Universitat Autònoma de Barcelona

DEPARTAMENT DE MEDICINA

Doctoral Thesis of the
"Internal Medicine Doctorate Program"

EVALUATION OF THE EFFICACY OF ACUPUNCTURE IN THE PREVENTION OF MIGRAINE ATTACKS

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Barcelona, July 2011

To my husband Paulo Borba Leite de Moraes who provided all support necessary to conclude this thesis: help, love and attention.

To all the people who suffer from their "migraines" and who sought or even begged for our help often shrouded in tears. These patients without even knowing it gave me the encouragement and the necessary strength to not give up halfway when the obstacles and excessive hours of work consumed all my energy and vitality.

A todas las personas que sufren con sus “jaquecas” e que buscaran o hasta mismo imploraran por nuestra ayuda, muchas veces con los ojos llenos de lágrimas. Esos pacientes, sin saberlo, me dieron el estímulo y fuerza necesarios para no desistir en la mitad del camino, cuando las dificultades y la extenuación por el exceso de trabajo parecían haber consumido todas mis energías.

A todas as pessoas que sofrem com suas “enxaquecas” e que buscaram, ou até mesmo imploraram pela nossa ajuda, muitas vezes envoltas em lágrimas. Esses pacientes sem sabê-lo, deram o estímulo e força necessários para que eu não desistisse na metade do caminho, quando os obstáculos e as excessivas horas de trabalho consumiam toda a minha energia e vitalidade.

AGRADECIMENTOS

Aos meus amigos e “pais adotivos”, Heleno Rodrigues Correa Filho e Ana Maria Segall Correa, pela carinhosa acolhida em Campinas e por terem aberto as portas e me ajudado a desvendar os caminhos na Unicamp.

Ao Dr. Jayme Antunes Maciel Júnior por ter aceitado a difícil tarefa de orientar e participar diretamente com seu trabalho como médico de todos os ensaios clínicos que resultaram nessa tese. Seu apoio foi imprescindível para a realização dessas atividades de pesquisa e assistência em acupuntura, área ainda de restrita inserção em uma das mais importantes instituições de ensino e pesquisa do Brasil - Universidade Estadual de Campinas (UNICAMP).

Ao Dr. Xavier Carnè que dispensou seu tão precioso tempo discutindo por tantas vezes o desenho dos ensaios clínicos e sugerindo possíveis caminhos a serem adotados quando apareciam as dúvidas e dificuldades. Sua vasta experiência como médico Farmacologista Clínico, sem dúvida, foi imprescindível para o sucesso dos nossos estudos.

A todos os pacientes que participaram dos estudos, por tanta dedicação e cuidado no preenchimento de seus diários de cefaleia durante tanto meses, pelos deslocamentos para serem consultados ou receberem o tratamento com acupuntura, mesmo sabendo que eles poderiam estar incluídos em um grupo de tratamento “falso”.

A FAPESP pelo financiamento desse projeto de pesquisa de acupuntura que resultou em três ensaios clínicos consecutivos. O apoio da FAPESP foi imprescindível para que houvéssemos recebido tanto apoio de todos os setores da Unicamp.

Ao Dr. Ivan Tóro que durante a realização de nossos estudos era o Superintendente do Hospital de Clínicas da Unicamp, e que até hoje não sabe o quanto contribuiu diretamente para que esses estudos se concretizassem.

A toda a equipe do Ambulatório de Neurologia do Hospital de Clínicas da Unicamp e aos funcionários do Departamento de Neurologia da Unicamp, em especial a Solange, Márcio, Edna, Rosa e Solaine.

A maravilhosa e competente enfermeira Leda Maria Fernandes por toda sua dedicação e empenho na fase de assistência aos pacientes, inclusive trabalhando sem nenhuma remuneração durante os atendimentos realizados pela noite e aos sábados.

Aos bolsistas da Unicamp, Geraldo Magela Severino Vasconcelos e Camila Queiroz que trabalharam incansavelmente inclusive nos finais de semana e noites.

A enfermeira Heloisa de Lima Gomes que voluntariamente cedeu muito do seu tempo assessorando esse trabalho, telefonando aos pacientes, digitando dados e organizando as salas de atendimento.
Aos colegas médicos especialistas em Acupuntura por suas importantes sugestões clínicas a respeito do tratamento dos pacientes: Dr. Norton Moritz Carneiro, Dr. Lo Sz Hsien, Dr. Carlos Moriyama, Dr. Ling Tung Yang e Dra. Isabel Giralt.

Serei eternamente grata a toda a equipe de relações públicas do Hospital de Clinicas da Unicamp e aos Assessores de Imprensa da Unicamp, em especial ao Antonio Alberto Ravagnani, Eliana Cristina Silva Pietrobom, Isabel Cristina Gardenal, Ani Seixas e Ronei Thezolin.

A Helcia Vasconcellos pelas inúmeras revisões do inglês e pelas preciosas sugestões de conteúdo. Acupuntura e Medicina Baseada em Evidências é sua expertise. Sorte a minha por ter tido uma revisora tão qualificada!!!!

Ao meu irmão Abnel pelo carinho e apoio logístico que permitiu que durante tantos anos eu me dedicasse a esses estudos simultaneamente ao meu trabalho como médica.

A minha mãe, Geny Alecrim, minha irmã, Yara Alecrim e minhas amigas Katie Argüelo, Isabel Giralt, Maria de Lourdes Brizot e Marajú Chagas que sempre me incentivaram quando o excesso de trabalho e dificuldades provocava muito cansaço e desânimo.

ACKNOWLEDGEMENTS

To my friends and "adoptive parents", Heleno Rodrigues Correa Filho and Ana Maria Segall Correa for their warm welcome to Campinas opening doors and helping me to unveil the paths towards a successful work at UNICAMP.

To Dr. Jayme Antunes Maciel Júnior for accepting the difficult task of directing and participating directly with his work as a doctor of all clinical trials that resulted in this thesis. His support was essential to carry out these research activities and assistance in acupuncture which is still a field which has limited insertion in one of the major teaching and research institutions in Brazil – State University of Campinas (UNICAMP).

To Dr. Xavier Carnè who so often spent his precious time discussing the protocol of clinical trials and suggesting possible paths to be followed when doubts and difficulties appeared. His vast experience as a clinical pharmacologist physician was undoubtedly essential to the success of our trials.

To all patients who participated in the trials, for all their dedication and care in filling out their headache diaries during so many months, for coming to hospital to be consulted or to receive acupuncture treatment, even though they knew they could be included in the “sham” (false) treatment group.

To FAPESP for funding this acupuncture research project that resulted in three consecutive trials. FAPESP's support was indispensable and helped get support from all Unicamp sectors.

To Dr. Ivan Tóro that during the course of our trials was the Superintendent of the Hospital of Clinics at Unicamp and never knew how much he directly contributed to the materialization of these studies.

To the entire team at the Neurology Clinic, Unicamp Clinical Hospital and the staff of UNICAMP Neurology Department, especially Solange, Márcio, Edna, Rosa and Solaine.

To the competent and wonderful nurse Leda Maria Fernandes for all her dedication and commitment during patient care phase, including unpaid work during the sessions held in the evenings and on Saturdays.

To the Fellows from Unicamp, Geraldo Magela Severino Vasconcelos and Camila Queiroz who worked tirelessly including weekends and nights.

To the nurse Heloisa de Lima Gomes, who voluntarily dedicated much of her time to assisting this work, calling up patients, entering data and organizing the treatment rooms.

To fellow specialists in acupuncture for their important suggestions about the clinical treatment of patients: Dr. Norton Moritz Carneiro, Dr. Lo Sz Hsien, Dr. Carlos Moriyama, Dr. Ling Tung Yang and Dr. Isabel Giralt.

I am forever grateful to the entire public relations staff of Unicamp Clinic Hospital and the Unicamp Press Assessory, in particular to Antonio Alberto Ravagnani, Eliana Cristina Silva Pietrobom, Isabel Cristina Gardenal, Ani Seixas and Ronei Thezolin.

To Helcia Vasconcellos who made countless English revisions and precious suggestions on the content. Acupuncture and Evidenced-Based Medicine is her area of expertise. I was very fortunate to have had such a qualified reviser.

To my brother Abnel for the affection and logistical support that allowed me to devote myself to these studies and simultaneously work as physician.

To my mother Geny Alecrim, my sister Yara Alecrim and my friends Katie Argüelo, Isabel Giralt, Maria de Lourdes Brizot and Marajú Chagas who have always encouraged me when overwork and difficulties made me feel exhausted.

AGRADECIMIENTOS

A mis amigos Heleno Rodrigues Correa Filho y Ana Maria Segall Correa por la acogida con tanto cariño en Campinas y por abrieren los caminos en la UNICAMP.

Al Dr. Jayme Antunes Maciel Júnior por haber aceptado la difícil tarea de orientar y participar directamente con su trabajo clínico en todos los ensayos clínicos presentes en la tesis. Además, fue imprescindible el sostenimiento que dio a una investigación en acupuntura y cefalea en una de las más importantes instituciones académicas de Brasil, la Universidad Estatal de Campinas (UNICAMP).

Al Dr. Xavier Carnè que dispendió su precioso tiempo hablando por tantas veces sobre el diseño del estudio y sugiriendo posibles soluciones en las dificultades.

A todos los pacientes que participaran de los estudios, por tanta dedicación y cuidado al rellenar por 4 veces al día sus diarios de cefalea por tantos meses, por los desplazamientos para las consultas y sesiones de acupuntura, mismo sabiendo que podrían estar sometidos a un tratamiento falso.

A FAPESP por la financiación de todo el proyecto de investigación y todos los sectores de la UNICAMP que apoyaran estos estudios.

Al Dr. Ivan Tóro, el Superintendente del Hospital de Clínicas de la Unicamp en el periodo de realización de los estudios clínicos, por el apoyo conjunto que dio permitiendo una mejor ejecución de las investigaciones.

A todo el equipo de enfermería del Ambulatorio de Neurología (Edna, Rosa y Solaine) y de la administración del Departamento de Neurología de la Unicamp, en especial a la Solange y el Márcio.

A la gran Enfermera, Leda Maria Fernandes por toda su dedicación y empeño en todas las etapas de esta investigación.

A los becários Geraldo Magela Severino Vasconcelos y Camila Queiroz.

A la enfermera voluntaria Heloisa de Lima Gomes que ha cedido mucho de su tiempo a esas investigaciones.

A los colegas médicos especialistas en Acupuntura por sus importantes sugerencias en el tratamiento de los pacientes: Dr. Norton Moritz Carneiro, Dr. Lo Sz Hsien, Dr. Carlos Moriyama, Dr. Ling Tung Yang e Dra. Isabel Giralt.

Eternamente tendré gratitud por todo el equipo de relaciones públicas del Hospital de Clínicas y los Asesores de Prensa de la UNICAMP, especialmente a: Antonio Alberto Ravagnani, Eliana Cristina Silva Pietrobom, Isabel Cristina Gardenal, Ani Seixas e Ronei Thezolin.

A Helcia Vasconcellos por sus revisiones del inglés y preciosas sugerencias de contenido. Acupuntura y Medicina basada en evidencias es su especialidad. Suerte por haber tenido una revisora tan calificada!

A mi hermano Abnel Alecrim por el cariño y apoyo logístico que permitió que durante tantos años yo me dedicase a esos estudios simultáneamente a mi trabajo como médico.

A mi madre, Geny Alecrim, mi hermana Yara Alecrim y mis amigas Katie Argüelo, Isabel Giralt, Maria de Lourdes Brizot y Marajú Chagas que siempre me han dado palabras de incentivo sobre todo cuando el exceso de trabajo y las dificultades provocaban cansancio y desanimo.

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ABSTRACT

The aim of this thesis is to discuss the results reached through two trials (Trial 1 and Trial 2) developed to reach a best methodological design to evaluate the role of acupuncture to prevent migraine attacks. Phase III trial was done using the knowledge background obtained after these referred trials.

Subjects with migraine were randomized to the real or sham acupuncture groups in two different trials.

Distinctive treatment approaches were tested as being real acupuncture. In the first one, the “individualized” treatment was applied. The “semi-standardized” acupuncture treatment was evaluated in the second trial. All patients were treated with 16 acupuncture sessions during twelve weeks. Post-treatment follow-ups were done during 6-months. The primary endpoints adopted were the percentage of patients with reduction ≥40% (Trial 1) and ≥50% in migraine attacks frequency (Trials 1 and 2) and the total of days with migraine (Trial 2). Headache diaries were used to obtain data in the baseline period and the full time of the study. Data from all diaries were compared with the baseline period.

Improvements with statistical significant differences appeared only in Trial 1. Real acupuncture group was superior to sham group in the second month of the treatment, when the percentage of patients with ≥50% reduction in migraine attack frequency was evaluated (P=0.021). The reported differences appeared also in two secondary endpoints: number of days with migraine per month (P=0.007) in the second month of the treatment and in the first (P=0.044) and second (P=0.004) months of the treatment when the percentage of patients with a ≥40% reduction in migraine attack frequency was measured.

The “individualized” treatment adopted in Trial 1 seemed to be the best approach to test the acupuncture effects in trials for migraine prophylaxis.

RESUMEN

El objetivo de esta tesis es discutir los resultados de dos ensayos clínicos (Ensayo 1 e Ensayo 2) desarrollados para que pudiéramos diseñar con mejor calidad metodológica un protocolo para evaluar el papel de la acupuntura en la prevención de las crises de migraña. Posteriormente, un ensayo clínico fase III fue ejecutado haciendo uso de toda esa bases de conocimiento alcanzado después de esos ensayos clínicos referidos.

En cada ensayo, los pacientes con migraña han sido asignados de manera aleatoria a dos grupos, el de acupuntura real y otro de acupuntura sham.

Dos abordajes terapéuticas con acupuntura real han sido empleadas. En el primero ensayo, ha sido hecho un tratamiento individualizado. En el otro ha sido aplicado un tratamiento semi-estándar. Todos los enfermos han recibido 16 sesiones de acupuntura en 12 semanas. El seguimiento ha sido hecho por 6 meses después del término del tratamiento. Los “primary endpoints” eran: el porcentaje de pacientes con reducción ≥40% (ensayo 1) y ≥50% in la frecuencia de las crisis de migraña (ensayo 1 y 2) y el número de días con migraña (ensayo 2). Diarios de cefalea han sido adoptados para la recogida continua de datos. Todos los diarios han sido comparados con el diario del periodo “baseline”.

Mejora con diferencia estadística significante apareció tan solo en el primero estudio. El grupo de acupuntura comparado al sham señalo mejora en el segundo mes de tratamiento cuando ha sido evaluado el porcentaje de pacientes con reducción ≥50% en el número de crisis de migraña (P=0.021). Hubo diferencias estadísticas también en dos variables secundarias: reducción en el número de días con migraña en el segundo mes de tratamiento (P=0.007) y el porcentaje de pacientes con reducción ≥40% de la frecuencia de crisis de migraña disminuyó en el primero (P=0.044) y segundo (P=0.004) mes de tratamiento.

El tratamiento con acupuntura individualizado adoptado en el primero estudio parece ser un abordaje más adecuado cuando el objetivo sea el de evaluar cuál sería el efecto de la acupuntura para la profilaxis de la migraña.

RESEARCH SUPPORT

The State of São Paulo Research Foundation (FAPESP) supported trials that are the subject of this doctoral thesis by grant n° 00/09985-0.

The State University of Campinas contributed a lot for the developing of these trials. It offered its entire physical infrastructure. The public relations staff of the Clinic Hospital and the Press Assessor made these trials possible.

GLOSSARY OF TERMINOLOGY

5-HT1 (5-hidroxitriptamin 1 = serotonin)
AEs (Adverse Events)
CNS (Central Nervous System)
DNIC (Diffuse Noxious Inhibitory Control)
FAPESP (State of São Paulo Research Foundation)
IHS (International Headache Society)
NSAID (non-steroidal anti-inflammatory drugs)
Qi (concept of “energy” in the traditional Chinese medicine)
TCM (traditional Chinese medicine)
UNICAMP (State University of Campinas)
USA (United States of America)
WHO (World Health Organization)
RCT (Randomized controlled trial)

PRESENTATION

The context where our trials were developed was completely different from the current setting. Up to the early years of this present century, there were few acupuncture clinical trials with adequate methodological design which could help us to define better ways to be followed to reach the goal that was to evaluate the role acupuncture plays in the treatment of many conditions, inclusive migraine and other pain conditions. At that time, many trials presented positive results, however many shortcomings made it impossible to confirm these data (1-6).

Our goal was to demonstrate the effects of acupuncture to control migraine attacks using the scientific way to traditional Western medical doctors. For that, we planned to develop a pilot trial to define the protocol of the master trial better.

To design our first trial (Trial 1), we looked for many resources that researchers have been using to develop trials with drugs (7-15). The classification of headache of the International Headache Society (IHS)(16) was rigorous followed by the experienced neurologist (one of the directors of this thesis - JAMJ) on the occasion of the selection and the follow-up visits. Guidelines to design clinical trials from IHS(11, 12), World Health Organization (WHO)(17), consensus from National Institutes of Health (USA)(18) and the International Acupuncture Research Forum(19), as well as many articles and systematic reviews about acupuncture research were utilized to define protocol details(1, 3, 5, 20-24). To design these trials better, we read the greater part of clinical acupuncture trials about headache published in English up to year 2001(25-44). Almost all methodological details from each trial were evaluated as well as the shortcomings, bias, suggestions made by authors for “next trials in future” before defining each point of our protocols.

Authors of some acupuncture articles and evaluative revisions suggested that acupuncture trials were developed by a group of professionals qualified in clinical investigation, research methodology and acupuncture to minimize problems in the design of the trials, shortcomings and inadequacies in the statistical analysis(5, 19, 45). For our researcher team, we looked for people qualified in several parts of the subject of

the researched theme. The team was composed for physicians specialized in acupuncture, neurology, headache, clinical pharmacology, epidemiology and statistics.

The evolution of each trial was assessed all the time and even sequential statistical analysis was conducted. In fact, each trial was a step to improve the next one. After finishing Trial 1 (pilot trial), we changed many details such as: headache diary, the explanation of the headache diary for patients (we adopted a group visit to clarify each point of diary), sham and real acupuncture treatment. Logistical details were performed and clinical research assistants were contracted to minimize the contact of the doctors involved in these trials with the patients. The team was worried with the interference of the frequently doctor's contact with patients in the results of the trials.

Thinking of the easier reproduction of the trial results in future trials as well as with the clinical practice adoption of the tested treatment, the research team decided to choose a semi standardized treatment in the real acupuncture group in Trial 2. During the development of this trial sequential statistical analysis was conducted. The trial was interrupted when the minimal pre-defined size of the sample was reached. At this time, we decided to develop the third sequential trial (Trial 3) that was not planned initially.

Results with the semi standardized treatment were negative and the individualized acupuncture treatment tested in Trial 1 was apparently promising. At this point, we had a good and trained clinical trial team. Therefore, we decided to go back and test the individualized treatment with the higher sample in the next trial, it was calculated using data from the first trial (Trial 1).

However, the greater problem of the acupuncture trials remained in the third trial. It was the chosen control group, acupuncture with penetrating needles. Lewith, stated in 1983 that sham acupuncture as rather a "poor form of acupuncture treatment"(46). Many trials had appointed that sham acupuncture with penetrating needle had higher improvement than the expected for inert placebo group. However, many researchers thought that superficial needling would not produce expressive acupuncture effects. Minimal acupuncture was defined as a very shallow penetrating needling. Up to 2002, many authors suggested that minimal acupuncture was a better approach for control group in acupuncture trials. They defended that shallow needling could minimize acupuncture

true physiological effects and contribute to avoid psychological impact(47). Therefore, this sort of control group could assure patient's blinding regarding the kind of treatment applied (4, 6, 42, 48, 49). Nevertheless, nowadays it is most clear that sham acupuncture with penetrating needles is not a placebo control. That point will be better explained in the discussion item of this thesis.

To better understand our explanation during this doctoral thesis, it is important to clarify an aspect. The first trial we published was not the first trial we developed. We sent them to the journals in a sequence. However, a very important journal "lost" our first article and published the second trial before the first one. Therefore, during the explanation in the next items, Trial 1 is the trial that we published in 2008. Trial 2 was published in 2006. Both trials were steps to develop phase III trial, Trial 3. The third trial was not published yet as an article. However, we presented it as posters in 2005 during the XII Congress of the International Headache Society, in Kyoto-Japan. The copy of posters and abstracts of this trial were included in the Appendix item.

These three trials were included in the last version of the Cochrane systematic review published in 2009 that evaluated the efficacy of acupuncture for migraine prophylaxis. Authors of the mentioned systematic review classified these two articles which are the subject of this thesis among the five high quality trials of this review (50).

1. INTRODUCTION

1.1. Migraine

Headache is one of the most common conditions for which adults seek neurological care (51-53). Headache is a subjective symptom. It could be only one symptom of a more complex disorder. Patients with primary headache suffer from intermittent or chronic pain, with no physical or laboratory abnormalities. The absence of objective markers for primary headaches creates the necessity to elaborate an accurate classification system to better diagnose these complaints(54). A specific headache diagnosis is important when determining the appropriate therapy and management of headache(55). The International Headache Society (IHS), in 1988, developed a classification, which facilitates the epidemiological research, and clinical trials on the field, and make the diagnosis and the primary headaches treatment more precise and adequate(16). Guidelines for research and clinical management of the patients were developed after the IHS classification (11). Our trials adopted all the recommendations from IHS, the headache classification and guidelines for research (11, 16).

Migraine is characterized by attacks that consist of various combinations of headache and neurological, gastrointestinal and autonomic symptoms, certainly involving intracranial structures(56). The migraine pathophysiology is based on the anatomical and physiological relationships of the trigeminovascular system (57). Migraine is considered a chronic disorder, which sufferers have in their neurovascular system a predisposition to react excessively to internal or external stimuli generating hyperactivity of the brain and of the trigeminovascular apparatus. Genetic factors are involved (57-59).

Migraine attack could be presented in four phases: the prodromal phase, which occurs hours or days before the headache; the aura phase, which immediately precedes the headache; the headache phase itself; and the headache resolution phase (60). The typical migraine headache is unilateral, throbbing, moderate to severe in intensity and aggravated by physical activity or head movements. However, migraine varies widely in its frequency, duration and severity, even between attacks in the same patient. The presence of all phases is not necessary for the migraine diagnosis. In fact, migraine attack could happen without the headache phase, with only the aura phase.

The degree and type of disability vary in different primary headaches (61). The impact of headache and associated symptoms for the psychological condition, social life and work productivity of migraine sufferers is greater than that of other causes of headache, including the most common primary headache, the tension-type headache (62).

The prevalence of migraine in the USA (United States of America) is about 18% for females and 5% for males(63). Migraine is a considerable socioeconomic burden, with a high cost to its sufferers(64). This cost is reflected in a reduced quality of life, an increase in medical expenditure, a decrease in productivity, reduced educational and occupational achievement and generated absenteeism. Migraine sufferers may limit their social and work activities in order to avoid factors that can trigger an episode or out of fear of having a migraine attack(65). In the USA, migraine is estimated to cost employers $13 billion each year because of missed workdays and reduced productivity(66).

