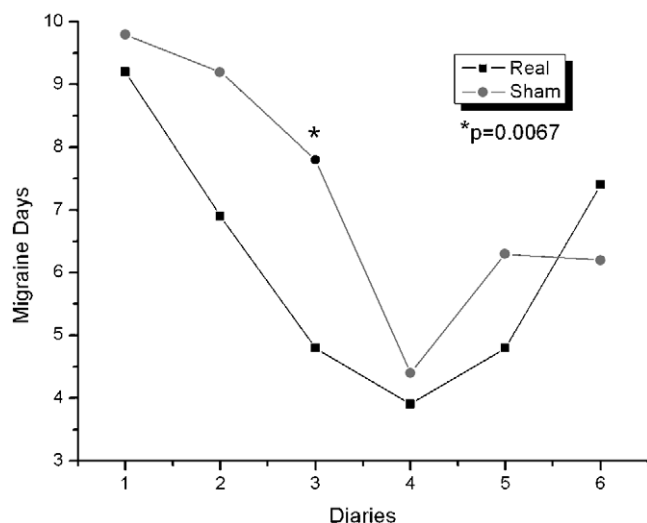


FIGURE 4. Total of migraine days in each diary (1 mo) in the real and the sham acupuncture groups. Diary 1=baseline period, diary 2=first month of the treatment, diary 3=second month of the treatment, diary 4=third month of the treatment, diary 5=first month after the treatment, and diary 6=sixth month after the treatment. In this figure, the *P* value is referred to the differences between groups.

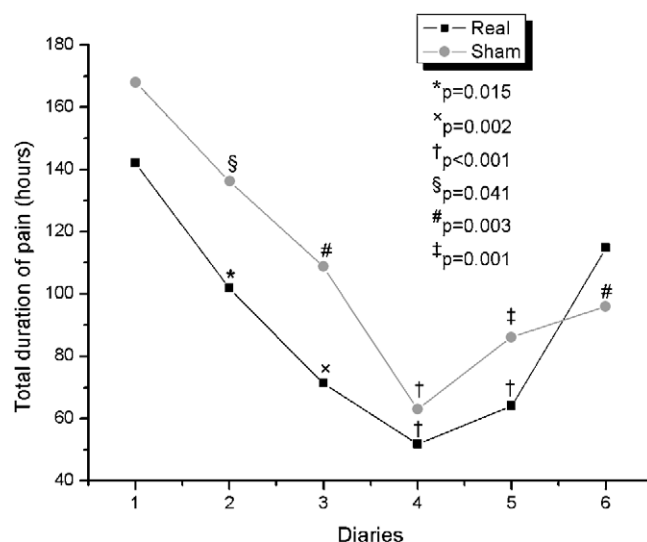


FIGURE 5. Total duration of pain in hours in each diary (1 mo) in the real and the sham acupuncture groups compared with their own baseline period. Diary 1=baseline period, diary 2=first month of the treatment, diary 3=second month of the treatment, diary 4=third month of the treatment, diary 5=first month after the treatment, and diary 6=sixth month after the treatment. In this figure, the *P* value is referred to the differences within each group compared with the baseline period.

AEs were observed in the 576 sessions carried out and about 8640 needles inserted. The AEs appeared mainly at the sites where needles were inserted. The most common event was ecchymosis. It was reported in only one out of 8 sessions without significant difference between groups. All AEs were classified as low risk.⁴⁰

Patients' Perceptions

At the end of acupuncture treatment, patients stated that they would like to be treated with acupuncture again classifying treatment as good, very good, or excellent. When asked about what type of treatment they received, the reply was "I don't know" for 52.5% of patients in the real acupuncture group and for 64.7% of patients in the sham group. Patients who correctly identified their treatment were 36.8% in the real acupuncture and 11.76% in the sham group. There was no statistical significant difference between the replies from the 2 groups, indicating that the blinding procedure was effective.

DISCUSSION

More women than men were studied in our sample. This may be a consequence of the higher number of women in the population; migraine is more common in females than in males⁴¹ and it is recognized that women seek medical care for headaches more often than men.⁴²

There was a significant statistical difference concerning migraine with aura in the sham acupuncture group compared with the real acupuncture group.

However, up to now, the literature has demonstrated that the presence or absence of aura has not affected the outcome of any applied treatment.⁴³

There were several positive features of this study including: the homogeneity of the sample in almost all demographic characteristics; the randomized design of the trial; the successful blinding of the patients, evaluator, statistician, and research assistants, the very low rate of drop-out with less than 10% of patients from the beginning up to the late follow-up period and finally, there was only one experienced medical doctor applying acupuncture treatments.

Efficacy

The end point adopted in this study was the percentage of the patients with $\geq 50\%$ reduction in migraine attack frequency. In the real acupuncture group, this parameter started to increase in the first month of treatment and the statistical significant difference between groups appeared in the second month of treatment ($P = 0.021$). When the parameter adopted was the percentage of the patients with $\geq 40\%$ reduction in migraine attack frequency, the improvement in the real acupuncture group appeared in the first month of the treatment ($P = 0.044$) and in the second month of treatment ($P = 0.004$). In the third month of the treatment, the sham acupuncture group had a very high improvement (Fig. 2). Consequently, at this point, the statistically significant difference between groups disappeared in all primary and secondary efficacy parameters adopted in this trial. In the first 2 months of treatment the sham group improved only slightly (5.9% and 11.8%, respectively). Thus, if the sham group remained at this level until the end of the trial it could probably indicate no prophylactic activity or analgesic effects.⁴⁴ The very high improvement occurred in the sham acupuncture group in the third month of the treatment remains unexplained to the authors. The most plausible hypothesis is that the result was due to chance. But, it would be important to observe in future trials if that kind of sham acupuncture called “minimal acupuncture” has any retarded analgesic effect when applied in true acupuncture points as in this trial. The majority of acupuncture trials in the sham group were done in false points.