The pharmacological treatment of migraine may be acute or prophylactic. Some patients should require both approaches.

Acute treatment could be done with many non-specific medications, like analgesics, antiemetics, anxiolytics, non-steroidal anti-inflammatory drugs (NSAID), steroids, major tranquillizers and narcotics. Ergots and 5-HT1 agonists have been largely used and they are considered migraine specific medications.

The prophylactic treatment is indicated when migraine attacks are becoming more frequent or the pain severity compromises the patient’s life. The United States Evidence-Based Guidelines for Migraine have outlined the circumstances that might warrant preventive treatment(56).

The efficacy of preventive treatment has been estimated to be about 60%, which include the placebo response to all first-line preventive medications(67). Preventive treatment includes a broad range of medication classes, including beta-blockers, calcium-channel blockers, antidepressants, serotonin antagonists, anticonvulsants and NSAID. However, several patients discontinued the migraine prophylactic treatment because of adverse events related to most of the drugs used. Co-morbid and coexistent diseases have

important implications for prophylactic treatment, and may impose certain therapeutic limitations(68). Using natural processes and other clinical interventions could enrich treatments for chronic headaches and migraine prophylaxis(69). In fact, the advance in prophylactic treatment has lagged behind the development of the new treatments for migraine attacks.

Acupuncture should contribute to overcome some of the therapeutic restrictions associated with established drugs and promote advances in this way(70).

1.2. Acupuncture

Acupuncture is only a part of the resources utilized for the traditional Chinese medicine (TCM) to treat patients. This technical approach remounts to the Neolithic period (10,000-3,500 BC). Probably, it was used empirically in many different cultures over the world. Actually, acupuncture was incorporated into the TCM framework between period 5 and 3 BC through the Huang Di Nei Jing, the Yellow Emperor's classic book of internal medicine. The background of Chinese medicine was the Naturalist School, which interprets the Nature in a positive way and defends that humans do not have to control and subdue Nature, but act in harmony with its laws(71).

The most singular philosophical basis of Chinese medicine is the concept of Yin-Yang. The Yin-yang theory, the concept of Qi and the 5 Element theory constitute the basis of the TCM. The "Qi" concept would be understood as an "energy" which circulates in the body through channels called meridians(72).

Classical Chinese acupuncture consists in treating some symptoms, signs and illnesses by insertion of needles in several parts of the body. These points are located along the meridians and provide one means to balance the flow of Qi. The flow and equilibrium of Qi determines the state of health. The diagnosis in the ancient TCM was done through some distinctive parameters utilizing for example, tongue, pulse and other signs and symptoms usually not very important for Western medicine diagnosis because they are not related with the actual disease process. The Western model of diseases did not exist in TCM. Migraine is not recognized as a specific disease in the theory of the ancient traditional Chinese medicine (73). The Chinese model adopts as diagnosis the patterns

of disharmony. Patients with migraine can have different diagnosis in TCM. Therefore the therapeutic approach could be changed from patient to patient; even distinctive points should be used during the treatment period. Nevertheless, acupuncture has been largely used for migraine sufferers in Western countries (70, 74, 75).

Originally, the philosophical basis of Chinese medicine was radically different from the Western medicine model. However, the gap between these models has been changing with the clinical practices, not only in the Western countries, but also Chinese hospitals have incorporated modern Western concepts. In fact, nowadays acupuncture is not practiced in the same way it was practiced centuries ago, especially during the last 30 years(76). New recent techniques and resources were incorporated to TCM such as laser, electrical machines to stimulate acupuncture points, ear and scalp acupuncture and new points have been used(77). Unfortunately, the advancement in the TCM practices and concepts constitutes one of the problems that researchers have to face when designing a trial. This item will be discussed below.

How does acupuncture work? This question could be explained by pondering over two paradigms: the oriental and the biomedical paradigms(78). This discussion is beyond the scope of our research. In fact, is not so productive to explain this topic because from a biomedical point of view, a comprehensive background explanation remains elusive. Acupuncture does not have a solid anatomical or physiological basis(79). Possibly, the physiological effects of acupuncture and its mechanisms of action could be revealed in light of the neuroscience knowledge. It is almost a consensus that acupuncture acts via neuroendocrine pathways. Experimental studies have demonstrated that acupuncture stimulates the central nervous system (CNS) to synthesize and release a large range of endogenous opioids in blood and cerebrospinal fluid, hormones and neurotransmitters: encephalin, endorphins, dynorphins, catecholamines, serotonin, norepinephrin and adrenocorticotropic hormones(39, 80-84). Recently published articles using several functional neuroimaging technologies in humans have confirmed the acupuncture action in the CNS. These studies showed that acupuncture may modulate the activity in many cortical and subcortical brain areas(85, 86).

Nevertheless, it is important to emphasize that despite the majority of studies and published data, the mechanisms that could explain the acupuncture action remain

unexplained. The endogenous peptides actions, for example, cannot explain the long-lasting effects of acupuncture(82), which is part of the objectives of the trials presented in this thesis. Another important aspect is that the majority of the studies that try to elucidate the acupuncture mechanism of action were done using the electro acupuncture, not the acupuncture alone.

At present there are two hypotheses to explain the needle-initiating event. They did not exclude each other: one says that the needles activate the nervous systems by stimulation of nerve endings, such as A beta, specially A delta fibers. Both afferent fibers send signs to the dorsal horn of the spinal cord and to other parts of the central nervous system (CNS), such as: mesencephalon, hypothalamus, hypophysis (pituitary gland), thalamus and cerebral cortex(71, 78, 82). Another theory defends that the event initiates in the connective tissue(87). In fact, the neural and connective tissue would interplay and every one could respond to a stimulus in the skin and muscles generating biomechanical and chemical changes in the body. Regardless of all the efforts made by the researchers during the last 30 years, the primary question remains. How does acupuncture work?

The use of alternative and complementary therapies have increased dramatically in recent years (74). Acupuncture has gained credibility for the treatment of painful conditions and people have searched this therapy to alleviate chronic pain and related problems (3). The safety of acupuncture treatment when practiced by qualified professionals is well known (88-94). Acupuncture involves no drug interactions and has few contraindications therefore it is theoretically applicable to all patients. Acupuncture could also help control symptoms commonly associated with migraine attacks, such as nausea and vomiting(18). For these reasons, it would be interesting if acupuncture was incorporated into alternative or complementary treatments for migraine prophylaxis. Some clinical trials have shown that acupuncture has some action against headaches(31, 32) and migraine(25, 28, 29, 34, 42, 95, 96). Two recent systematic reviews published by Cochrane Library confirm these effects (50, 97).

1.3. Challenges on developing trials to test acupuncture efficacy

The role acupuncture plays in the migraine prophylaxis remained unclear up to six years ago. At that time, many trials had been developed but the majority of them had methodological problems that compromised their results (1, 4, 50). Therefore, this knowledge gap remained. Between March 2005 and September 2008 the results of many well designed acupuncture trials for headache were published (98-103). However, a lot of doubts were still unsolved.

Researchers have been facing many problems to design acupuncture trials(19). The two major problems are: what kind of acupuncture approach has to be followed and what should be the best option for the control group. When we say acupuncture treatment, it is not a clear concept. In fact, the historical basis of acupuncture follows the traditional Chinese medicine grounding. However, sometimes, in Western countries and even in Chinese hospitals, the practice follows the paths of neurophysiology, neuromuscular and other modern concepts and principles(5, 76, 104). There are many ways to do acupuncture. One of them would be to adopt the experts' opinions, however the "experts' opinions" are questionable. Consensus does not exist. There are as many ways to conceive and practice acupuncture as there are acupuncture practitioners in the world.

The control group is another great problem. In fact, there is no suitable control group when treatment requires a skilled practitioner (105). To reach more trustable results researchers need to blind acupuncturists and patients. At present, there is no way to blind acupuncturists. However, it is possible to blind patients and evaluators. Nevertheless, patients blinding is not successful when needles are not used in the control group. For this reason, researchers have usually opted for the superficial needling, called minimal acupuncture, in a control group. Unfortunately, another problem emerged. All types of needling have specific results over pain complaints, including the superficial techniques (24). We could not forget that Japanese-style acupuncture is done with superficial needling without manipulation(106). This fact leads us to rethink all the fundamentals of the traditional acupuncture are based on. If analgesic effects appeared when all types of needling are done, how important is the explicative model (Chinese, Japanese or other) on the practice of this technical approach called acupuncture?

Many problems remain unsolved. What are the best points and the best acupuncture approach to test migraine treatments? How long should the treatment last? How many sessions should be carried out? How often should the sessions happen? How long should the needles stay in the points?

We certainly do not know how to answer these questions so far. There are controversial opinions about all these topics. Taking Evidence-Based Medicine into account, something must be done to better establish the acupuncture clinical practice and research. In this context, we developed these two trials which are the subject of the present thesis. To elucidate some of the questions reported above, explore the best methodological design for future trial and answer if acupuncture is an option to prevent migraine attacks, we developed three trials.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

- To develop a better methodology to test the acupuncture efficacy in migraine prophylaxis in larger trial (phase III trial);
- To test the acupuncture efficacy in migraine prophylaxis.

2.2. Hypothesis

2.2.1. Primary end points:

- Acupuncture is an effective procedure to prevent migraine attacks reducing in 50% the number of monthly/diary migraine attacks (Trial 1 and Trial 2);
- Acupuncture is an effective procedure to prevent migraine attacks reducing in 40% the number of migraine attacks per diary (Trial 2);
- Acupuncture can reduce the number of the migraine days per diary (Trial 2);

2.2.2. Secondary end points:

- Acupuncture can reduce the intensity of pain in migraine attacks;
- Acupuncture can reduce the frequency of migraine attacks;
- Acupuncture can reduce the duration of migraine pain in hours per diary/month;
- Acupuncture can reduce the duration of migraine attacks;
- Acupuncture can reduce the analgesic medication intake during the migraine attacks;
- Acupuncture can reduce the frequency of the nausea and vomiting during the migraine attacks.

3. METHODS

Both trials were developed in the Headache Clinic of Department of Neurology in the Clinical Hospital of the State University of Campinas (UNICAMP), Brazil. The Institutional Ethics Committee approved them in June 2000, and trials were done in accordance with the Declaration of Helsinki. The patients were recruited via an advertising campaign in the media. The State of São Paulo Research Foundation funded these trials (FAPESP, grant no. 00/09985-0).

Common points in the design of both trials:

1) Subjects included were migraine patients with or without aura for at least one year according to the International Headache Society criteria(16);

2) Inclusion and exclusion criteria are shown in Table 1;

Table 1: Inclusion and exclusion criteria

Inclusion	***Exclusion***
Male or female;	Patients with any other pain syndrome;
Age: 18 to 50;	Patients who had used any migraine prophylactic drugs in the three months prior to inclusion;
Migraine with or without aura as defined by the International Headache Society criteria;	Patients with non-migraine types of headache;
Migraine present for at least one year;	Pregnancy or women who were not using any contraceptive;
Patients with only one type of headache (exclusively migraine);	Patients who had been treated with acupuncture in the three months prior to inclusion;
Patients who had experienced at least two and, at most, six migraine attacks in the month preceding the intervention (baseline period). The events of the preceding month were recorded in a diary;	Patients who had used drugs for the treatment of migraine attacks for more than ten days a month.
Patients who had not used drugs with migraine prophylactic effects in the last three months;	Patients who were unable to understand and maintain headache diaries;
Patients who could come to the hospital weekly for three consecutive months;	Patients who were misusing drugs or alcohol;
Patients who had accepted to be included in the study after oral and written explanations about the clinical trial.	Patients who occasionally used a minor tranquilizer or sedative;

3) All participants provided written informed consent;

4) A text containing information about some aspects of the trial's design was offered by the neurologist to patients after first selection. Patients were informed that there were two groups of treatment. One would receive true acupuncture and the other false acupuncture called placebo acupuncture (we adopted exact these terms to explain treatments to candidates);

5) Pain, analgesic drugs intake and associated symptoms measures were done through analysis from headache diaries that included a four-point scale to evaluate pain severity. The severity of headache was evaluated on a four-point scale: 0 for no headache, 1 for mild headache (migraine not interfering with daily activities), 2 for moderate headache (migraine interfering with daily activities) and 3 for severe headache (migraine making normal daily activities impossible), following International Headache Society guidelines recommendations(11, 12).

6) Patients in Trial 1 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 months after the last acupuncture session).

7) In Trial 2, patients filled in 10 diaries: one at the baseline, three in the treatment period and all post-treatment period (six diaries).

8) Immediately prior to the first acupuncture session, the subjects were randomly assigned to the real or sham acupuncture groups through opaque, numbered and sealed envelopes containing a letter that determined the group. To prepare these envelopes, a research assistant used a random digit list(9) to determine the order of randomization. The random digits list determined 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. The meaning of each letter was revealed for all team after all statistical analyses were finished;

9) All research team and patients involved in the research project were blinded, including the statistician with an exception: the physician responsible for all acupuncture treatments (Jerusa Alecrim-Andrade, JA-A);

10) The neurologist who evaluated and consulted patients could not ask nor answer anything about acupuncture treatment to the patients;

11) Neurologist visits were scheduled at weeks 0, 5, 18, 25, 33 and 42;

12) Treatment of migraine attacks, if they happened, was done in the customary manner by each patient. The neurologist withheld any suggestions as to changes in the ongoing rescue medication and any comments on the acupuncture treatment with the patients;

13) Acupuncture treatment was done for 12 consecutive weeks. That included 16 sessions, twice a week during the first 4 weeks and weekly during the following 8 weeks. To evaluate the long-lasting acupuncture effects, in both trials the post–treatment follow-up evaluation were kept for 6-months;

14) Medical acupuncturist could not explain anything about acupuncture treatment to any patient;

15) Disposable and sterile needles were used. No moxa or electrical stimulation was done. Each session lasted 30 minutes and the patients were kept laying down;

16) The type of sham acupuncture applied was “minimal acupuncture” in true acupuncture points which have no reported effects on headaches in the consulted literature (72, 107-111). In research, when needles are inserted very superficially in the skin, it is called “minimal acupuncture”. No manipulation of the needles was done. Some sham points were placed in the head to preserve the patients blinding.

17) Needling in real acupuncture groups contemplated manipulative technique to produce a characteristic sensation known as “De Qi”, which was explained to the patients during the first session;

18) After the last acupuncture session, the trial blinding was evaluated by applying a questionnaire asking about the acupuncture treatment to all patients;

19) Outcome measures: the percentage of patients with reduction ≥40% and ≥50% in migraine attacks frequency, the total migraine days, frequency of migraine attacks, average duration of a migraine attack, average headache severity, total duration of migraine pain in hours per diary, rate of rescue medication used, nausea and vomiting frequency. The percentage of reduction of migraine attacks was measured as well;

20) Two of the most important parameters utilized to measure efficacy of the treatment are: percentage of patients with reduction ≥40% and percentage of patients with reduction ≥50% in migraine attacks frequency. Both parameters are arbitrary. The first one was suggested by our statistician and the second one is the most utilized parameter used in trials to measure efficacy of drugs and other therapies in migraine prophylaxis(112). The Guidelines for controlled trials of drugs in migraine of the International Headache Society recommended this second parameter(12).

21) Trial 1 was previously designed to estimate the data variability to allow for calculations of an ideal sample, as well as to better define the design of a larger trial. The sample size was determined considering the results of the sequential statistical analyses done after the end of each headache diary during Trial 1. The endpoint considered to calculate this sample was the percentage of patients with reduction of ≥40% in their migraine attacks in the second month of treatment with sham or real acupuncture. The equivalence range was 11.8–57.9% for patients with a reduction of the attack rate of 40% and with $\alpha=0.05$ and $\beta=0.20$. The number of patients required was 26 divided into two groups. As a drop-out rate of 15% was expected, 30 patients had to be enrolled into the trial. We interrupted Trial 1, a pilot study, when 37 patients were randomized. The randomization was interrupted in Trial 2 when 31 patients were enrolled.

22) Statistical analysis was done within and between groups, with the reference point being the baseline period (first diary) in each group (Table 2). Each parameter was evaluated comparing their evolution with the baseline period. A new migraine attack was recorded when the patient had been free of headaches for 48 hours before the pain returning.

Table 2: Statistical analysis performed in both trials.

Statistical Analysis	Trial 1	Trial 2
Comparisons between groups were made using	Analysis with the Chi-Square test, Fisher's exact test and Mann-Whitney test	Analysis with the Chi-Square test, Fisher's exact test and Mann-Whitney test
Comparisons within each group for the migraine parameters between the baseline period (diary one) and the other diaries were made using:	Non-parametric Mann-Whitney test	Tukey test
Differences within each group were estimated using:	Wilcoxon Signed Rank test	Wilcoxon Signed Rank test and profile test by contrasts
Repeated measures were used to compare numbered measures between groups and between diaries within each group:	ANOVA test	ANOVA test
The significant level used for the statistical analysis:	It was 5%, therefore $p<0.05$ indicates significance	It was 5%, therefore $p<0.05$ indicates significance

Design differences between these trials:

1) Trial 1

Treatment applied to the real acupuncture group was individualized following the traditional Chinese medicine principles. Each patient received treatment in accordance with his or her “unbalanced pattern of disease”. The treatment was individualized and changed from session to session in accordance with the practice of acupuncture in the real condition.

The sham treatment as well as real group varied from session to session, minimal acupuncture was adopted, the number of the needles was similar to real treatment group, nevertheless needles were placed in points not reported to treat headache in the classical acupuncture literature(72, 107-111). In Trial 1 a total of 272 sessions were carried out. The average of needles used in each session was 13. Points and the

frequency of use of each one is presented in Table 3;

Table 3: Points used in 272 sessions in Sham group in Trial 1

Points	Frequency	
	Number	%*
LU-5 (chize)	220	81%
CV-10 (xiawan)	197	72%
ST-37 (shangjuxu)	189	69%
SP-7 (lougu)	172	63%
TB-17 (yifeng)	167	61%
CV-7 (yinjiao)	155	57%
Xiyan	149	55%
TB-20 (jiaosun)	133	49%
Bitong	112	41%
P-5 (jianshi)	38	14%
KI-5 (shuiquan)	35	13%
SI-5 (yanggu)	33	12%
SP-8 (diji)	30	11%
LI-3 (sanjian)	29	11%
LR-4 (zhongfeng)	29	11%

***Percentage of use of each point in the total of sessions carried out in all groups (272 sessions)**

The primary outcome was the percentage of patients with reduction ≥50% in their migraine attacks frequency in the second, third, fourth, fifth and sixth headache diaries compared with the first one (baseline period).

2) Trial 2

One of the aims of this study was to test the effects of the kind of acupuncture, the semi-standardized treatment following partially the traditional Chinese medicine principles. The predominant location of the patient's pain determines the formulae used in all acupuncture sessions. The research team decided to test the semi-standardized treatment in the real acupuncture group because a less variable therapeutic scheme would be easily reproduced in future trials or in clinical practice. For the semi-standardized treatments details see Table 4.

Sham treatment group was standardized as well. Only twelve needles (six on each side) were inserted in each session. Fixed acupuncture treatments were applied in all 16 sessions. Details about points are shown in Table 5.

The primary outcomes were the percentage of patients with reduction ≥40% and ≥50% in migraine attacks frequency and the total migraine days compared with the baseline period.

Table 4: Protocol treatment in the real acupuncture group in Trial 2

	Points	Location
All patients (local points)	**GB 12 (Wan Gu)**	in the depression dorso-cranial to the mastoid process
	GB 20 (Feng Chi)	in the depression between the start of the sternocleidomastoid process and the trapezius muscle
	GB 21 (Jian Jing)	at the midpoint between the depression below the spinous process C7 and the acromium
	Bl 10 (Tian Zhu)	0,5 inch within the ideal anterior hairline, 1,3 inch lateral to the midline in the depression at the lateral edge of the trapezium muscle
Occipital headache	**Bl 60 (Kun Lun)**	at the midpoint between the prominence of the lateral malleolus and the Achilles tendon
	SI 3 (Hou Xi)	with the patient's fist loosely clenched, at the ulnar end of the proximal crease of the fifth metacarpophalangeal joint, on the dividing line between red and white flesh
Frontal headache	**Bl 2 (Zuan Zhu)**	in the depression at the medial end of the eyebrow in the incisura frontalis
	St 36 (Zu San Li)	one middle fingerbreadth lateral to the anterior crest of the tibia, at the level of distal edge of the tuberosity of the tibia
	Du 23 (Shang Xing)	on the midline, 1 inch within the midpoint of the ideal anterior hairline
	Li 4 (He Gu)	on the dorsum of the hand, to the side of the midpoint of the second metacarpal bone, in the adductor pollicis muscle
Temporo-pariental headache and orbitary headache and hemicrania	**SJ 5 (Zhi Gou)**	2 inch proximal to the dorsal wrist crease between the ulna and radius
	GB 34 (Yang Ling Quan)	in the depression ventral and distal to the head of the fibula
	GB 8 (Shuai Gu)	directly above the auricular apex
Holocranea / uphead	**SI 3 (Hou Xi)**	with the patient's fist loosely clenched, at the ulnar end of the proximal crease of the fifth metacarpophalangeal joint, on the dividing line between red and white flesh
	Du20 (Bai Hui)	at the middle of the vertex, at the midpoint between the two auricular apices
	Lv3 (Tai Chong)	on the dorsum of the foot, in the depression distal to the proximal corner between the first and second metatarsal bones
Anxious patients	**P 6 (Nei Guan)**	2 inches proximal to the distal wrist crease, between the palmaris longus and flexor carpi radialis tendons
Patients with liver symptoms (TCM)	**Lv3 (Tai Chong)**	on the dorsum of the foot, in the depression distal to the proximal corner between the first and second metatarsal bones

Yu-Lin Lian, Chun-Yan Chen, Michael Hammes, Bernard C. Kolster. The Seirin Pictorial Atlas of Acupuncture.2000, 2nd ed(113).

Table 5: Protocol treatment in the sham acupuncture group in Trial 2

	Points	Location
All patients	**Ex-B1 (Ding Chuan)**	at the level of the depression below the spinous process C7. 0,5 inch lateral to the dorsal midline
	TE17 (Yifeng)	posterior to the lobule of the ear, in the depression between the mandible and mastoid process
	TE20 (Jiao Sun)	directly above the auricular apex, on the hairline
	SP7 (Lou Gu)	6 inch proximal to the prominence of the medial malleolus, dorsal to the medial crest of the tibia
	ST37 (Shangjuxu)	3 inch inferior to St36 (described above), one middle finger breadth lateral to the anterior crest of the tibia
	LU5 (Chize)	in the cubital fold in the depression at the radial side of the biceps brachii muscle

Yu-Lin Lian, Chun-Yan Chen, Michael Hammes, Bernard C. Kolster. The Seirin Pictorial Atlas of Acupuncture.2000, 2nd ed(113).

4. PUBLICATIONS

ORIGINAL ARTICLE

Acupuncture in Migraine Prevention

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

Jerusa Alecrim-Andrade, MD, MSc,† Jayme Antunes Maciel-Júnior, MD, PhD,†‡ Xavier Carnè, MD, PhD,§ Geraldo Magela Severino Vasconcelos, BSc,† and Heleno Rodrigues Correa-Filho, MD,†‖*

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. 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

(*Clin J Pain* 2008;24:98–105)

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

Received for publication April 8, 2007; revised June 15, 2007; accepted August 17, 2007.

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Supported by a grant from the State of São Paulo Research Foundation (FAPESP, grant no. 00/09985-0). ISRCTN 93327878. Competing interests: None.

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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 Migraine[30] 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 Society[32] 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 list[33] 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.

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

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

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

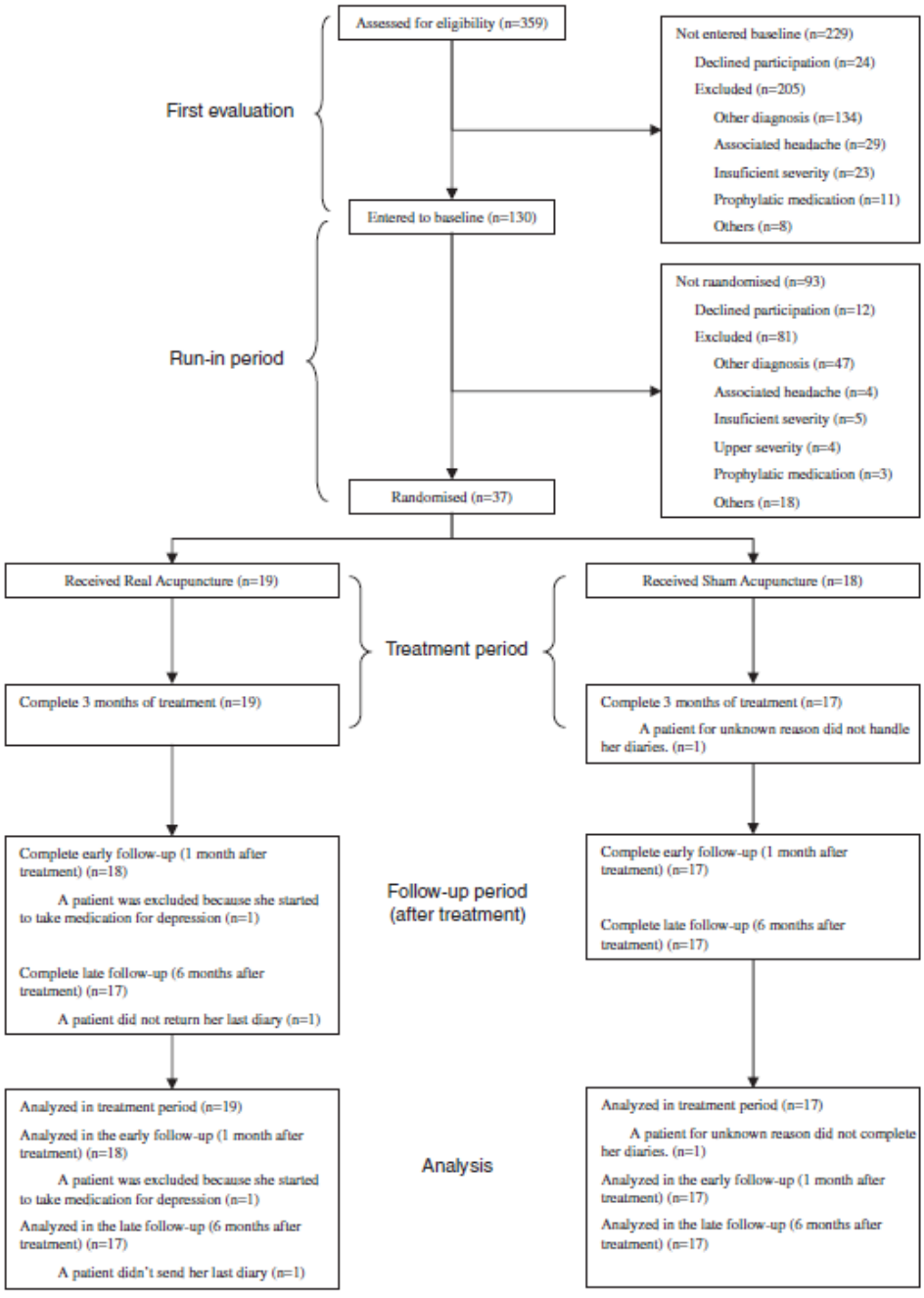

FIGURE 1. Flow of participants through the trial.

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

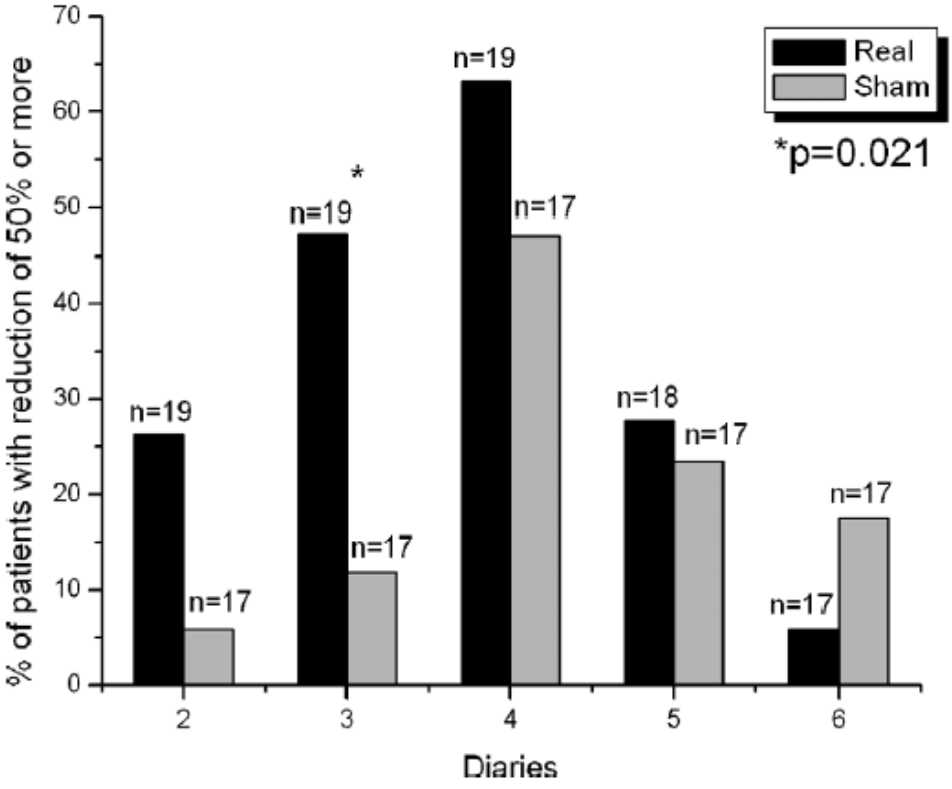

FIGURE 2. Percentage of responders (reduction 50% in migraine attack frequency) in each diary (1 mo) compared with the baseline period (diary 1) in the real and the sham acupuncture groups. Diary 2 = first month of the treatment, diary 3 = second month of the treatment, diary 4 = third month of the treatment, 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.

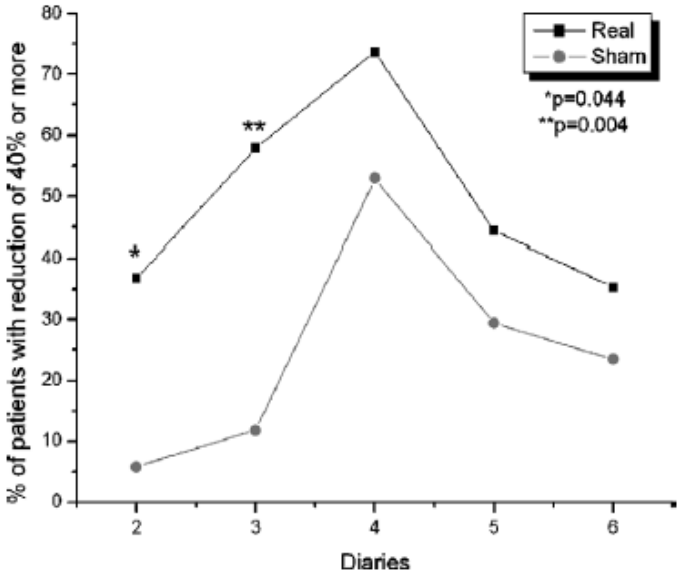

FIGURE 3. Percentage of patients with reduction of 40% or more in migraine attacks frequency in the real and sham acupuncture groups compared with the baseline period. Diary 2 = first month of the treatment, diary 3 = second month of the treatment, diary 4 = third month of the treatment, diary 5 = first 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 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]

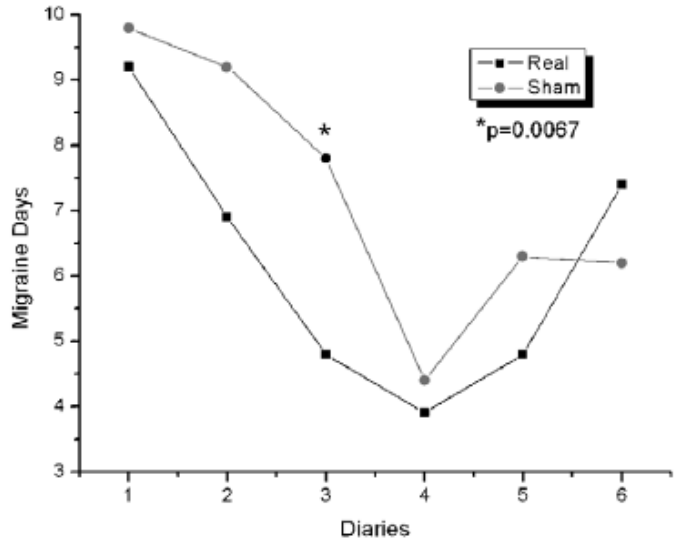

FIGURE 4. Total of migraine days in each diary (1 mo) in the real and the sham acupuncture groups. Diary 1 = baseline period, diary 2 = first month of the treatment, diary 3 = second month of the treatment, diary 4 = third month of the treatment, diary 5 = first month after the treatment, and diary 6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

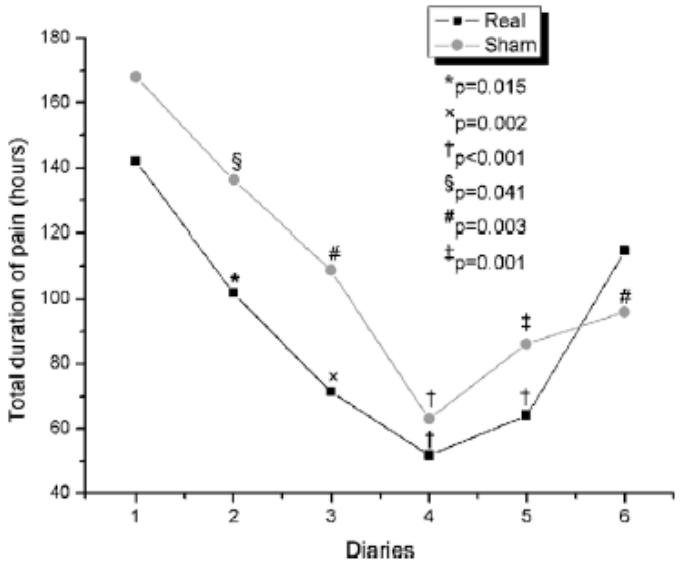

FIGURE 5. Total duration of pain in hours in each diary (1 mo) in the real and the sham acupuncture groups compared with their own baseline period. Diary 1 = baseline period, diary 2 = first month of the treatment, diary 3 = second month of the treatment, diary 4 = third month of the treatment, diary 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.

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 males[41] 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 Loman[44] 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 pain[48] 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 Goadsby[50] 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 nauseas 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.

ACKNOWLEDGMENTS

The authors thank Drs Lo Sz Hsien, Carlos Moriyama, Norton Moritz Carneiro, and Isabel Giralt for their helpful suggestions about acupuncture treatment. They thank Vanessa Monteiro Bugni, Ana Luisa Vidigal Soares de Andrade, Heloisa de Lima Gomes, Ernani Azevedo, and Gina Goulart for their help in organizing the study and data, and especially Leda Fernandes for opening ways in the University Hospital. They also thank the Clinic Hospital Public Relations and Press Assessor, Antonio Alberto Ravagnani and Isabel Cristina Gardenal, respectively, for their great help with the media. The principal investigator wrote her study protocol, which is part of the PhD thesis (Jerusa Alecrim-Andrade).

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4.2. Trial 2

doi:10.1111/j.1468-2982.2006.01062.x

Acupuncture in migraine prophylaxis: a randomized sham-controlled trial

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Cephalalgia

Alecrim-Andrade J, Maciel-Júnior JA, Cladellas XC, Correa-Filho HR & Machado HC. Acupuncture in migraine prophylaxis: a randomized sham-controlled trial. Cephalalgia 2006; 26:520–529. London. ISSN 0333-1024

The purpose of the present trial was to evaluate semi-standardized acupuncture efficacy in migraine prophylaxis. Twenty-eight subjects with migraine were randomized to the real or sham acupuncture groups. Semi-standardized and standardized minimal acupuncture were used, respectively, in the two groups of patients. They were all treated with 16 acupuncture sessions in 12 weeks. Both groups exhibited similar reductions in: percentage of patients with reduction of migraine ≥40% and ≥50% regarding frequency of migraine attacks, days with migraine, frequency of migraine attacks, average duration of a migraine attack, rate of rescue medication used, average headache severity rate and other parameters compared with the baseline period. Associated symptoms, such as nausea and vomiting, also showed equal estimates in both groups. These findings showed that semi-standardized acupuncture shows no difference from sham acupuncture in preventing migraine attacks. □*Acupuncture, efficacy, headache, migraine, prophylaxis, randomized controlled trial*

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Introduction

Acupuncture has been largely used for migraine sufferers in western countries, although the role it may play in migraine treatment remains unknown (1–3). Some trials have pointed out some effects of acupuncture in migraine, but no conclusive results have been reached, probably because there have been only a few high-quality trials in this area (4, 5).

Migraine does not exist as an entity in the theory of traditional Chinese medicine (TCM) (6). The basis of acupuncture follows the TCM grounding. However, there are serious methods of diagnosis, treatment and practice as far as acupuncture is concerned. In western countries practice sometimes follows the paths of neurophysiology, neuromuscular and other modern concepts and principles (7). According to TCM's principles, treatment should be individualized (8). Each acupuncturist should treat accordingly to their own experience and feelings. In fact, acupuncture can be applied in different ways. Traditional Chinese acupuncture basis has been disregarded in most trials. Usually, a standard treatment has been adopted regardless of the previous TCM diagnosis (9, 10). Furthermore, several acupuncture techniques have also been applied, although they cannot be matched to the original technique (7, 11). Therefore, comparisons of acupuncture trials are very difficult (7). Is there a midway betwwen traditional concepts and the scientific approach? The authors thought that the semi-standardized acupuncture treatment could be the best way, because TCM would be partially respected and the treatment would be easily reproduced in other trials in the future as well as in clinical practice.

The present trial was developed to evaluate the efficacy of semi-standardized acupuncture in migraine prophylaxis.

Methods

Study design

The present study was developed in the Headache Clinic of the Department of Neurology, in the Clinical Hospital, State University of Campinas (UNICAMP), Brazil. The protocol and supporting documents (information sheet, consent form, protocol) were approved by the institutional Ethics Committee in June 2000.

The recruitment of patients was done from August 2002 to March 2003, and the trial was completed in February 2004 (including all follow-up periods). Patients were recruited via a media campaign. They were scheduled by the research assistants and evaluated by an experienced neurologist.

Twenty-eight patients suffering from migraine, with or without aura, in accordance with the diagnostic criteria of the International Headache Society (IHS) (12), present for at least 1 year, male and female, aged 18–50 years, were enrolled. Other inclusion criteria were: patients with only migraine, patients who had not used drugs with migraine prophylactic effects or acupuncture in the previous 3 months, patients who could come to the clinical hospital 17 times only in the following 12 weeks (acupuncture treatment period) and patients who had accepted inclusion in the study after oral and written explanations about the clinical trial. The exclusion criteria were patients with any other chronic pain syndrome, who were unable to understand and maintain headache diaries, who were misusing drugs or alcohol and who occasionally used a minor tranquilizer or sedative.

Prior to enrolment there was a 4-week preliminary phase (baseline period) when patients kept a diary recording the frequency and intensity of headache, menstruation, drug intake and associated symptoms in each migraine attack. By that time, the selected patients had received a written text with information about all aspects of the trial, including possible adverse events and their right to withdraw from the trial at any time without giving reasons. During that period at least three, but not more than six migraine attacks, had to occur. A new attack was considered as such when the patient had been headache free for at least 48 h (13). Patients with non-migraine types of headaches were excluded as well as patients who had used drugs for the treatment of migraine attacks for more than 10 days in 4 weeks. After the baseline period, during the second neurologist visit, the selected patients signed the written informed consent. Before acupuncture treatment, the patients were evaluated by a general physician, who is also an acupuncture specialist (J.A-A.). At this time, the clinical history and physical evaluation based on the principles of Chinese medicine were recorded, including examination of the pulse and tongue. The evaluation was done and the probable treatment following TCM principles was planned for all patients in order not to break the 'blinding'.

After the acupuncture doctor's evaluation, patients were randomly assigned to two acupuncture groups, group C and group D, by a research assistant. The research assistant prepared opaque, numbered and sealed envelopes containing one of the two above letters. They were divided into six blocks. A block had six letters, three letter Cs and three letter Ds. The random digits (14) were used to define the sequence of the letters in each block. Therefore, the order of the letters was different for each block. That sequence was unknown by the medical acupuncturist. The identification of each letter was unknown by the first and second research assistants, the statistician, the neurologist (evaluator) and the patients. Only the medical acupuncturist knew the meaning of each letter, but she had not revealed any code before completing all the data analysis. The second research assistant was responsible for sending the randomization list to the statistician at the end of the trial. Group C received the real acupuncture and group D the sham acupuncture. The acupuncturist doctor did not give any information to the patients, neurologist or research assistants about the acupuncture treatment.

Real and sham acupuncture are defined in World Health Organization (WHO) Guidelines for Clinical Research on Acupuncture (15) as being 'acupuncture given as a real clinical treatment' and 'inappropriate acupuncture for the condition being treated taking into account the acupuncture microsystem'.

The patients were submitted to the acupuncture treatment for 12 consecutive weeks. That included 16 sessions, twice a week during the first 4 weeks and weekly during the following 8 weeks. Patients had to keep a headache diary from the baseline period (diary 1) up to follow-up period (diaries 5–10), which was for 24 weeks after the last acupuncture session (approximately 6 months). The follow-up period was designed to test the longer-lasting effects of acupuncture on migraine. During the acupuncture treatment, the patients completed three diaries (diaries 2–4). Neurologist visits were scheduled at weeks 0, 5, 18, 25, 33 and 42.

Treatment of migraine attacks, if they happened, was done in the customary manner by each patient. The neurologist withheld any suggestions as to changes in the ongoing rescue medication and any comments on the acupuncture treatment with the patients.

Treatments

Sham acupuncture treatment

1 Twelve needles (six on each side) were inserted in each session (see Table 1).
2 Minimal acupuncture was used and consisted of very shallow needle insertion in the acupuncture points.
3 No manipulation was done.
4 The points in the sham acupuncture group were selected after an extensive consultation of the classical acupuncture literature to confirm that they had minimal or no influence on headaches (16–21).
5 Standardized and fixed acupuncture treatments were applied to the 16 sessions.

Real acupuncture treatment

1 The treatment was semi-standardized (see Table 2). The chosen points were related to the pain topography of the most frequent migraine attacks in each patient and based on some principles of traditional Chinese medicine.
2 From 6 to 10 points were used in each session (12–20 needles were inserted).
3 Each patient had a fixed treatment in their 16 sessions.
4 The needles were manipulated by rotation methods to produce a characteristic sensation known as De Qi. The 'Qi sensation' was explained to the patients of this group in the first session as an awareness of numbness, strange aching or tingling radiating from the point of needling.

Treatment design in both groups

1 The skin was disinfected with 70% alcohol.
2 Sterile disposable and steel needles (0.25 × 40 mm) were used.
3 Moxa or electrical stimulation was not used.
4 The patients were kept lying down for 30 min with the needles in place.
5 Body acupuncture was done bilaterally.

Efficacy evaluation

Efficacy was measured by comparing the first diary, which was made in the baseline period, with the diaries of the treatment period (diaries 2–4) and of the follow-up period (diaries 5–10). Each diary covered 4 weeks.

Primary efficacy parameters

1 The percentage of patients with a reduction of ≥40% in migraine attack frequency from the second to the fourth diaries compared with the first diary (baseline period).
2 The percentage of patients with a reduction of ≥50% in migraine attack frequency from the second to the fourth diaries compared with the first diary (baseline period).
3 Total migraine days from the second to the fourth diaries compared with the first diary (baseline period).

Table 1 Protocol treatment in the sham acupuncture group (points)

	Points	Location
All patients		
	Ex-B1 (Ding Chuan)	At the level of the depression below the spinous process C7. 12.7 mm lateral to the dorsal midline
	SJ17 (Yifeng)	Posterior to the lobule of the ear, in the depression between the mandible and mastoid process
	SJ20 (Jiao Sun)	Directly above the auricular apex, on the hairline
	Sp7 (Lou Gu)	15 cm proximal to the proeminence of the medial malleolus, dorsal to the medial crest of the tibia
	St37 (Shang Ju Xu)	76 mm inferior to St36 (described above), one middle finger breadth lateral to the anterior crest of the tibia
	Lu5 (Chi Ze)	In the cubital fold in the depression at the radial side of the biceps brachii muscle

Lian YL, Chen CY, Hammes M, Kolster BC. The Seirin pictorial atlas of acupuncture. An illustrated manual of acupuncture points. Cologne: Könemann Verlagsgesellschaft mbH Press 2000.