The present trial showed that in the third month of the treatment 63.2% and 47.1% of the patients in the real and sham group, respectively, reached $\geq 50\%$ reduction in their migraine attacks frequency. Reduction in migraine attacks reached was 48.1% and 44.1% in the real and sham groups, respectively. The very high improvement at the end of the treatment period in both groups is higher than it was shown in the majority of the trials, which tested drugs for migraine prophylaxis. van der Kuy and Loman⁴⁴ evaluated 22 relevant migraine prophylactic trials (double-blind and randomized) and no placebo response was seen with more than 35% of the patients who had $\geq 50\%$ reduction in the frequency of migraine attacks. When the reduction in the frequency of migraine attacks was analyzed, improvement in the

placebo setting was not observed above 40%. Therefore, effects noted in the sham group in this present trial differ from the expected for “inert” placebo^{3,4,26,27,45} in randomized and blinded migraine trials.⁴⁴ That improvement confirms the impression that sham acupuncture promotes analgesic effects^{3,46,47} by unknown mechanism, probably with physiologic and psychologic components.

In this study, to protect the patient's blinding, in the sham group 3 points were adopted in the head. These points are in the same nervous segment that was under treatment, the head. Did it influence the results? There is no scientific evidence for that effect. Several other nonspecific effects observed in trials could explain the high improvement of the sham group, such as the patient's belief in positive results of the acupuncture treatment, the frequent patient's contact with the acupuncturist doctor (16 visits in 3 mo) and the “magic power” of the nonconventional therapies have on people. In fact, the placebo effect is expected in any therapeutic intervention, independent of whether we are testing an active drug or not, an active proceeding or not. Therefore, the placebo effects could be present in the real acupuncture group as well. However, it seems to be greater in people with pain⁴⁸ particularly with invasive procedures.⁴⁹ In migraine studies to test acute drugs such as analgesics or triptans, the authors verified that the placebo power changes depending on the access type of the intervention. They have seen that subcutaneous placebo has higher efficacy (34%) than oral application (26%).⁴⁹ Therefore, whether the placebo power of the invasive methods adopted as a control proceeding in the present trial (minimal acupuncture) have increased the effects in the sham acupuncture group is unknown. In fact, the use of sham acupuncture as a control group may be a greater problem in studies involving pain than in measuring other sort of symptoms.⁴

Silberstein and Goadsby⁵⁰ stated that in controlled clinical trials to evaluate drugs in migraine prophylaxis, the efficacy is often first noted in 4 weeks and continues to increase for 3 months. In the analysis within the real acupuncture group, improvement in several variables with statistical significant differences could be detected in the first month of treatment and it increased up to the third (last) month of the treatment. In the sham acupuncture group, the improvement with statistically significant difference appeared only from the third month of the treatment to the late posttreatment follow-up period. Therefore, these data indicate that the effect in the real acupuncture group started faster and it increased with continued treatment.

The effects of the acupuncture groups (real and sham) decreased when the treatment was interrupted. Nevertheless, part of these improvements was preserved slightly in both groups through the early up to the late posttreatment follow-up period. The long-lasting effects of acupuncture intervention were observed in most recent and well-designed trials.^{26–29,51–53} This trial confirms the results of previous trials,^{54,55} which showed that no significant changes happened in the headache severity

with all kinds of acupuncture interventions either real or sham.

The analysis within each group showed improvement of all parameters evaluated except for the headache severity and vomiting in the real acupuncture group and headache severity, nausea, and vomiting in the sham group. The improvement of nausea appeared with statistical significant difference in the analysis within the real acupuncture group from the first month of treatment to the late posttreatment follow-up period. The acupuncture effect to control nausea is known and it has been demonstrated in several high-quality clinical trials.⁴

The trial indicated of 2 different pathways for devising adequate sample sizes in future essays. The evidences found here in the improvement for both groups supports the need for blinding patients undergoing invasive sham procedures supports the requirements up to a 50% reduction. Then it would be necessary to have 2 groups of at least 22 each one (total = 44) to fulfill the requirements of a 5% α and 20% β errors. To evaluate differences in the third month of treatment, the estimated sample size would need to grow sharply to at least 2 groups of 146. Estimates for the late posttreatment follow-up are unstable due the large sampling variability.

Limitations of the Study

Enrollment of patients was difficult and most were excluded, 286/359 (79.7%), because of the strict inclusion and exclusion criteria. The patients might have heard about the benefits of "acupuncture" and might have expected a good treatment response. Therefore, the influence in the results of the patient's belief and high expectation on acupuncture treatment could not be excluded.

Several factors could have contributed to the results found in this trial. Few statistical significant differences between real and sham acupuncture groups could be a consequence of the presence of the great intergroups variability, the small size of the sample, the sort of control group adopted as sham acupuncture in this trial (minimal acupuncture in true acupuncture points), and the strong placebo effects identified in all kinds of the headache trials.⁵⁶

In conclusion, statistical significant differences observed between groups in some pain parameters evaluated were transient. Analysis within each group demonstrated that the sham and real acupuncture had effects in almost all pain parameters evaluated and they were maintained for a long time after the last acupuncture session. The improvement in both groups was superior to the expected placebo prophylactic effects with drugs. The small size of the sample and the absence of another type of control group did not allow for major conclusions. We expect that this trial contribute to reach a more adequate methodology to achieve the response in the future about the role acupuncture plays to prevent attacks in migraine sufferers.

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