Table 2 Protocol treatment in the real acupuncture group (points)

	Points	Location
All patients (local points)	GB12 (Wan Gu)	In the depression dorso-cranial to the mastoid process
	GB20 (Feng Chi)	In the depression between the start of the sternocleidomastoid process and the trapezius muscle
	GB21 (Jian Jing)	At the midpoint between the depression below the spinous process C7 and the acromium
	Bl10 (Tian Zhu)	12.7 mm within the ideal anterior hairline, 33 mm lateral to the midline in the depression at the lateral edge of the trapezium muscle
Occipital headache	Bl60 (Kun Lun)	At the midpoint between the prominence of the lateral malleolus and the Achilles tendon
	SI3 (Hou Xi)	With the patient's fist loosely clenched, at the ulnar end of the proximal crease of the fifth metacarpophalangeal joint, on the dividing line between red and white flesh
Frontal headache	Bl2 (Zuan Zhu)	In the depression at the medial end of the eyebrow in the incisura frontalis
	St36 (Zu San Li)	One middle fingerbreadth lateral to the anterior crest of the tibia, at the level of distal edge of the tuberosity of the tibia
	Du23 (Shang Xing)	On the midline, 25 mm within the midpoint of the ideal anterior hairline
	Li4 (He Gu)	On the dorsum of the hand, to the side of the midpoint of the second metacarpal bone, in the pollicis muscle adductor
Temporo-pariental headache and orbitary headache and hemicrania	SJ5 (Zhi Gou)	5 cm proximal to the dorsal wrist crease between the ulna and radius
	GB34 (Yang Ling Quan)	In the depression ventral and distal to the head of the fibula
	GB8 (Shuai Gu)	Directly above the auricular apex
Holocranea/uphead	SI3 (Hou Xi)	With the patient's fist loosely clenched, at the ulnar end of the proximal crease of the fifth metacarpophalangeal joint, on the dividing line between red and white flesh
	Du20 (Bai Hui)	At the middle of the vertex, at the midpoint between the two auricular apices
	Lv3 (Tai Chong)	On the dorsum of the foot, in the depression distal to the proximal corner between the first and second metatarsal bones
Anxious patients	P6 (Nei Guan)	50 mm proximal to the distal wrist crease, between the palmaris longus and flexor carpi radialis tendons
Patients with liver symptoms (TCM)	Lv3 (Tai Chong)	On the dorsum of the foot, in the depression distal to the proximal corner between the first and second metatarsal bones

Lian YL, Chen CY, Hammes M, Kolster BC. The Seirin pictorial atlas of acupuncture. An illustrated manual of acupuncture points. Cologne: Könemann Verlagsgesellschaft mbH Press 2000.

Secondary efficacy parameters

1 Frequency of migraine attacks.
2 Average duration of a migraine attack.
3 Average headache severity.
4 Total duration of migraine pain in hours per diary.
4 Rate of rescue medication used.
5 Nausea frequency.
6 Vomiting frequency.

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 IHS recommendations (13).

Safety measures

The patients were instructed to report all adverse events to the medical acupuncturist in each session as well as in a paper that they had received before

the first session. Adverse events were listed descriptively and comparison between groups was done, ascribing some statistical significant difference to some effects.

Subjects' evaluation

Patients were fully informed that two kinds of acupuncture would be done. One would be real and the other would be false, placebo. No additional information was given.

At the end of the study, patients were invited to fill in a questionnaire evaluating the acupuncture treatment and to give their impression about which treatment group (real or sham acupuncture) they thought they had been included in.

Statistical analysis

The sample size was determined considering the results shown in an unpublished pilot trial that had been done before this present trial. The endpoint considered to calculate this sample was the percentage of patients with reduction of ≥40% in their migraine attacks in the second month of treatment with sham or real acupuncture. The equivalence range was 11.8–57.9% for patients with a reduction of the attack rate of 40% and with $\alpha = 0.05$ and $\beta = 0.20$. The number of patients required was 26 divided into two groups. As a drop-out rate of 15% was expected, 30 patients had to be enrolled into the study.

Statistical comparisons were done using univariate analysis with the χ^2 test and Fisher's exact test. Analysis of variance (Anova) for repeated measures was used to compare both groups. Comparisons within groups for the migraine parameters in each one of the periods were done using the Tukey's post-hoc test. Differences within each group were estimated using the profile test by contrasts. The significant level used for the statistical analysis was 5%, therefore $P < 0.05$ indicates significance.

Results

Patients

The selection of patients for the trial took place from August 2002 to March 2003. The follow-up period was from July 2003 to February 2004. Thirty-one migraine sufferers were enrolled in the study. They were randomly assigned to the real (16 patients) and sham acupuncture (15 patients) groups. However, only 28 patients completed the treatment and they were included in the statistical analysis. The flow of participants through each stage of the trial is presented in Fig. 1. There was no significant difference between study completers and drop-outs in diary scores, group of treatment, age or headache characteristics.

Table 3 Patient demographic characteristics

	Real acupuncture ($n = 14$)	Sham acupuncture ($n = 14$)	*P*-value
Mean age (years)	32.5 ± 8.0	39.1 ± 7.7	0.0242
Sex (F/M)	11/3	11/3	NS
Duration of disease (years)	16.9 ± 9.4	20.0 ± 7.1	NS
Number of attacks (baseline)	4.3 ± 0.7	4.2 ± 0.9	NS
Type of migraine			
with aura	5	1	NS
without aura	9	13	NS

The groups' demographic data are presented in Table 3. There was only one statistically significant difference between groups, the age mean. The patients in the sham acupuncture group were older than in the real acupuncture group ($P = 0.024$).

Efficacy and long-term follow-up (24 weeks)

No statistically significant difference between groups was observed in any pain parameter evaluated in this trial. Nevertheless, comparisons within each group found that all migraine pain parameters had improved with statistically significant differences in both groups. There was one exception: headache severity when the patients were experiencing pain.

Associated symptoms

The Tukey test showed that the real acupuncture group had significantly reduced nausea during the follow-up period when compared with the sham acupuncture group ($F_{(9,198)} = 2.09$; $P = 0.0372$). The variance analysis showed that the variability in the graph lines is not attributable to chance.

There was no statistically significant difference between groups regarding the number and frequency of vomiting during attacks.

Rescue medication

No statistically significant difference appeared between groups or within each group.

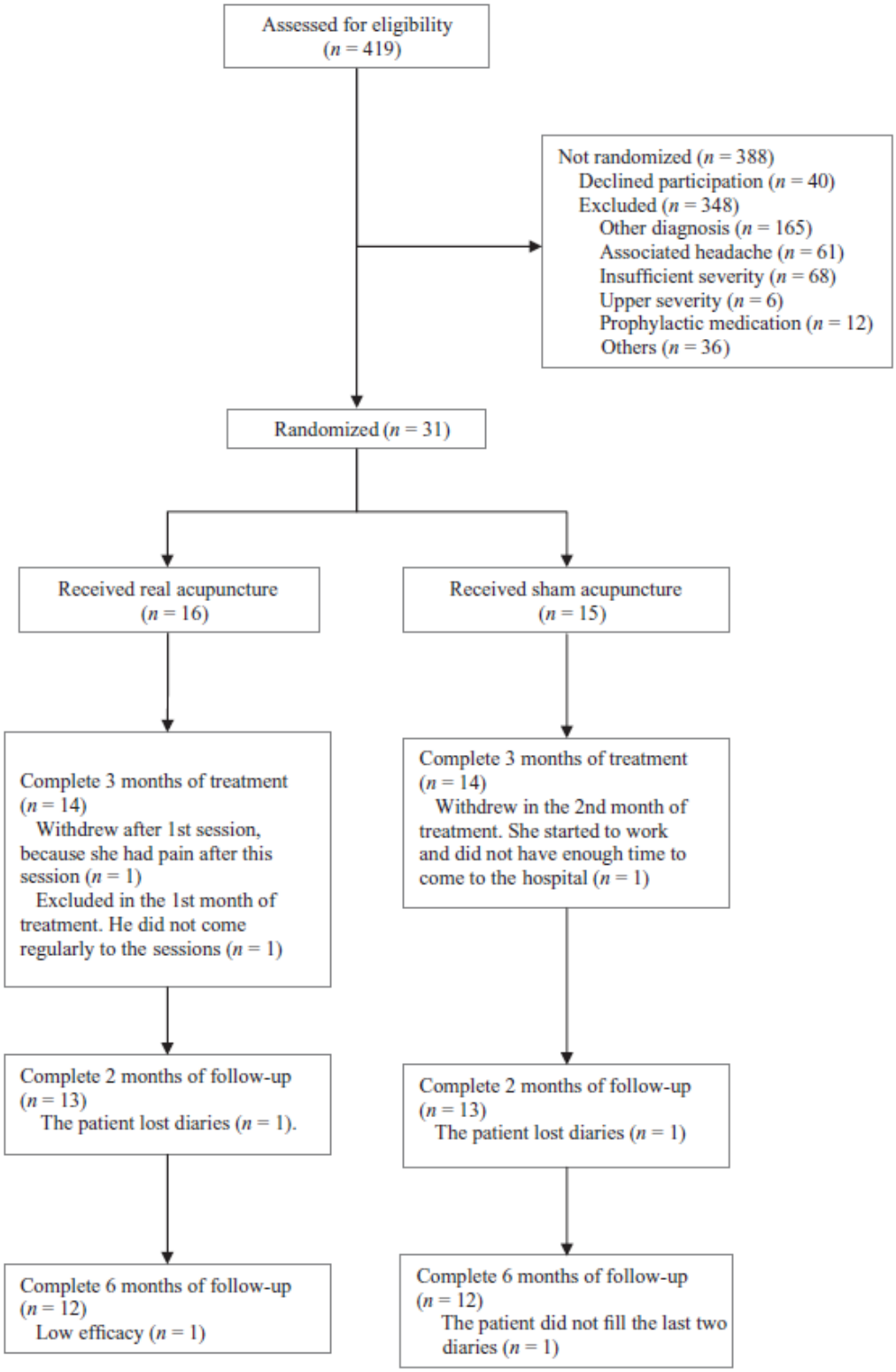

Figure 1 The flow of participants

Adverse effects

No serious adverse effect (AE) was notified. Most AEs observed were related to the local insertion of the needles, such as: local pain after session, ecchymosis, small haematomas, nodule and local paraesthesia during session. General effects were sleepiness and relaxing sensation; however, a statistically significant difference was observed in sleepiness in the real acupuncture group ($P = 0.008$), as

well as in local nodules ($P = 0.008$) and local pain after sessions ($P = 0.002$).

Treatment impressions

All patients announced their intention to be treated with acupuncture in future. When they were asked how they would classify the treatment, patients who received real acupuncture classified it as good (28.6%), very good (42.8%) and excellent (28.6%). Patients who were in the sham acupuncture group rated it as regular (14.3%), good (35.7%) and very good (50%). In the sham acupuncture group nobody classified the treatment as excellent. Likewise, in the real acupuncture group, every patient qualified the treatment as good although there was no statistically significant difference between groups.

When they were asked about the kind of treatment that they received, patients in the real acupuncture group answered: 'real treatment' (28.7%), 'placebo acupuncture' (7%) and 'I don't know' (64.3%). In the sham acupuncture group, they answered: 'real treatment' (28.6%) and 'I don't know' (71.4%). There was no significant statistical difference between the replies from the two groups, indicating that the blinding (keeping the patients unaware of their treatment) was successful.

Discussion

Only one statistically significant difference appeared between groups in demographics characteristics (see Table 3). The age of the patients selected to the real acupuncture group varied from 22 to 50 (mean 32.50) and in the sham acupuncture group from 23 to 49 (mean 39.14). Despite sparse longitudinal prospective epidemiological data and information about the prognosis and natural history of migraine (22, 23), authors considered that this difference did not influence the results. Also, in the present trial the age span for patient selection was not large (18–50 years old). Therefore, no statistical correction for age was applied.

Efficacy

There were no statistically significant differences between the real and the sham acupuncture groups in any pain parameters evaluated in this trial during the treatment or follow-up periods, such as: percentage of patients with reduction ≥40% and ≥50% in migraine attack frequency, total migraine days, frequency of migraine attacks, mean duration of a migraine attack, mean headache severity and total duration of migraine pain in hours per diary (see Figs 2, 3 and 4). No differences were observed between groups in the rate of rescue medication used or frequency of nausea and vomiting. These results are in accordance with three sham-controlled trials testing the efficacy of acupuncture in treating migraine (24–26).

Improvement within each group could be observed during the treatment up to 20 weeks after the last acupuncture session (most of the follow-up

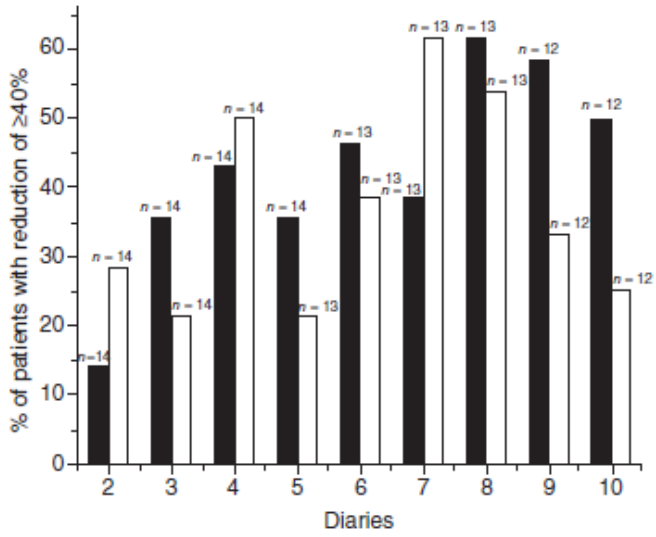

Figure 2 Percentage of responders (reduction ≥40% in migraine attack frequency) in each diary (4 weeks) compared with the baseline period (diary 1) in the real (■) and sham (□) acupuncture groups. Diaries 2, 3 and 4 correspond to the treatment period (12 weeks). Diaries 5–10 correspond to the follow-up period (24 weeks)

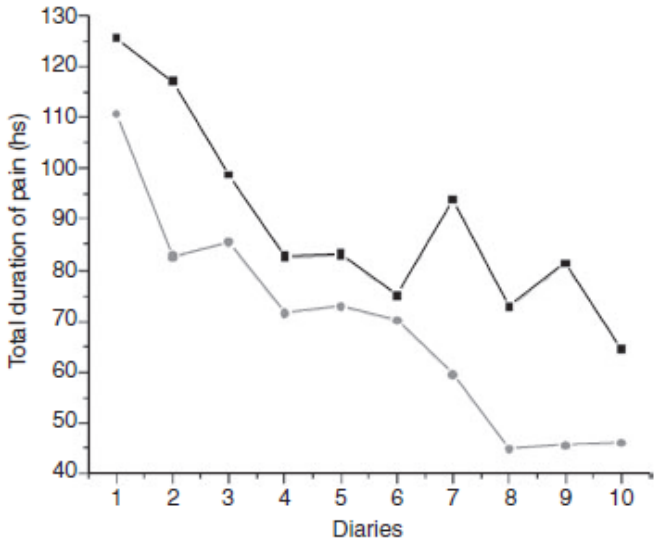

Figure 3 Total duration of pain in each diary (4 weeks) in the real (■) and sham (●) acupuncture groups. Diaries 2, 3 and 4 correspond to the treatment period (12 weeks). Diaries 5–10 correspond to the follow-up period (24 weeks)

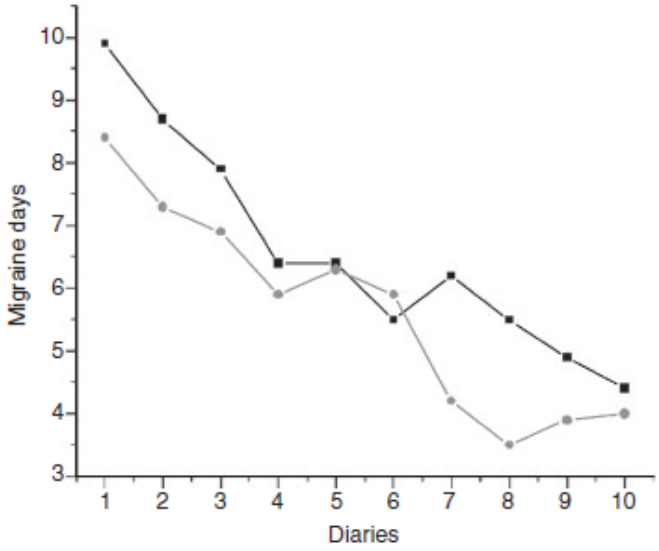

Figure 4 Total of migraine days in each diary (4 weeks) in the real (■) and sham (●) acupuncture groups. Diary 1 = baseline period (4 weeks), diaries 2, 3 and 4 correspond to the treatment period (12 weeks) and diaries 5–10 correspond to the follow-up period (24 weeks)

period) in almost all pain parameters evaluated, with the exception of pain intensity during the migraine attack. Although several trials testing acupuncture or drugs showed improvement of the frequency of migraine attacks, the same was not verified for headache severity (10, 11, 27–31).

It is widely known that:

1 The placebo effects are higher in pain sufferers than in patients suffering from other complaints (32).
2 Invasive technical proceedings have higher analgesic effects than oral drugs (2, 33, 34).
3 The majority of acupuncture trials that tested the efficacy of acupuncture in pain conditions had identified that sham acupuncture could result in a positive response, reducing the possibility of identifying statistically significant differences between real and sham acupuncture (2, 4, 5, 7, 15, 35).

Therefore, the improvement achieved for both groups (real and sham) could be a result of the combination of the three factors referred to above more than the specific effects of the needling. The non-specific effects depend on the patients' beliefs, such as: the magic effects of the eastern techniques in the western patient's mind, the patients' beliefs that they are being treated, the acupuncture consultation, the practioners' expectations of acupuncture effects and the general results of needle insertion (15, 25, 36).

Another point should be highlighted: the improvement rate reached for both acupuncture groups in the present trial was below that of two previous high-quality trials (9, 25). It could be determined by several factors: chance, bias, the sort of semi-standardized acupuncture chosen by medical acupuncturists, the small size of the sample, or large variability of the results observed in both groups. It is important to recall that the patients were aware that the placebo acupuncture treatment was being applied. It is known that in pain studies the response to an active drug is lower in placebo-controlled trials than in open trials or in trials when patients were informed that they would receive only active treatments (32).

Persistence of the improvement lasted up to 24 weeks after the period of treatment (approximately 6 months) in both groups, in accordance with the long-lasting acupuncture effects related previously in three well-designed clinical trials (8, 25, 37). Guidelines and an article containing methodological suggestions for trials in acupuncture also suggested it (4, 15).

The number of days with nausea decreased slightly in the real acupuncture group from the first month of treatment up to the fifth month of the follow-up period, contrasting with the increase of the same variable in the sham acupuncture group. There was a statistically significant difference between them from the third to the fifth month of the follow-up period and the variance analysis did not attribute this result to chance. Nevertheless, the rate of rescue medication used and vomiting in both groups did not change in any phase of the trial.

Adverse events

Effects such as: local nodule ($P = 0.008$) and local pain after session ($P = 0.002$) appeared with a statistically significant difference in the real acupuncture group, which is understandable because the depth of needle insertion was very superficial in the sham group. In the real group, damage of superficial vessels and nerves is more likely. Sleepiness was significantly more frequent in the real acupuncture group ($P = 0.008$) and this is also attributable to the depth of needle insertion.

Limitations

Selection of patients was difficult because of the very strict inclusion and exclusion criteria adopted in this trial, which followed all suggestions presented in two guides: Guidelines for controlled trials of drugs in migraine (13), edited by the IHS, and Guidelines for Clinical Research on Acupuncture (15), edited by

the WHO. Most of the volunteers for the trial were eliminated because they had other kinds of headache, mainly chronic daily headache.

The treatment adopted in the real acupuncture group (the semi-standardized treatment) was based on the experience of three medical doctors who have worked with acupuncture from 14 to 20 years. The treatment protocol was based on the topography of the headache related to the theory of traditional Chinese medicine. Therefore, our therapeutic scheme would not be the widespread treatment applied for acupuncturists. In fact, acupuncture practice is very different between acupuncturists throughout the world. The advantage of the semi-standardized treatment is that it could easily be reproduced in future trials, had the results been positive. In fact, acupuncturists know that there is a gap between their practice and what has been done in research. It is a common criticism when acupuncturists and some researchers comment on the scientific approach to the evaluation of acupuncture effectiveness (2, 4, 9).

Conclusion

The aim of the present trial was to verify the efficacy of the semi-standardized acupuncture treatment in migraine prophylaxis. All pain parameters evaluated showed that this approach is not better than sham acupuncture to prevent attacks in migraine sufferers. Results of a previous trial (pilot study) not yet published, where authors used the individualized treatment in the real acupuncture group, seem to offer the best approach. It takes into account all clinical signs and symptoms presented by each patient. However, it is a complex therapeutic scheme and difficult to reproduce.

Acknowledgements

We would like to thank Drs Lo Sz Hsien and Ling Tung Yang for their suggestions about the treatment through Traditional Chinese Medicine. We would also like to thank Leda Fernandes and Heloisa de Lima Gomes for their help in organizing the study and the data. The authors also thank the staff from UNICAMP Press Assessory, the Clinic Hospital Public Relations, Mr Antonio Alberto Ravagnani and the journalist Ani Seixas for their great help with the media. The study protocol was written by the principal investigator (JAA). This work was supported by the State of São Paulo Research Foundation (FAPESP, grant no. 00/09985-0).

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5. RESULTS

5.1. Common results

Table 6 shows demographic and clinical characteristics at the baseline period in both trials.

Table 6: Demographic and clinical characteristics of each group in both trials

	Trial 1			Trial 2		
	Real Acupuncture (*n* = 19)	Sham Acupuncture (*n* = 17)	p-value	Real Acupuncture (*n* = 14)	Sham Acupuncture (*n* = 14)	p-value
Mean age (years)	36.7±9.2	33.2±9.2	ns	32.5±8.0	39.1±7.7	0.0242
Sex (F/M)	17/2	15/2	ns	11/3	11/3	ns
Duration of disease (years)	20.6±10.8	14.5±7.6	ns	16.9±9.4	20.0±7.1	ns
Number of attacks (baseline)	4.5±0.9	4.7±1.0	ns	4.3±0.7	4.2±0.9	ns
Type of migraine						
with aura	2	8	0.025	5	1	ns
without aura	17	9	ns	9	13	ns

ns = no statistical significance

Patients' replies about their treatment perceptions showed no statistical significant differences between groups in both trials. Therefore blinding was successful. See Table 7.

Table 7: Patients' replies about their treatment perceptions (Trial 1 + Trial 2)

	Real Acupuncture *(n=33)*		Sham Acupuncture *(n=31)*	
	Yes	%	Yes	%
Would like to be treated with acupuncture in the future	33	100	31	100
Quality of treatment received				
Regular / Good	7	21.2	10	32.2
Very good / Excellent	26	78.8	21	67.8
Patient's believe that kind of acupuncture received				
Real acupuncture	11	33.4	8	25.8
Placebo acupuncture (sham)	3	9	2	6.4
Don't know	19	57.6	21	67.8

No statistical significant differences appeared between groups in both trials.

No serious adverse events were reported in both trials. Ecchymosis was the most common event as well. Adverse events registered in both trials are summarized in Table 8 and Table 9.

Table 8: Frequency of adverse events registered in 576 sessions of acupuncture in Trial 1

Event	Real Acupuncture *(n=19)*		Sham Acupuncture *(n=17)*		p-value
	Yes	%	Yes	%	ns
Ecchymosis/ haematoma	12	63.2	13	76.5	ns
Pain in the puncture region (during or after session)	3	15.8	3	17.7	ns
Wrist paresthesia	2	10.5	0	0	ns
Itching	1	5.3	0	0	ns
Headache (during or after session)	0	0	4	23.5	0.04
Skin reactions	4	17.8	3	21.0	ns
Relaxing sensation after session	1	5.3	0	0	ns
Sleepiness (during or after session)	1	5.3	1	5.9	ns
General discomfort	1	5.3	0	0	ns

ns = no statistical significance

Table 9: Frequency of adverse events registered in 448 sessions of acupuncture in Trial 2

Event	Real Acupuncture *(n=14)*		Sham Acupuncture *(n=14)*		p-value
	Yes	%	Yes	%	
Ecchymosis/ haematoma	7	50.0	9	64.3	ns
Pain in the puncture region during session	3	21.5	0	0	ns
Pain in the puncture region after session	10	71.4	3	21.5	0.008
Headache during or after session	3	21.5	1	7.1	ns
Skin reactions	9	64.3	9	64.3	ns
Relaxing sensation after session	1	7.1	2	14.3	ns
Sleepiness during or after session	7	50.0	0	0	0.016
Parestesia	4	28.6	1	7.1	ns

ns = no statistical significance

5.2. Trial 1

Thirty-seven patients were randomized between December 2001 and July 2002. The post-treatment follow-up period ended in June 2003. Thirty-six patients were included in the statistical analysis. Figure 1 illustrates the flow of patients. Statistical significant differences appeared in the real acupuncture group compared to the sham group in the second month of the treatment, when the percentage of patients with >50% reduction in

migraine attack frequency was evaluated (P=0.021), as well as in two secondary endpoints: number of days with migraine per month in the second month of the treatment (P=0.007) and in the first (P=0.044) and second (P=0.004) months of the treatment when the percentage of patients with a >40% reduction in migraine attack frequency was measured.

All results concerning migraine pain parameters, associated symptoms and rescue medication used are summarized in Tables 10 and 11. These same data are better displayed in Figures 2, 3 and 4a to 11.

Comparisons within each group showed that all migraine pain parameters evaluated improved significantly in both groups except for headache severity. This data are illustrated in Figures 4b to 10b.

Figure 1: Flow of patients in Trial 1

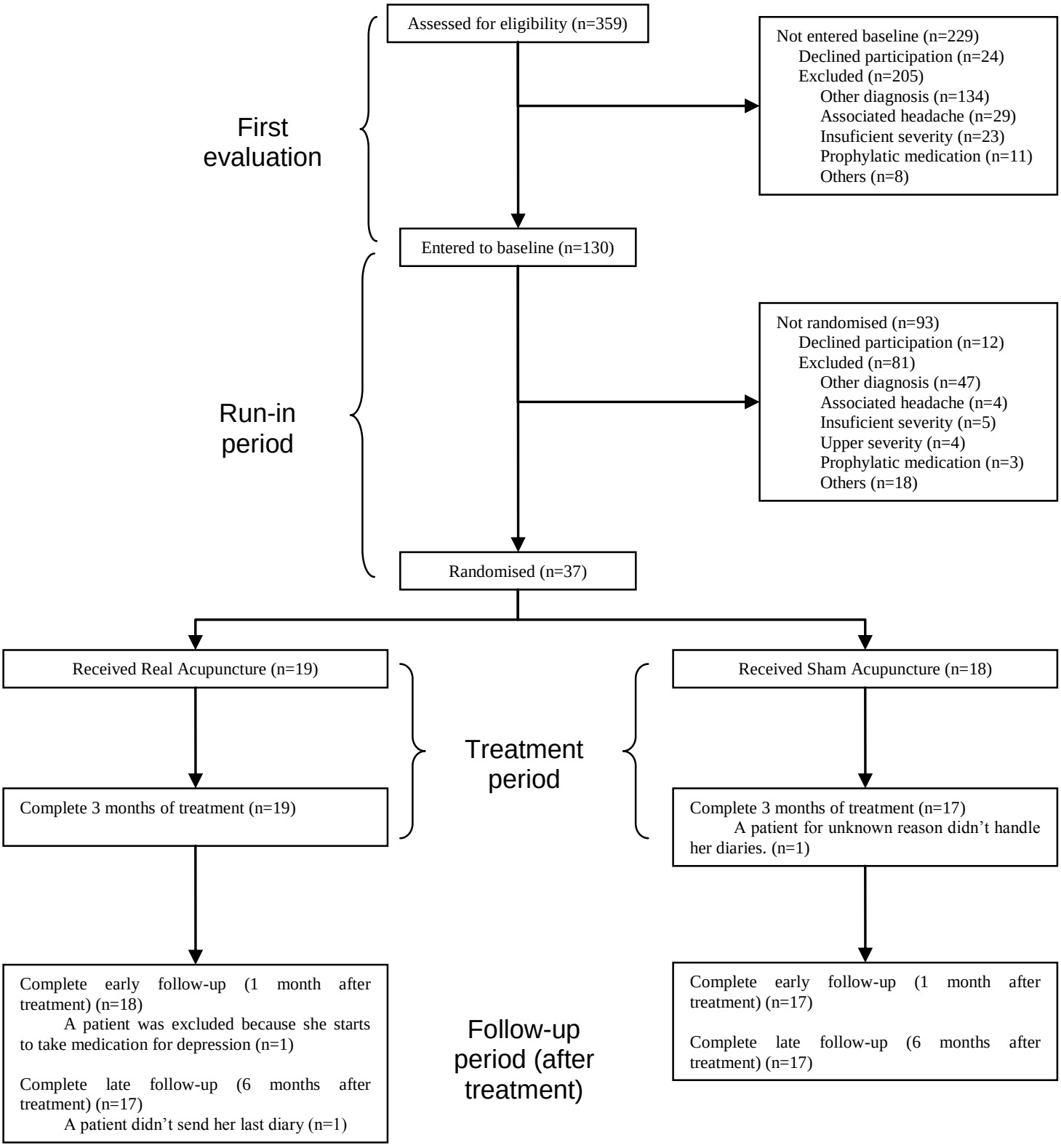


Table 10: Migraine characteristics during baseline and the treatment period of Trial 1

	Baseline period			First month of treatment			Second month of treatment			Third month of treatment		
	Diary 1			Diary 2			Diary 3			Diary 4		
	Real	Sham	p-value	Real	Sham	p-value	Real	Sham	p-value	Real	Sham	p-value
Patients with reduction of migraine attack				5/19	1/17	ns	9/19	2/17	0.021	12/19	8/17	ns
frequency of ≥ 50% **(endpoint)**				(26.3%)	(5.9%)		(47.4%)	(11.8%)		(63.2%)	(47.1%)	
Patients with reduction of migraine attack				7/19	1/17	0.044	11/19	2/17	0.004	14/19	9/17	ns
frequency of ≥ 40%				(36.8%)	(5.9%)		(57.9%)	(11.8%)		(73.7%)	(52.9%)	
Attacks per month (mean±SD)	4.5±0.9	4.7±1.0	ns	3.5±1.4	4.4±1.3	ns	3.1±1.7	4.0±1.4	ns	2.3±1.1	2.6±1.3	ns
Total migraine days per month (mean±SD)	9.2±3.6	9.8±3.7	ns	6.9±3.8	9.2±4.5	ns	4.8±3.7	7.8±3.7	0.007	3.9±1.9	4.4±2.6	ns
Mean duration of a migraine attack (hours±SD)	42.2±15.1	45.7±26.5	ns	42.0±36.6	45.3±30.3	ns	30.7±20.3	39.5±20.5	ns	34.3±24.1	27.3±16.0	ns
Total duration of migraine pain per month (hours±SD)	142.1±72.2	168.0±93.7	ns	101.7±76.8	136.2±80.5	ns	71.4±50.5	108.7±75.1	ns	51.8±31.1	63.2±45.5	ns
Amount of rescue medication used per month (units)	7.2±6.4	8.9±10.4	ns	5.9±7.2	9.1±8.3	ns	5.0±4.7	6.3±5.3	ns	4.5±3.7	4.9±6.9	ns
% Migraine days with nausea (mean±SD)	31.1±26.6	24.1±17.7	ns	11.0±14.7	18.8±22.4	ns	17.6±27.0	18.8±21.8	ns	11.6±20.3	21.9±27.3	ns
% Migraine days with vomiting (mean±SD)	4.6±9.5	8.1±13.0	ns	3.9±10.0	4.3±17.6	ns	1.3±5.8	3.5±8.3	ns	3.1±7.5	11.3±28.9	ns

ns = no statistical significance

Table 11: Migraine characteristics during baseline, first and sixth months after treatment of Trial 1

	Baseline period			First month after treatment			Sixth month after treatment		
	Diary 1			Diary 5			Diary 6		
	Real	Sham	p-value	Real	Sham	p-value	Real	Sham	p-value
Patients with reduction of migraine attack frequency of ≥ 50% **(endpoint)**				5/18 (27.8%)	4/17 (23.5%)	ns	1/17 (5.9%)	3/17 (17.7%)	ns
Patients with reduction of migraine attack frequency of ≥ 40%				8/18 (44.4%)	5/17 (29.4%)	ns	6/17 (35.3%)	4/17 (23.5%)	ns
Attacks per month (mean±SD)	4.5±0.9	4.7±1.0	ns	3.1±1.5	3.2±1.5	ns	3.7±0.9	3.2±0.9	ns
Total migraine days per month (mean±SD)	9.2±3.6	9.8±3.7	ns	4.8±3.0	6.3±3.7	ns	7.4±4.4	6.2±4.5	ns
Mean duration of a migraine attack (hours±SD)	42.2±15.1	45.7±26.5	ns	24.2±17.0	33.8±18.9	ns	41.2±28.6	42.2±26.0	ns
Total duration of migraine pain per month (hours±SD)	142.1±72.2	168.0±93.7	ns	64.0±41.4	86.1±53.0	ns	114.7±69.6	96.0±69.5	ns
Amount of rescue medication used per month (units)	7.2±6.4	8.9±10.4	ns	4.5±4.3	4.7±4.3	ns	8.5±7.7	6.7±6.3	ns
% Migraine days with nausea (mean±SD)	31.1±26.6	24.1±17.7	ns	8.2±18.3	17.0±27.4	ns	17.0±13.9	23.3±31.8	ns
% Migraine days with vomiting (mean±SD)	4.6±9.5	8.1±13.0	ns	8.2±18.3	15.6±38.8	ns	7.1±12.5	15.8±34.6	ns

ns = no statistical significance

Figure 2: Percentage of responders (Trial 1)

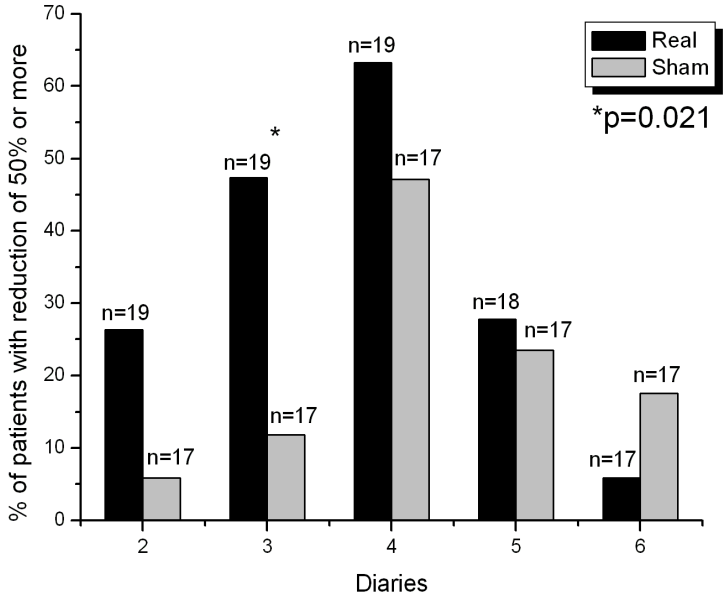


Figure 2: Percentage of responders (reduction ≥50% in the frequency of migraine attacks) in each headache diary (one month) compared with the run-in period (Diary 1) in the Real and the Sham acupuncture groups. Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. In this Figure the p value is referred to the differences between groups.

Figure 3: Percentage of responders (Trial 1)

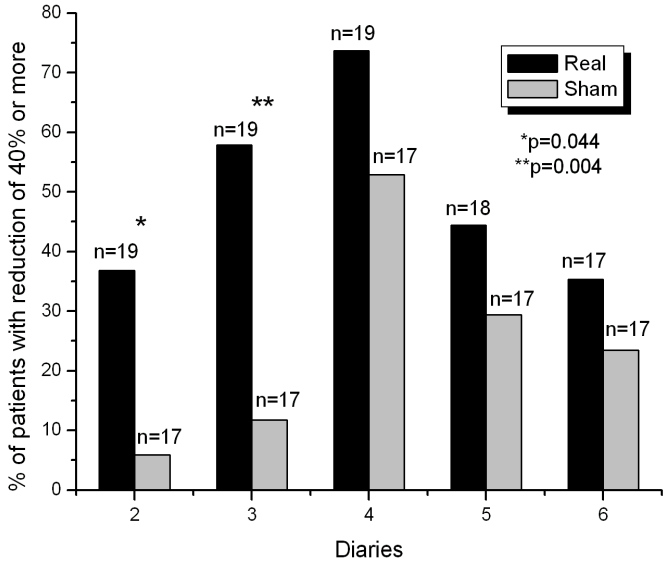


Figure 3: Percentage of responders (reduction ≥40% in the frequency of migraine attacks) in each headache diary (one month) compared with the run-in period (Diary 1) in the Real and the Sham acupuncture groups. Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. In this Figure the p value is referred to the differences between groups.

Figure 4: Number of attacks (Trial 1)

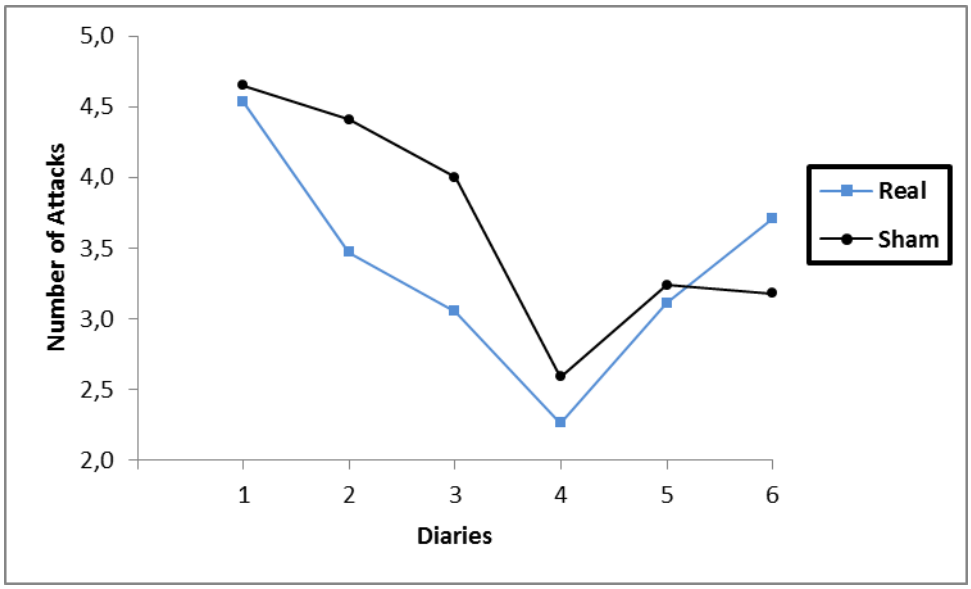


Figure 4a: Number of attacks in each diary (one month) in the Real and the Sham acupuncture groups compared with their own run-in period. Diary 1 = run-in period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. **The p value is referred to statistical analysis between groups in each point. There wasn't any statistical significant difference between groups.**

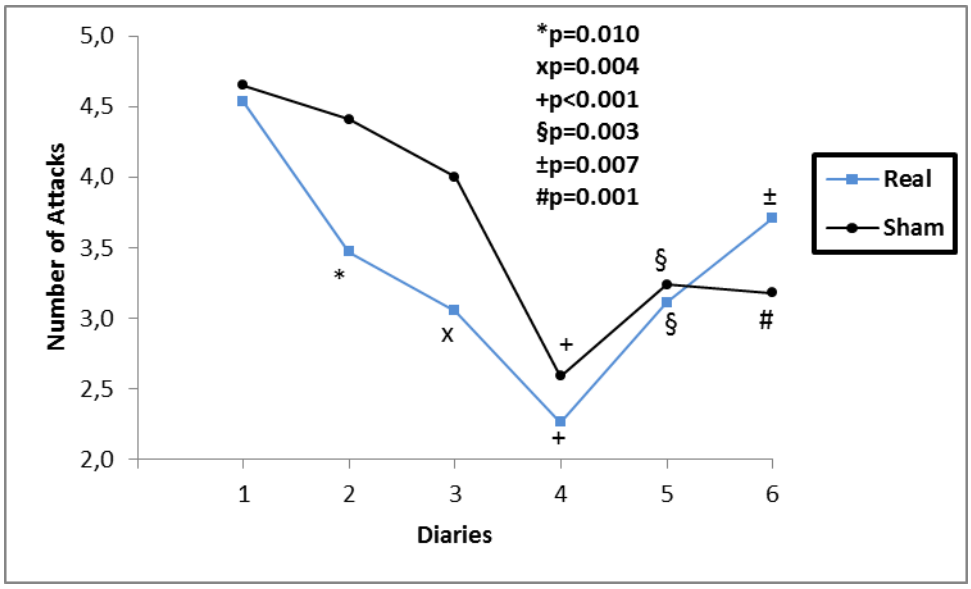


Figure 4b: Number of attacks in each diary (one month) in the Real and the Sham acupuncture groups compared with their own run-in period. Diary 1 = run-in period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. **The p value is referred to the differences within each group compared with its run-in period.**

Figure 5: Total of migraine days (Trial 1)

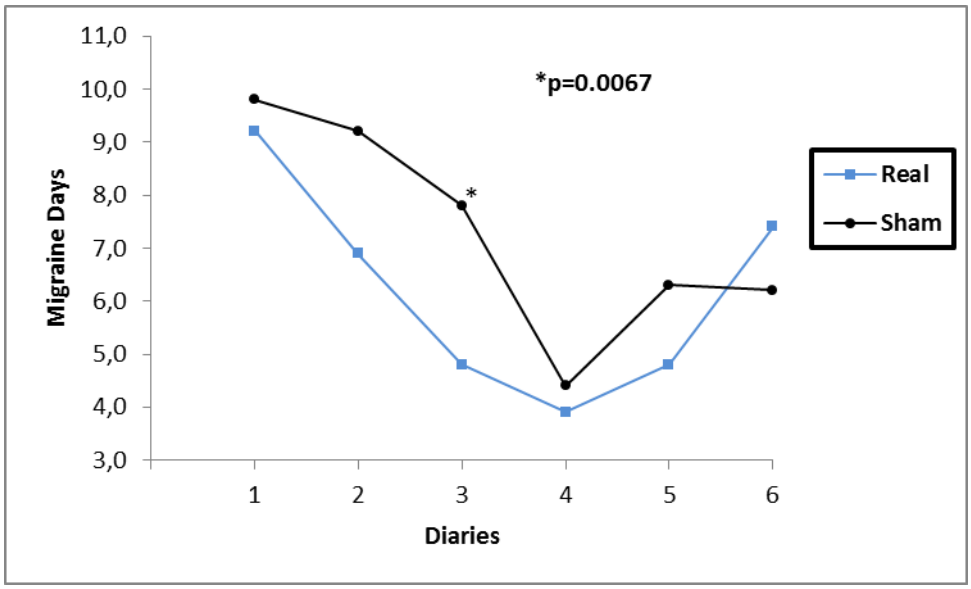


Figure 5a: Total of migraine days in each diary (one month) in the Real and the Sham acupuncture groups. Diary 1 = run-in period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. In this Figure the p value is referred to the differences between groups. **The p value is referred to statistical analysis between groups in each point.**

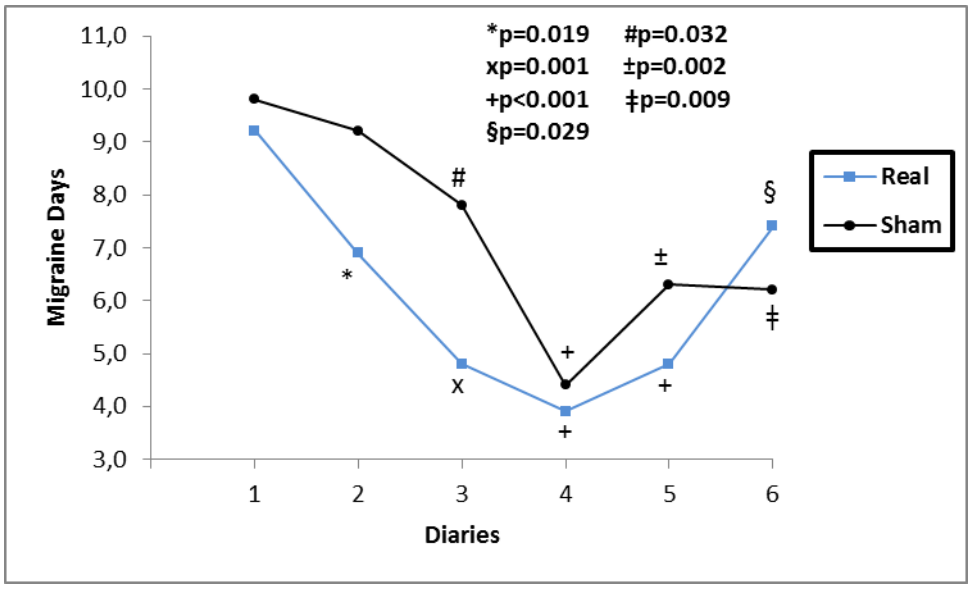


Figure 5b: Total of migraine days in each diary (one month) in the Real and the Sham acupuncture groups. Diary 1 = run-in period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. In this Figure the p value is referred to the differences between groups. **The p value is referred to the differences within each group compared with its run-in period.**

Figure 6: Duration of each attack in hours (Trial 1)

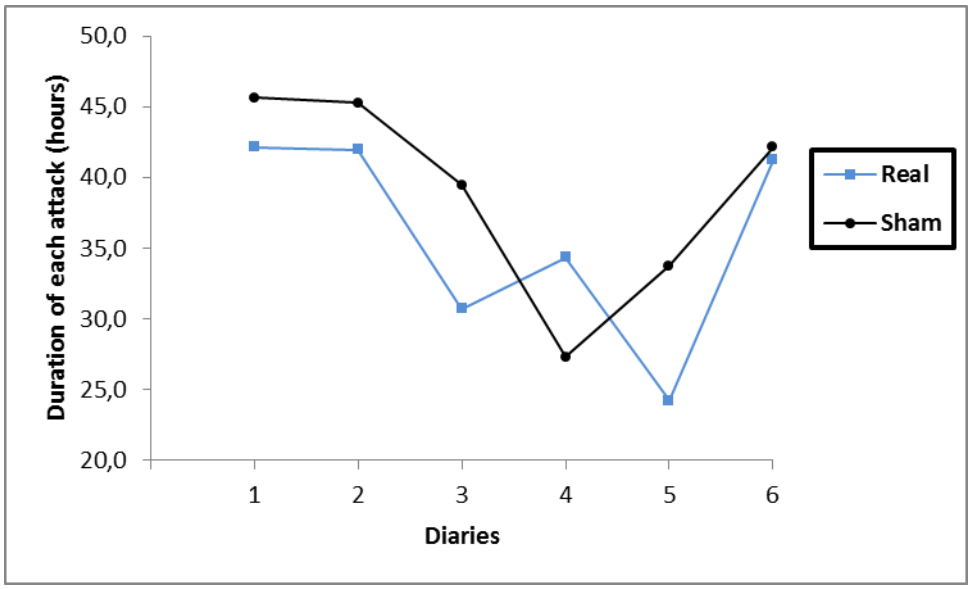


Figure 6a: Duration of each attack in hours in each diary (one month) in the Real and the Sham acupuncture groups compared with their own run-in period. Diary 1 = run-in period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. **There wasn't any statistical significant difference between groups.**

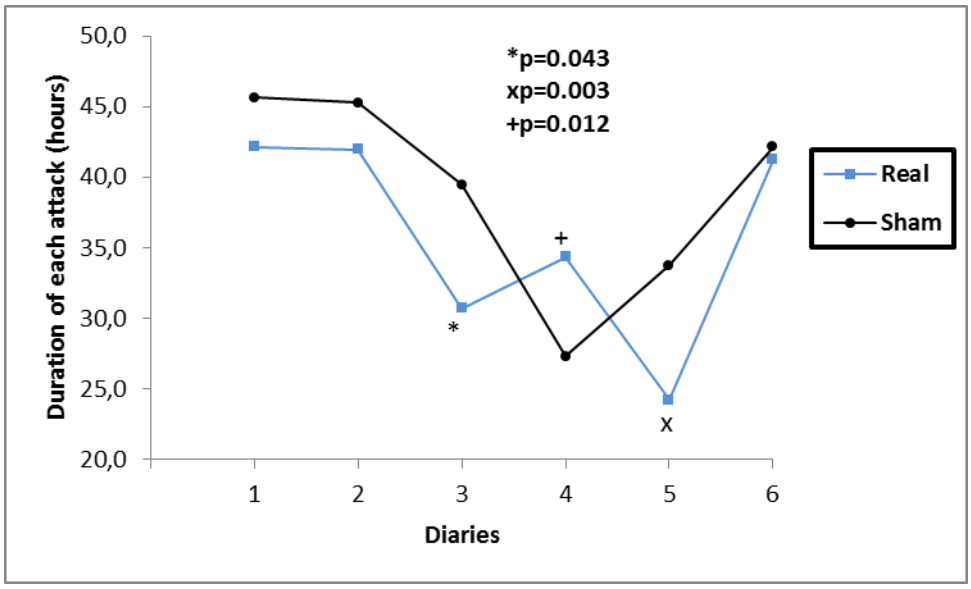


Figure 6b: Duration of each attack in hours in each diary (one month) in the Real and the Sham acupuncture groups compared with their own run-in period. Diary 1 = run-in period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. **The p value is referred to the differences within each group compared with its run-in period.**

Figure 7: Total duration of pain in hours in (Trial 1)

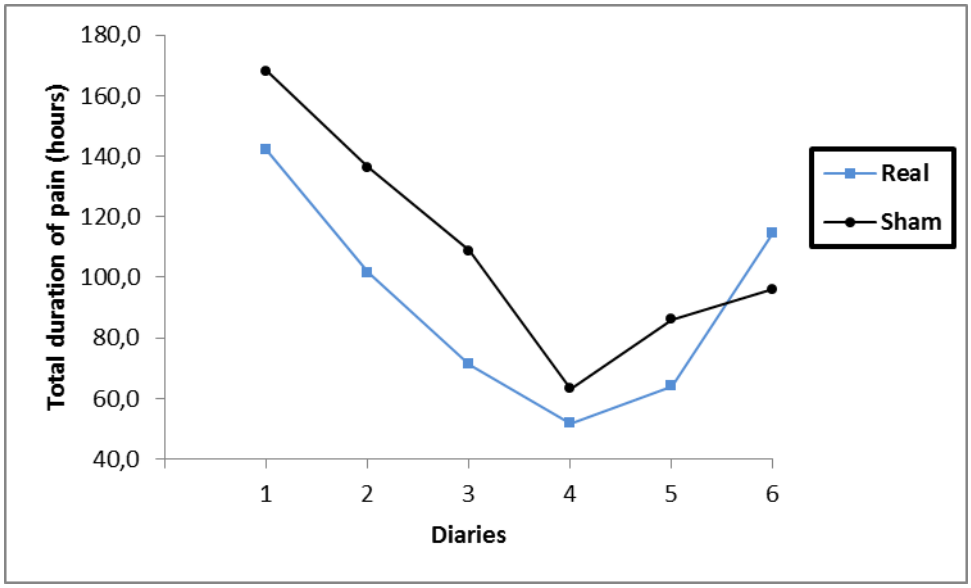


Figure 7a: Total duration of pain in hours in each diary (one month) in the Real and the Sham acupuncture groups compared with their own run-in period. Diary 1 = run-in period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. **The p value is referred to statistical analysis between groups in each point. There wasn't any statistical significant difference between groups.**

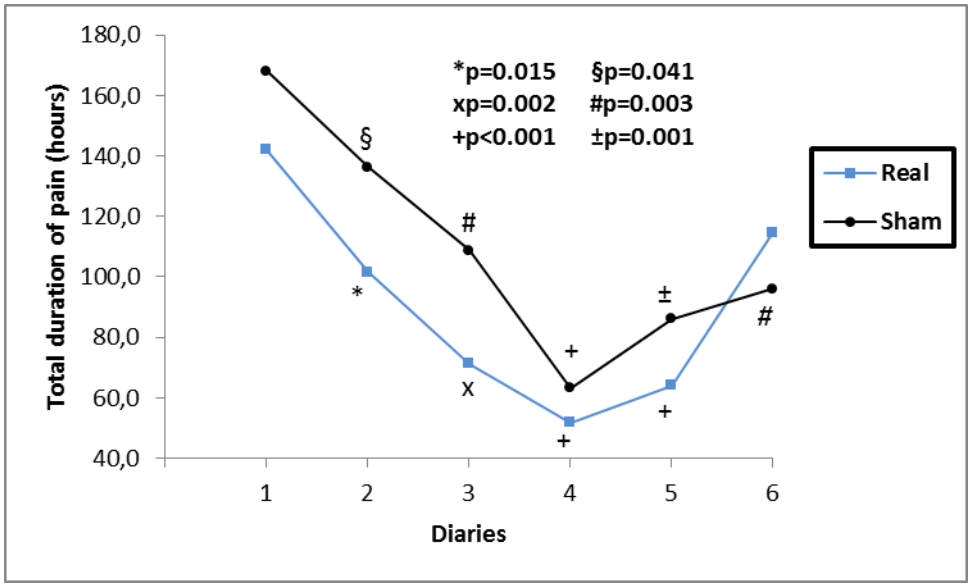


Figure 7b: Total duration of pain in hours in each diary (one month) in the Real and the Sham acupuncture groups compared with their own run-in period. Diary 1 = run-in period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. **The p value is referred to the differences within each group compared with its run-in period.**

Figure 8: Mean headache severity (Trial 1)

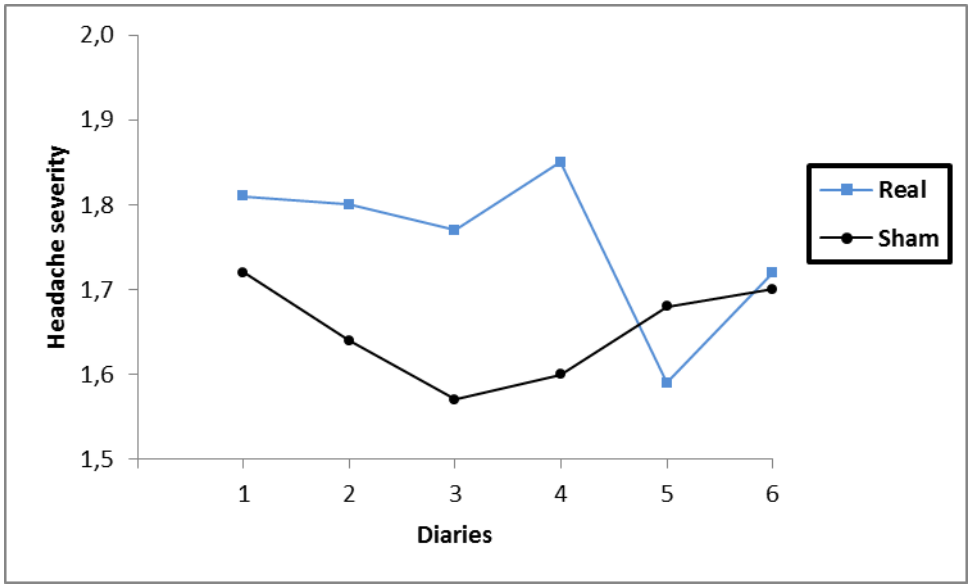


Figure 8: Mean headache severity (media of the intensity of pain considering only when patients are in painful condition in each migraine attack). Analysis was done comparing each diary (one month) in the Real and the Sham acupuncture groups with their own baseline period. Diary 1 = baseline period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. **Comparisons between and within groups did not show any statistical significant differences.**

Figure 9: Rescue medication used (Trial 1)

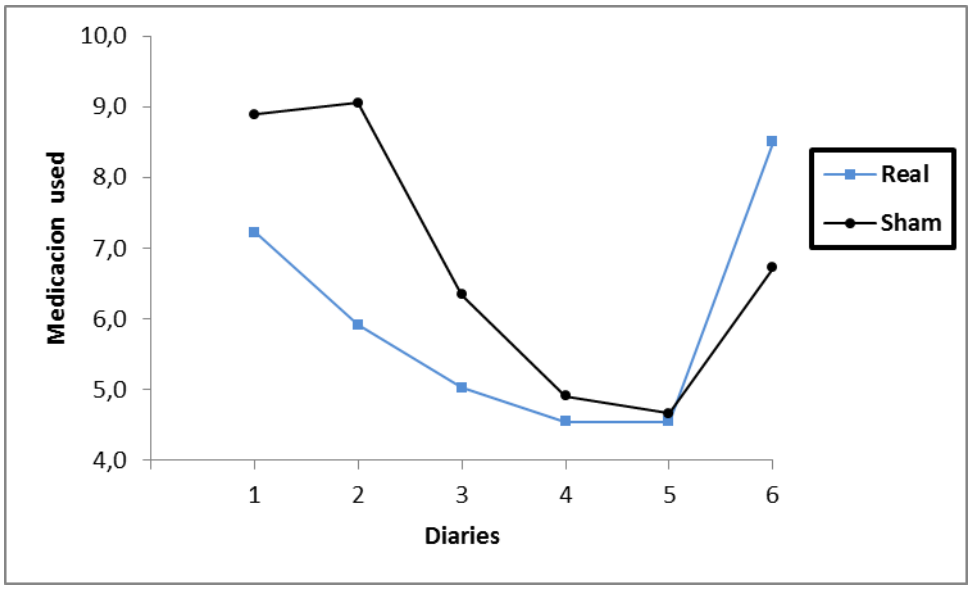


Figure 9a: Rescue medication used in each diary (one month) in the Real and the Sham acupuncture groups compared with their own run-in period. Diary 1 = run-in period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. **The p value is referred to statistical analysis between groups in each point. There wasn't any statistical significant difference between groups.**

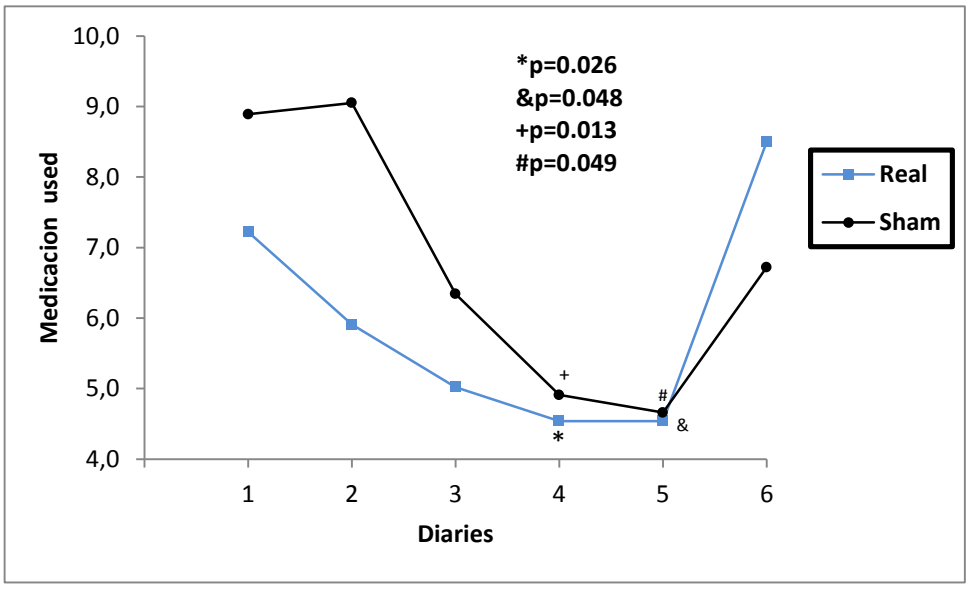


Figure 9b: Rescue medication used in each diary (one month) in the Real and the Sham acupuncture groups compared with their own run-in period. Diary 1 = run-in period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. **The p value is referred to the differences within each group compared with its run-in period. There wasn't any statistical significant difference between groups.**

Figure 10: Frequency of nausea (Trial 1)

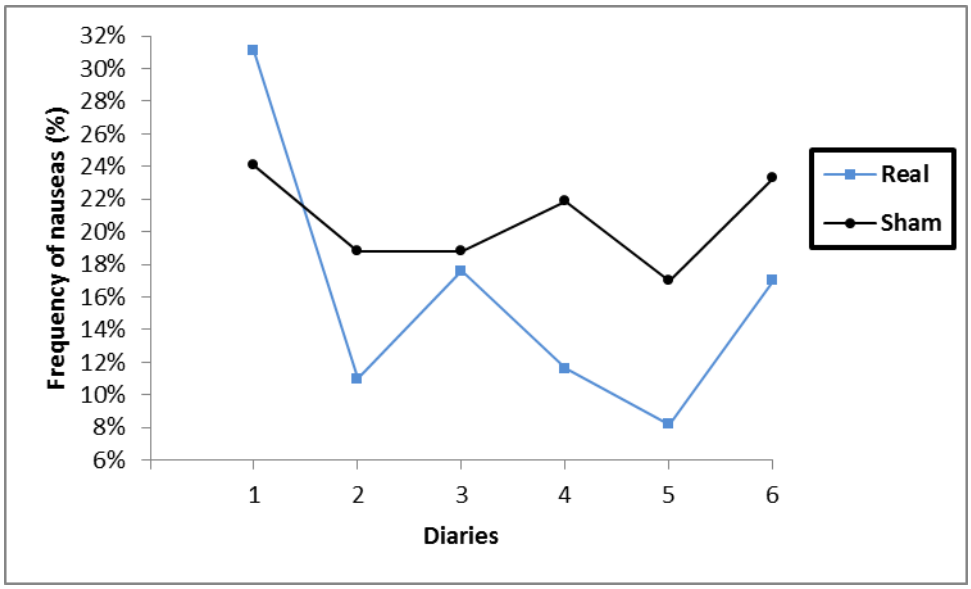


Figure 10a: Frequency of nausea in each diary (one month) in the Real and the Sham acupuncture groups compared with their own baseline period. Diary 1 = baseline period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. **The p value is referred to statistical analysis between groups in each point. There wasn't any statistical significant difference between groups.**

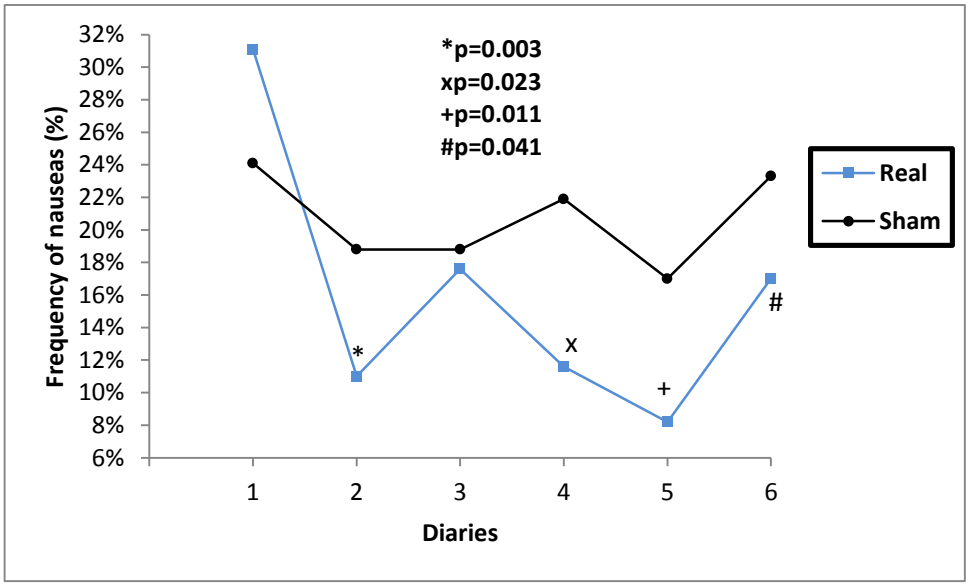


Figure 10b: Frequency of nausea in each diary (one month) in the Real and the Sham acupuncture groups compared with their own baseline period. Diary 1 = baseline period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. **The p value is referred to the differences within each group compared with its run-in period.**

Figure 11: Frequency of vomiting (Trial 1)

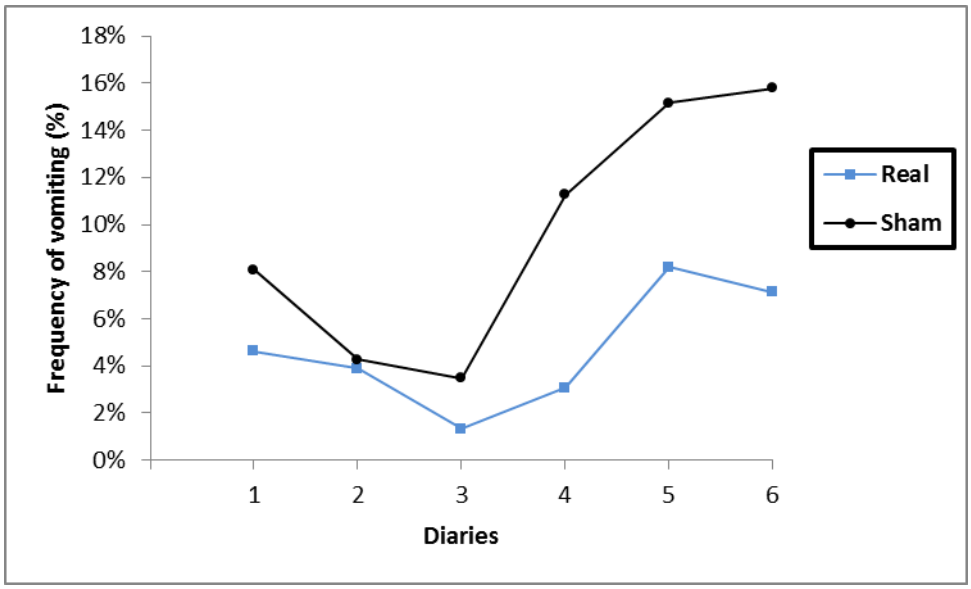
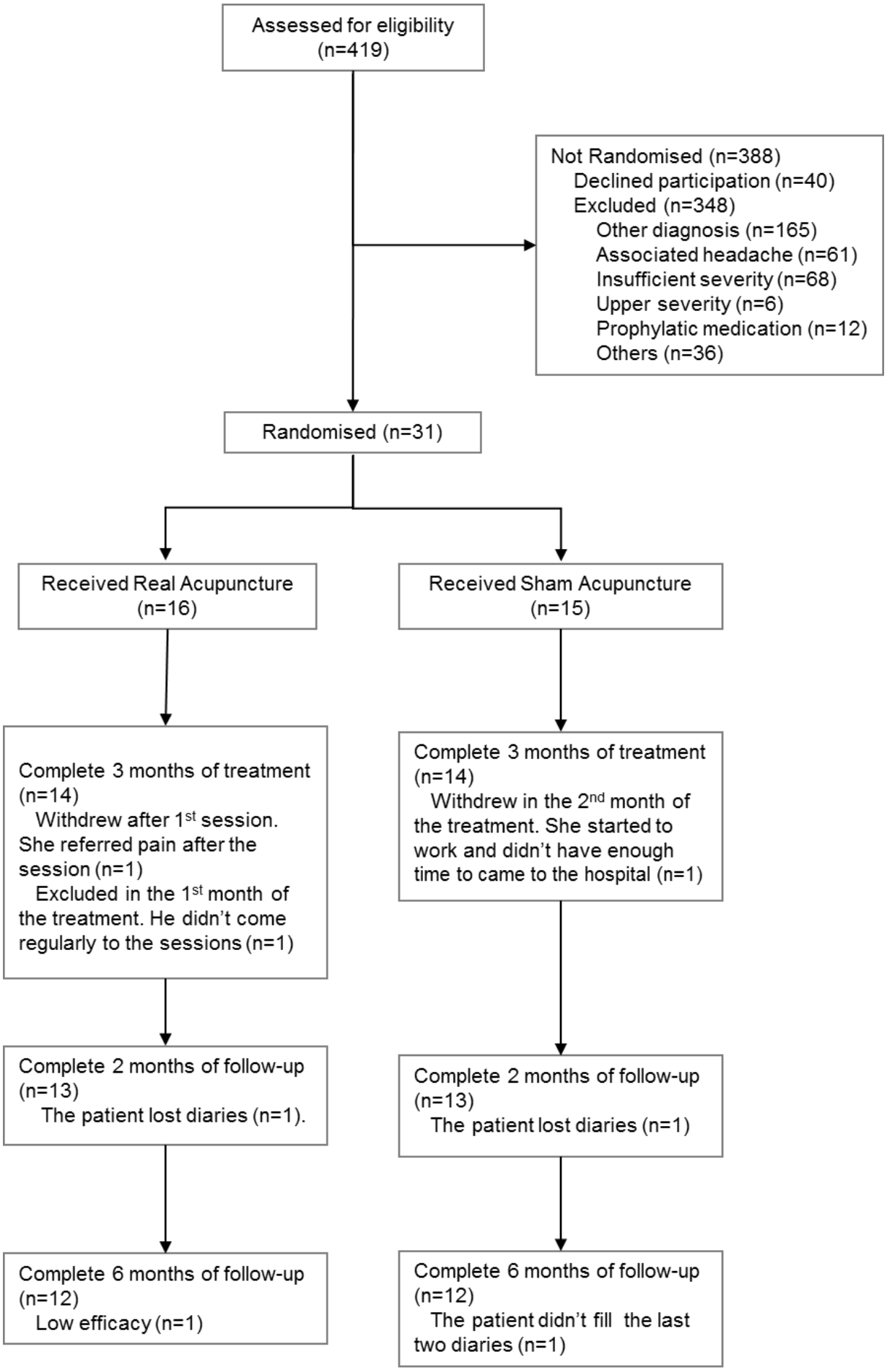


Figure 11: Frequency of vomiting in each diary (one month) in the Real and the Sham acupuncture groups compared with their own baseline period. Diary 1 = baseline period, Diary 2 = 1st month of the treatment, Diary 3 = 2nd month of the treatment, Diary 4 =3rd month of the treatment, Diary 5= 1st month after the treatment and Diary 6 = 6th month after the treatment. **There wasn't any statistical significant difference between groups.**

5.3. Trial 2

Thirty-one patients were enrolled and randomized from August 2002 to March 2003, and the trial was completed in February 2004 (including all post-treatment follow-up period). However, the statistical analysis was done with twenty-eight patients. See participants' flow in Figure 12.

Figure 12: Flow of patients in Trial 2



There were no statistical significant differences between the real and the sham acupuncture groups in all parameters evaluated in this trial during the treatment and the post-treatment follow-up periods. See Tables 12 and 13. Results are showed in Figures 13 to 22.

Nevertheless, comparisons within each group found that all migraine pain parameters had improved with statistical significant difference in both groups. There was one exception, the headache severity when the patients were having pain (See figure 19).

Table 12: Migraine characteristics during baseline and treatment periods of Trial 2

	Baseline period			weeks 0-4 of the treatment period			weeks 5-8 of the treatment period			weeks 9-12 of the treatment period		
	Diary 1			Diary 2			Diary 3			Diary 4		
	Real	Sham	p-value	Real	Sham	p-value	Real	Sham	p-value	Real	Sham	p-value
Patients with reduction of migraine attack frequency of ≥ 50% **(endpoint)**				1/14 (7.1%)	4/14 (28.6%)	ns	4/14 (28.6%)	2/14 (14.3%)	ns	4/14 (28.6%)	6/14 (42.9%)	ns
Patients with reduction of migraine attack frequency of ≥ 40% **(endpoint)**				2/14 (14.3%)	4/14 (28.6%)	ns	5/14 (35.7%)	3/14 (21.4%)	ns	6/14 (42.9%)	7/14 (50.0%)	ns
Attacks per month (mean±SD)	4.3±0.7	4.2±0.9	ns	4.5±1.3	3.9±1.7	ns	3.4±1.5	3.6±1.1	ns	3.2±1.4	3.1±1.2	ns
Total migraine days per month (mean±SD) **(endpoint)**	9.9±3.1	8.4±3.7	ns	8.7±3.2	7.3±3.3	ns	7.9±4.7	6.9±3.9	ns	6.4±3.8	5.9±3.3	ns
Mean duration of a migraine attack (hours±SD)	50.5±26.4	38.9±23.9	ns	41.5±32.7	39.1±33.1	ns	50.4±38.4	34.7±26.2	ns	38.8±27.5	34.7±17.5	ns
Total duration of migraine pain per month (hours±SD)	125.6±58.1	110.6±67.9	ns	117.0±65.9	82.7±48.2	ns	98.6±67.9	85.3±65.4	ns	82.7±48.2	71.6±54.2	ns
Amount of rescue medication used per month (units)	10.9±8.1	7.9±7.6	ns	6.5±4.4	8.7±6.5	ns	9.3±11.3	6.8±5.1	ns	7.6±7.4	6.7±9.4	ns
% Migraine days with nausea (mean±SD)	13.9±14.3	27.9±29.1	ns	20.8±20.5	8.5±20.1	ns	12.1±15.4	9.7±18.5	ns	9.4±26.9	14.0±24.2	ns
% Migraine days with vomiting (mean±SD)	7.9±26.7	17.5±33.7	ns	7.2±17.2	6.1±22.9	ns	10.7±28.9	7.9±18.1	ns	9.3±26.7	6.0±15.5	ns

ns = no statistical significance

Table 13: Migraine characteristics during baseline and points of the post-treatment period (weeks 0-4 and 21-24) of Trial 2

	Baseline period			weeks 0-4 after the treatment period			weeks 21-24 after the treatment period		
	Diary 1			Diary 5			Diary 10		
	Real	Sham	p-value	Real	Sham	p-value	Real	Sham	p-value
Patients with reduction of migraine attack frequency of ≥ 50% **(endpoint)**				4/14 (28.6%)	3/13 (23.1%)	ns	6/12 (50.0%)	3/12 (25.0%)	ns
Patients with reduction of migraine attack frequency of ≥ 40% **(endpoint)**				5/14 (35.7%)	3/13 (23.1%)	ns	6/12 (50.0%)	3/12 (25.0%)	ns
Attacks per month (mean±SD)	4.3±0.7	4.2±0.9	ns	3.5±1.5	3.8±1.7	ns	2.8±1.9	2.9±1.4	ns
Total migraine days per month (mean±SD) **(endpoint)**	9.9±3.1	8.4±3.7	ns	6.4±3.3	6.3±3.1	ns	4.4±2.8	4.0±2.3	ns
Mean duration of a migraine attack (hours±SD)	50.5±26.4	38.9±23.9	ns	35.1±22.9	35.8±32.5	ns	34.6±41.2	20.7±11.7	ns
Total duration of migraine pain per month (hours±SD)	125.6±58.1	110.6±67.9	ns	83.1±57.9	72.9±40.0	ns	64.5±51.7	46.0±25.8	ns
Amount of rescue medication used per month (units)	10.9±8.1	7.9±7.6	ns	6.5±6.0	7.6±7.7	ns	7.3±8.7	4.4±3.1	ns
% Migraine days with nausea (mean±SD)	13.9±14.3	27.9±29.1	ns	12.5±22.3	17.9±29.3	ns	17.6±33.3	19.4±30.6	ns
% Migraine days with vomiting (mean±SD)	7.9±26.7	17.5±33.7	ns	14.3±53.5	10.7±22.1	ns	3.3±11.5	6.3±21.7	ns

ns = no statistical significance

Figure 13: Percentage of responders

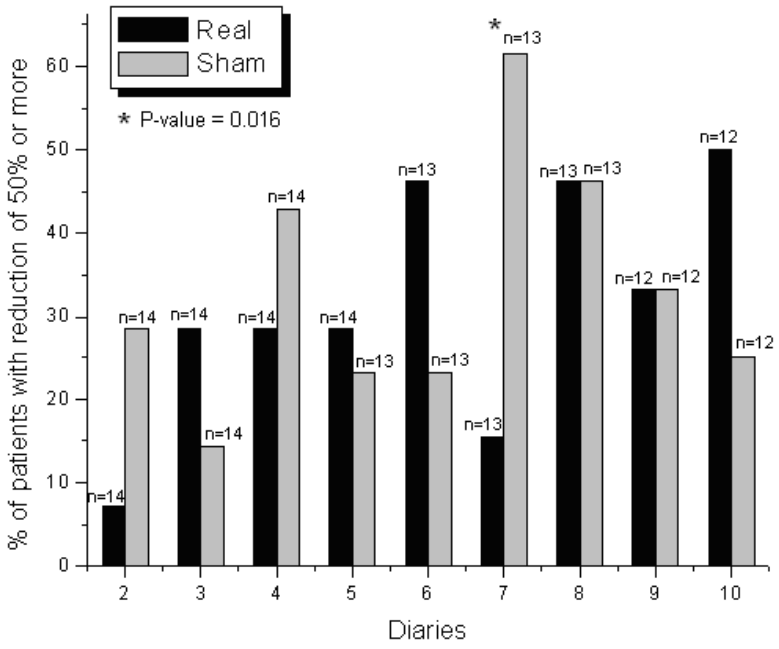


Figure 13: Percentage of responders (reduction ≥50% in migraine attacks frequency) in each diary (4 weeks) compared with the baseline period (Diary 1) in the Real and the Sham acupuncture groups. The diaries 2, 3 and 4 correspond to the treatment period (12 weeks). The diaries 5-10 correspond to the follow-up period (24 weeks).

Figure 14: Percentage of responders (Trial 2)

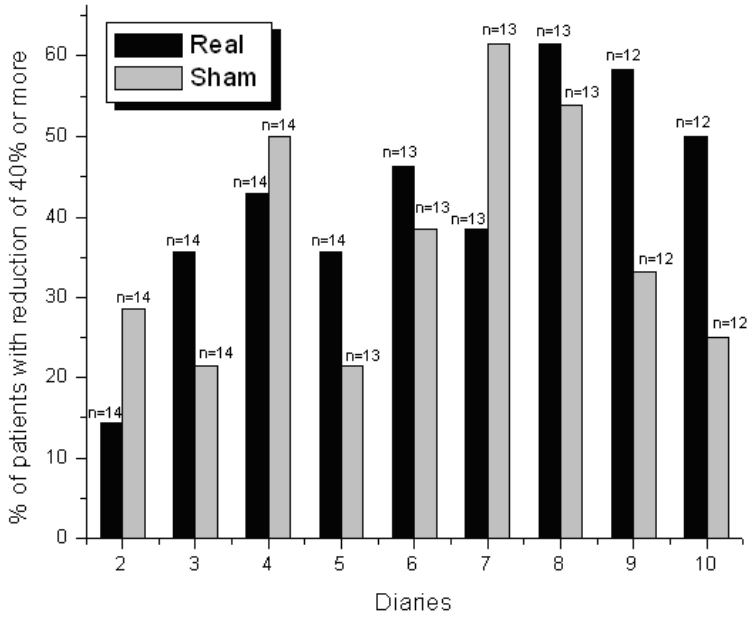


Figure 14: Percentage of responders (reduction ≥40% in migraine attacks frequency) in each diary (4 weeks) compared with the baseline period (Diary 1) in the Real and the Sham acupuncture groups. The diaries 2, 3 and 4 correspond to the treatment period (12 weeks). The diaries 5-10 correspond to the follow-up period (24 weeks).

Figure 15: Number of attacks in each diary (Trial 2)

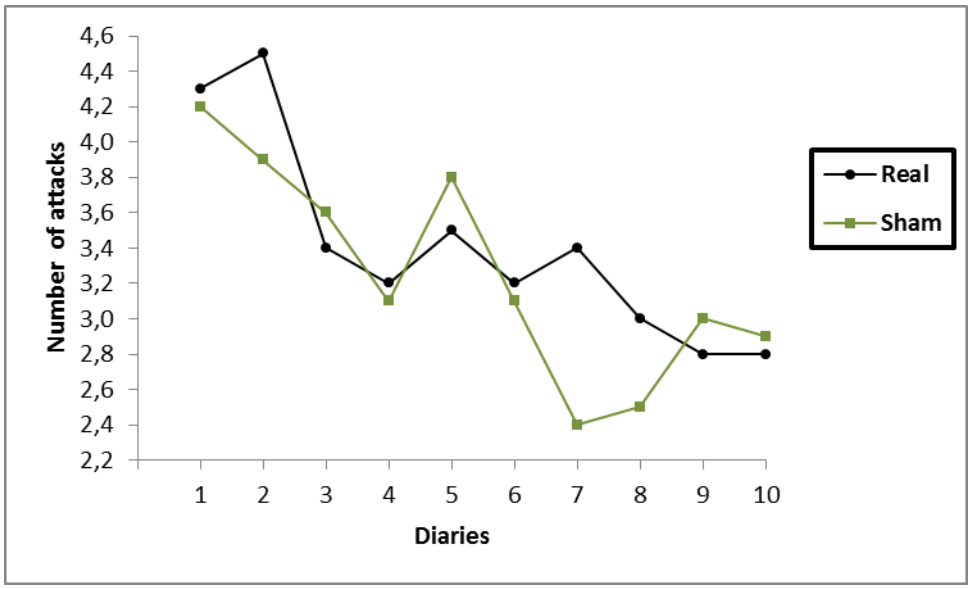


Figure 15: Number of attacks in each diary (4 weeks) in the Real (■) and the Sham (●) acupuncture groups. Diary 1 = baseline period (4 weeks), diaries 2, 3 and 4 correspond to the treatment period (12 weeks) and diaries 5-10 correspond to the follow-up period (24 weeks).

Figure 16: Total of migraine days in each diary (Trial 2)

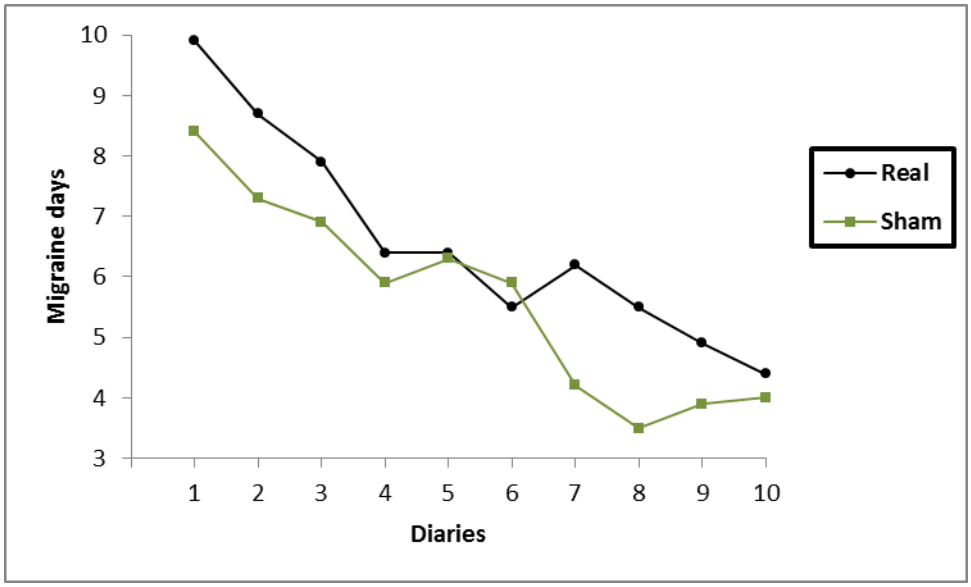


Figure 16: Total of migraine days in each diary (4 weeks) in the Real (■) and the Sham (●) acupuncture groups. Diary 1 = baseline period (4 weeks), diaries 2, 3 and 4 correspond to the treatment period (12 weeks) and diaries 5-10 correspond to the follow-up period (24 weeks).

Figure 17: Mean duration of migraine attacks in hours (Trial 2)

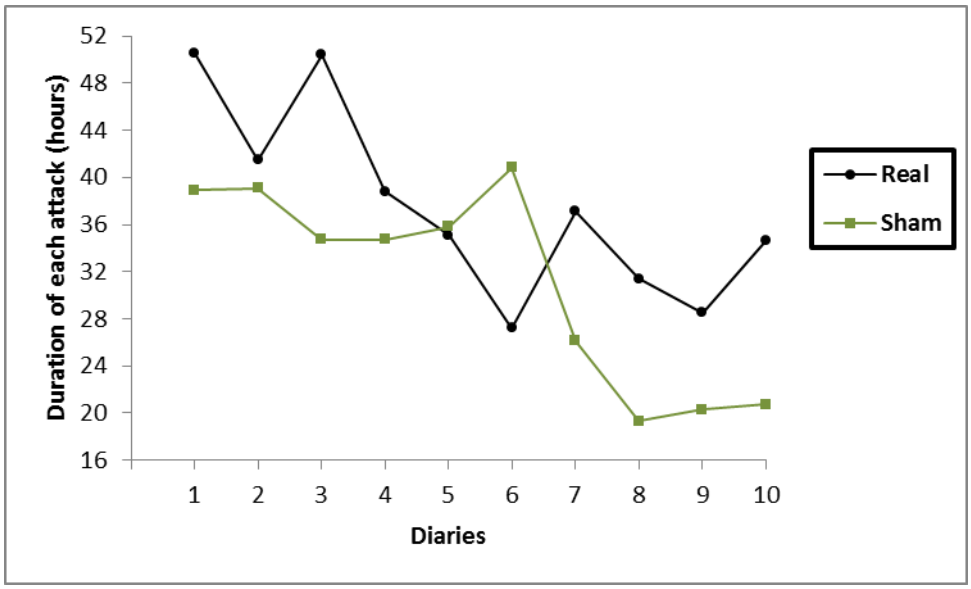


Figure 17: Mean duration of migraine attacks in hours in each diary (4 weeks) in the Real (■) and the Sham (●) acupuncture groups. Diary 1 = baseline period (4 weeks), diaries 2, 3 and 4 correspond to the treatment period (12 weeks) and diaries 5-10 correspond to the follow-up period (24 weeks).

Figure 18: Total duration of pain in hours (Trial 2)

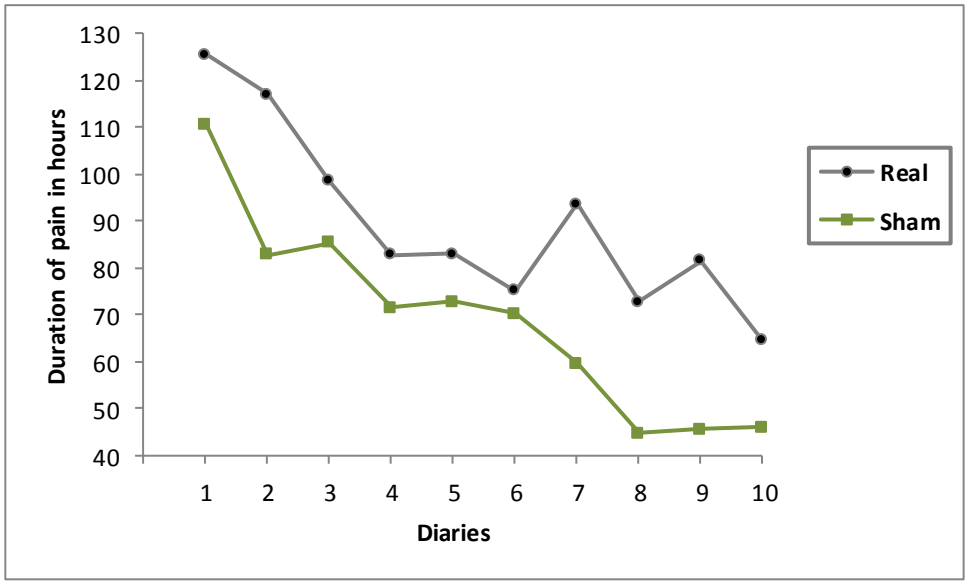


Figure 18: Total duration of pain in hours in each diary (4 weeks) in the Real (■) and the Sham (●) acupuncture groups. The diaries 2, 3 and 4 correspond to the treatment period (12 weeks). The diaries 5-10 correspond to the follow-up period (24 weeks).

Figure 19: Mean headache severity (Trial 2)

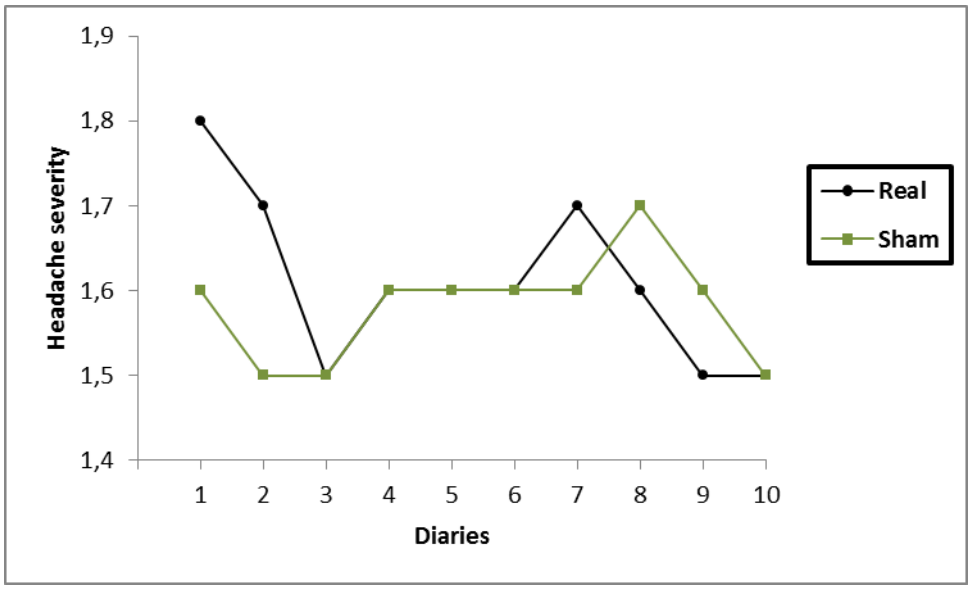


Figure 19: Mean headache severity (media of the intensity of pain considering only when patients are in painful condition in each migraine attack). Analysis was done comparing each diary (one month) in the Real(□) and the Sham(●) acupuncture groups with their own baseline period. Diary 1 = baseline period (4 weeks), diaries 2, 3 and 4 correspond to the treatment period (12 weeks) and diaries 5-10 correspond to the follow-up period (24 weeks). **Comparisons between and within groups did not show any statistical significant differences.**

Figure 20: Rescue medication used (Trial 2)

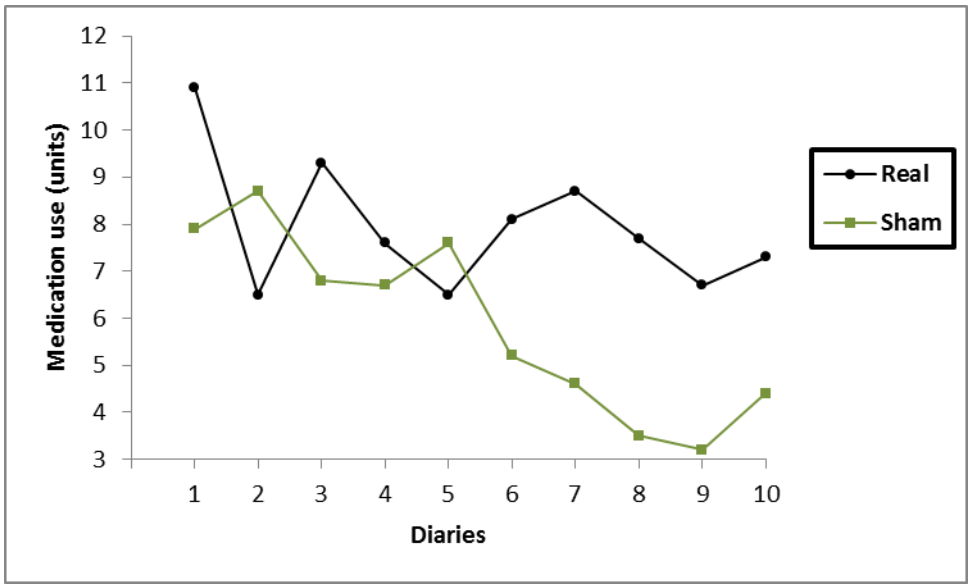


Figure 20: Rescue medication used in each diary (4 weeks) in the Real (■) and the Sham (●) acupuncture groups. The diaries 2, 3 and 4 correspond to the treatment period (12 weeks). The diaries 5-10 correspond to the follow-up period (24 weeks). **Comparisons between and within groups did not show any statistical significant differences.**

Figure 21: Frequency of nausea (Trial 2)

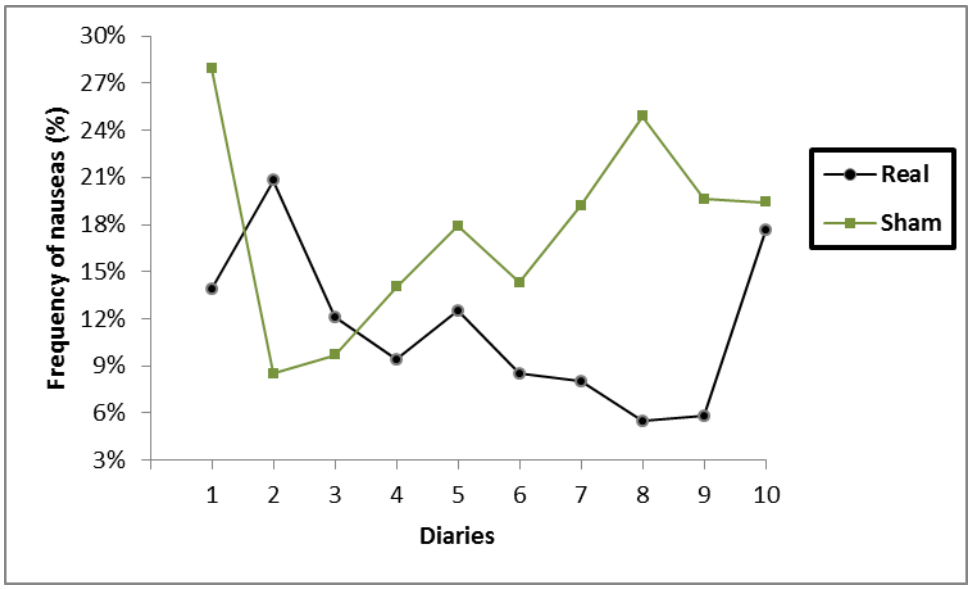


Figure 21: Frequency of nausea in each diary (4 weeks) in the Real (■) and the Sham (●) acupuncture groups. The diaries 2, 3 and 4 correspond to the treatment period (12 weeks). The diaries 5-10 correspond to the follow-up period (24 weeks). **Comparisons between and within groups did not show any statistical significant differences.**

Figure 22: Frequency of vomiting (Trial 2)

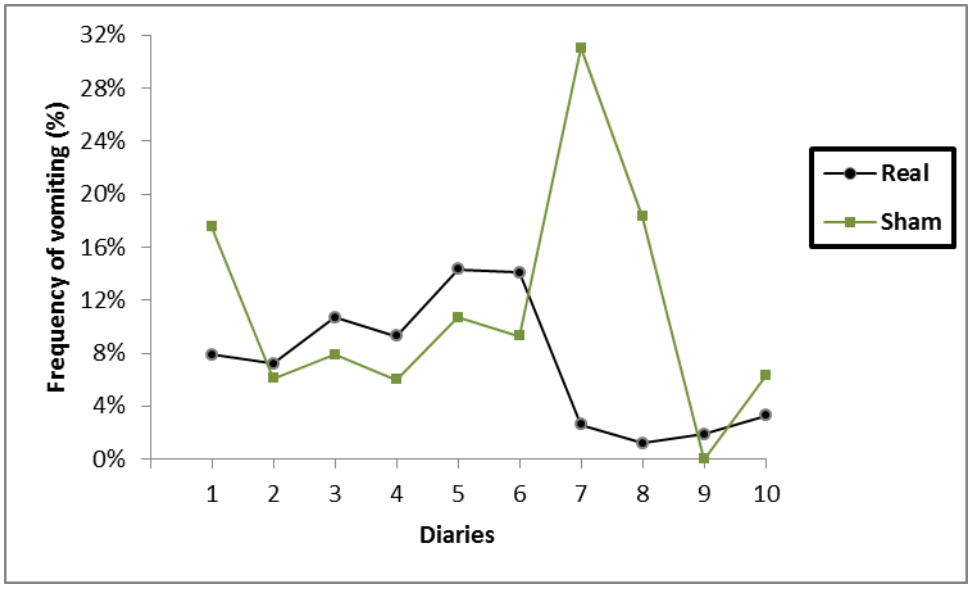


Figure 22: Frequency of vomiting in each diary (4 weeks) in the Real (■) and the Sham (●) acupuncture groups. The diaries 2, 3 and 4 correspond to the treatment period (12 weeks). The diaries 5-10 correspond to the follow-up period (24 weeks). **Comparisons between and within groups did not show any statistical significant differences.**

6. DISCUSSION

Statistical significant differences between groups appeared in demographic data in both trials. In Trial 1, migraine patients with aura were significantly more numerous in the sham group. In Trial 2, patients in the sham acupuncture group were older than in the real acupuncture group (P=0.024). These differences were not considered in statistical analysis, because they did not affect the treatment outcomes. Literature could confirm this impression (114-116).

When migraine parameters were analyzed, the statistical significant differences between groups appeared only in Trial 1. Results showed a fast improvement of the real acupuncture group compared to the sham group in the endpoint adopted: the percentage of patients with reduction ≥50% in their migraine attack frequency. Other pain parameters showed improvement with statistical significant differences: the total of migraine days and the percentage of patients with reduction ≥40% in migraine attack frequency. The improvement started very early, almost in the first month of treatment. However, all differences between groups disappeared in the third month of the treatment as a consequence of the high improvement in the sham group at that time. In trials testing drugs for migraine prophylaxis, improvements were observed only in the second or third month of the treatment (56, 60, 68). Although statistical significant differences between groups disappeared; results showed the continuous improvement in almost all pain parameters in both groups. Therefore, it is evident that one great problem was the kind of control group adopted: penetrative needles were utilized in the sham group. When these protocols were designed and the minimal acupuncture was chosen for control group, authors thought that the very superficial needle skin insertion could promote lesser stimulation of the pain control system and minimize the psychological effects of the acupuncture. Many authors and guidelines recommended minimal acupuncture to control group up to 2002 (4, 6, 42, 48, 49). Yamashita et all, objected to this idea and said that very superficial needling is considered a “real technique” in Japan(106). Actually, there are many ways and technical approach in acupuncture. At this time, there are different styles of acupuncture in Japan. One used to be a very superficial insertion of needle. Another method uses non-penetrative needling. In Western countries the Chinese acupuncture model is the most used and needling was not superficial in this approach.

Despite all methodological care, the results were shocking. Sham acupuncture in Trial 1 and Trial 2 showed higher response than the expected for placebo. Two meta-analysis that evaluated placebo response in randomized trials for migraine prophylaxis showed that placebo responses in this condition are not so different from other different clinical situations(112, 117). This data are displayed in Table 14.

Table 14: Treatment response in migraine prophylaxis in randomized placebo-controlled trials

<table>
<tr><th rowspan="2">Study</th><th colspan="2">Responders* (%)</th><th colspan="2">% reduction in migraine attacks frequency</th></tr>
<tr><th>Active</th><th>Placebo</th><th>Active</th><th>Placebo</th></tr>
<tr><td>Van der Kuy, 2002 (meta-analysis with 22 trials)</td><td>45,5% ± 15,5</td><td>23,5% ± 8</td><td>41,8% ± 11,7</td><td>16,8% ± 12,7</td></tr>
<tr><td rowspan="5">Macedo, 2008 (meta-analysis with 22 trials)</td><td rowspan="3">RCT 41% ± 8</td><td>RCT 21% ± 7</td><td rowspan="4">36%</td><td rowspan="4">18%</td></tr>
<tr><td>Parallel Design 22%</td></tr>
<tr><td>Cross-over 10%</td></tr>
<tr><td>Europe 43%</td><td>Europe 25,9%</td></tr>
<tr><td>North Am. 39%</td><td>North Am. 16,8%</td></tr>
<tr><td>Trial 1</td><td>63,2%</td><td>47,10%</td><td>48,10%</td><td>44,50%</td></tr>
<tr><td>Trial 2</td><td>28,60%</td><td>42,90%</td><td>20,80%</td><td>23,10%</td></tr>
</table>

***Responders = percentage of patients with 50% or more reduction in migraine attack frequency during treatment compared with the baseline period.**

Many high quality trials developed to assess efficacy of acupuncture in treating migraine and chronic pain identified the same phenomena - effects of sham acupuncture with penetrating needles were superior to expected for placebo (3, 50, 118, 119). In fact, several trials demonstrated that all kinds of invasive technical procedures have higher placebo effects than oral treatment of migraine (120, 121). Some trials could better evidence the magnitude of the analgesic sham acupuncture effects because they included in their trials another control or treatment group (99, 100). Two systematic reviews evaluating acupuncture effects in migraine prophylaxis conclude that acupuncture is as effective as drug therapy but the 'sham acupuncture' is as effective as 'real acupuncture'(50, 122). In editorial evaluating the results of many large-scale and well-designed acupuncture trials(100, 103), Diener advocates the adoption of control group with established preventive drugs like β-blockers or neuromodulators in acupuncture migraine trials(123). That was a gap in our trials.

Almost all trials published in the last five years consolidated the evidence that the superficial needling promotes physiological and analgesic effects(124) and improves migraine(50). This is a dilemma in acupuncture research. Part of the problem could be the penetrating needling used in control groups. Indubitably, this stimulus with needles in the skin promotes physiological responses. The connective tissue and peripheral nervous system were stimulated promoting effects in the pain control system of the human body(87). Certainly, the advances of the knowledge in neurosciences will become more clear as the slightly stimulus of the skin, like minimal acupuncture, could alleviate several types of chronic pain. Neuromodulation would be the most probable mechanism of the phenomena.

In Trial 2, where formulae acupuncture was used, the improvement of the headache was lower than the observed results in Trial 1, where the individualized treatments were employed. The methodology between the first and second trial varied in the sort of the treatment applied to the real and sham acupuncture groups. Therefore, they could be the factor that had determined the poor results. The outcomes of the semi-standardized treatment in real and sham could be determined by the therapeutic scheme adopted. In the Real group, points were selected in accordance with experience of the 3 trained medical doctors who worked with acupuncture every day from 14 to 20 years. Nevertheless, in 2001, in a critical analysis about acupuncture research, authors said: “The importance of individualization in comparison with the formulae acupuncture has not been demonstrated in clinical trials”(19). Many trials revealed the same thing (100, 102). However, results in Trial 2 were lower than the expected effects for treatment and placebo groups in trials with drugs or in developed migraine acupuncture trials (112, 125). See Table 14.

Another aspect needs to be considered to understand small differences in the statistical analysis between groups: the informed consent and the information text presented to the patients. Researchers informed that two kinds of acupuncture would be tested, the true and the false one. This mention should influence results. Trials where the placebo group is included and this information communicated to patients are related to less expressive effects in both groups (126-128). Diener opened his heart in a Cephalalgia’s Editorial dedicated exclusively to the placebo effects in headache trials: “Reading over the last two decades of ‘Cephalalgia’ and ‘Headache’ it is amazing how many treatment options were effective in open trials and failed in a spectacular way in clinical trials”. In the same

Editorial, Diener suggested: “new strategies to minimize the placebo response have to be used. One possibility would be to treat consecutive migraine attacks with a decreasing placebo response over time”(129).

Many factors contribute to the outcomes. The individual patients’ expectation determines a part of the effects of any active treatment tested by trials. The context of the treatment could not be forgotten as well.

Considering the poor effects reached with the semi-standardized therapeutic scheme, our research group decided to adopt in phase III trial the individualized treatment for the real acupuncture group. See Table 14. Results of Trial 3 could confirm our first impression. Individualized acupuncture treatment is a better choice to treat patients. Outcomes of this trial were not completely published yet, but some data will be attached to this thesis in the published abstracts (130, 131) and posters presented in the XII Congress of the International Headache Society, in Kyoto-Japan.

Comparisons within each group showed that all migraine pain parameters evaluated improved significantly in both groups except for headache severity. In fact, we measured the average headache severity and observed that the intensity of headache when patient is having pain did not change. Even in statistical analysis within each group no differences appeared. It must be evaluated in future trials.

Statistical analysis within each group showed that improvement appeared with statistical significance in the real acupuncture group from the first month of the treatment to the late post-treatment follow-up. In the sham acupuncture group the improvement started only in the second month of the treatment and then remained right through. It would be possible that the effects of superficial needling appeared only after several sessions of acupuncture. This impression has to be observed and confirmed in other trials in the near future. The neurophysiology model probably could better explain why the superficial needling promotes a retarded response.

It is important to outline that effects reached for both groups in these two trials were preserved for 6 months after the last acupuncture session. The long lasting effects of acupuncture were related by other published acupuncture trials (40, 43, 95, 98-100, 131).

Another aspect observed in these trials was the reduction of the improvement when the acupuncture sessions were interrupted. Even results of the third trial confirm it. What would happen if the treatment could be continued for many months in a planned schedule?

No serious adverse events were reported in 1024 sessions of acupuncture. These two trials confirmed that acupuncture could be a safe procedure when applied by qualified professionals using disposable and sterilized needles. Large number of publications since 2nd century BC mentioned adverse effects of acupuncture(132). Curiously, some symptoms described at that time correspond to a most frequent serious complication stated in the scientific literature nowadays, pneumothorax. Many surveys or systematic reviews conducted in Australia, Britain, Germany and Japan concluded that the practice of acupuncture is not risk-free. However, serious adverse events are directly related to the years of training, knowledge of anatomy and the professional qualification to prevent infections (91, 92, 132-136). In a recent systematic review, authors summarized reports of serious adverse effects published since 2000. They included in this review all literature available without language restrictions (137). They concluded that: “Serious complications after acupuncture continue to be reported. Many are not intrinsic to acupuncture, but caused by malpractice of acupuncturists”.

Trials which are subjects of this thesis were structured on the pharmacological model of testing efficacy. Placebo-controlled randomized trials (RCT) are the gold standard in evidenced based medicine context. They offer the most reliable evidence because of their internal validity. However, RCT is more appropriate to study drugs. Complex interventions, like acupuncture and surgery, have been suffering with this evaluation model to measure efficacy of interventions(138).

It is known that many factors contribute to patients’ recovery. The process of cure is complex. Any therapeutic result is composed by specific and nonspecific effects. Treatment effects are the sum of these two factors plus the natural evolution of the diseases. Placebo effects are present in every treatment and promote physiological changes in the human body(139). Psychological, socio-cultural, emotional, positive expectations of the patient, patients’ beliefs and the total context behind patients play an important role in the cure process(140, 141). The individualization of the treatment, the high presence of the doctors in patients’ life (in our trials patients had contact with

physicians over 20 times in 4 months), the credibility of the institution where trials were developed (UNICAMP), the fascination promoted by Oriental medicine and nonconventional therapies in the Westerner's mind, the invasive intervention (needling) and the high presence of the headache diary in patients' life certainly influence the results of these trials(142). Everything leads to the probable high nonspecific effects of the acupuncture intervention. However, it is not true to say that acupuncture does not work. Results displayed in many figures in this thesis appointed to the expressive effects of the acupuncture intervention. In fact, what is not clear yet is the real weight of the specific and nonspecific effects when this technical approach was applied. Indubitably, superficial needling promotes neurophysiological responses. Physiological effects of needling in the "proper" locations or anywhere have to be taken into account (143). Any stimulus in the skin stimulates the connective tissue and peripheral nervous system(87). The interaction between them promotes many physiological effects (144, 145). Massage promotes responses of the neuroendocrine and immune system (146-148). Invasive procedures promote more results than non-invasive interventions(120). Many trials to test drugs evidenced this fact.

Could the lack of statistical significant differences between sham and real acupuncture groups in the majority of the well-designed trials, almost in all measured variables be understood by the neuroscience? Probably, this response exists, but it was not the objective of the present trials and thesis. Nevertheless, it would be a challenge for researchers in their future trials. It should be a goal to develop acupuncture trials based on modern concepts.

Certainly, a major knowledge of the molecular and neurophysiological mechanisms over the pain control systems could elucidate the majority of the results in acupuncture trials(149). All kinds of treatment have no specific effects. But, if acupuncture has specific effects, it could not be explained by the traditional Chinese medicine knowledge basis. High advancement of neuroscience in the last decades has made many contributions to better understand the probable mechanisms of action of the acupuncture intervention(149). "Neuroscience-based framework is vital" to understand the effects of acupuncture(149). There is no reason to hold on our medical practices and knowledge in non-scientific grounds. Medical acupuncturists and acupuncture practitioners have to open their minds and disrupt the high force of the tradition in order to promote advances in acupuncture knowledge to benefit patients.

7. LIMITATIONS AND ADVANTAGES OF THESE TRIALS

1) The strict inclusion and exclusion criteria contributed to the fact that both trials had very selected sample including less than 9% of the candidate population. Before the scheduling evaluation by a neurologist, some inclusion and exclusion criteria were verified by research staff. Many patients were excluded before the neurologist evaluation. They are not included in the flow chart of both trials. The total of patients evaluated by neurologist was 778 patients. Only 68 were randomized, about 8.75% of the total. Most exclusion was because patients had other types of headache. The majority of them had chronic migraine or chronic tension-type headache or they were using medications for migraine prophylaxis or depression. See Figure 1 and Figure 12.

2) Patients were evaluated by a neurologist specialized in headache twice before being included in these trials. The patients screening by qualified neurologist and the adoption of the headache diaries during the baseline period certainly contributed for a better selection of the patients.

3) Media resources were used to recruit volunteers for trials. It is probable that the majority of people tried to participate in the trials because they believed that any treatment done in this important university hospital in Brazil (Clinic Hospital of the UNICAMP) could offer good results. Therefore, the patient's belief associated with a high expectation of great results could not be excluded as a factor that increased the responses.

4) Several factors could contribute for few statistical significant differences between real and sham acupuncture groups. They are: great inter-groups variability, small sample size, type of control group adopted as sham acupuncture in these trials (minimal acupuncture in true acupuncture points) as well as the strong placebo effects identified in all kinds of headache trials(129) and acupuncture trials(3).

5) The reported research project was idealized when the majority of the published trials had many shortcomings and controversial results. Therefore, at that time, the role that acupuncture would play in migraine prophylaxis was unknown(1). The researcher's major goal through these present trials was to reach higher methodological quality to

better investigate the reported question. To plan these trials, authors used guidelines from the International Headache Society(11), the World Health Organization(17), the Acupuncture Consensus Conference of the National Institutes of Health (USA)(18), the International Acupuncture Research Forum(19), and many articles about migraine and acupuncture research. Methodological quality was tested using the Jadad scale (13). Both trials reached the maximal punctuation, 5 points each.

6) The research team was composed of experienced neurologist, medical acupuncturist, epidemiologist, clinical pharmacologist and statisticians. The blinding of all the team (except the medical acupuncturist) was preserved up to the end of the statistical analysis. In both trials, all statistical analysis was done over 90% or more of the real data. More than 90% of the patients filled out their headache diaries up to the 6th month after treatment period. Probably, as a consequence of these factors, the small size of the samples did not prevent them from reaching very similar results met by larger and high quality migraine trials recently published (99, 100). Gluud stated in an article that “small randomized trials of good methodological quality may predict results of larger trial”(150).

8. CONCLUSIONS

1) Few statistical significant differences were observed between real and sham acupuncture groups in Trial 1. Real acupuncture group showed faster response to control the frequency of migraine attacks and associated symptoms than results showed for trials testing drugs for migraine prophylaxis. Nevertheless, differences between groups were not persistent with the advancing of the treatment. However, almost all variables studied showed progressive improvement, but with no statistical significant differences between groups.

2) No statistical significant differences appeared between real and sham acupuncture groups in Trial 2.

3) No statistical significant differences between groups in all variables evaluated in Trial 2 could be related with the therapeutic scheme used. In Trial 1, patients were treated with individualized treatment as recommended by the traditional Chinese theory. Better results were reached in Trial 1 where the individualized treatment was adopted.

4) Improvements in the sham acupuncture groups in both trials were superior to the expected effects for placebo in trials to test drugs for migraine prophylaxis. Improvements in the sham group were probably a consequence of the model of sham group adopted, sham with penetrative needling. Certainly, superficial penetrate needling stimulates the peripheral nervous system promoting response in the pain control regulation of the central nervous system. Effects of sham acupuncture have specific and non-specific components. Therefore, in future studies the inclusion of other sort of control group is advisable. Trials should also be longer to minimize the placebo effects.

5) Statistical analysis within each group showed improvement of most of the studied variables. However, these progressive improvements of most variables evaluated reduced or finished after the interruption of the acupuncture sessions. Nevertheless, effects reached were maintained for a long time after the last acupuncture session, six months. The long lasting effects were probably a consequence of the physiological and placebo factors.

6) The improvement of the sham group contributes to raise the doubt about the importance of the TCM rules to choose points to treat patients. Superficial needling without using the TCM rules has effects to prevent migraine attacks superior than to the expected for placebo controls. If the results of these trials were true, the field of the acupuncture practice has to be better evaluated. Why use more aggressive technical approach and complicated theory basis if results could be reached with a less invasive technique (minimal acupuncture) without any complex reasoning?

7) Several factors could contribute for few statistical significant differences between real and sham acupuncture groups. In addition to the factors mentioned previously, other aspects could also have influenced the few statistically significant differences between real and sham acupuncture, i.e., great inter-groups variability, small sample size, acupuncture points adopted as sham treatment, as well as the strong placebo effects identified in all kinds of headache and acupuncture trials.

8) The neurophysiological pathways could better explain the reason why the superficial stimulation of the skin can promote improvement of the pain in patients with migraine. It would be interesting to plan future trials thinking about acupuncture treatments based on neuroscience knowledge.

9) These trials confirm literature data that acupuncture is a safe procedure when practiced by qualified professionals. Adverse events were rare and all of them could be classified as minor events.

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APPENDIX

FACULDADE DE CIÊNCIAS MÉDICAS
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PARECER PROJETO 90/2.000

I- IDENTIFICAÇÃO:

PROJETO: "AVALIAÇÃO DA EFICÁCIA TERAPÊUTICA DA ACUPUNTURA NA PROFILAXIA DAS CRISES DE MIGRÂNEA."
PESQUISADOR RESPONSÁVEL: Jayme Antunes Maciel Júnior/Jerusa Alecrin Andrade
INSTITUIÇÃO: Departamento de Neurologia/FCM/UNICAMP
APRESENTAÇÃO AO CEP : 21/03/2.000

II- PARECER CEP

O Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da UNICAMP, após acatar os pareceres dos membros-relatores previamente designados para o presente caso e atendendo todos os dispositivos das Resoluções 196/96 e 251/97, bem como ter aprovado todos os anexos incluídos na Pesquisa, resolve aprovar sem restrições o Protocolo de Pesquisa supracitado.

III- HOMOLOGAÇÃO

A ser homologado na V Reunião Ordinária de 13 de junho de 2.000.

Prof. Dr. SEBASTIÃO ARAÚJO
VICE-PRESIDENTE do COMITÊ DE ÉTICA EM PESQUISA
FCM / UNICAMP

UAB Escola de Postgrau
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Vista la instància presentada per na Jerusa Alecrim Andrade de sol·licitud de presentació de tesi doctoral com a compendi de publicacions,

De conformitat amb el Text Refós de la Normativa de Doctorat aprovat el 27 de febrer de 2003 (última modificació març de 2006) pel Consell de Govern,

RESOLC

Acceptar la presentació de la tesi doctoral de Jerusa Alecrim Andrade com a compendi de publicacions amb els següents articles:

- Alecrim-Andrade, J.; Maciel-Júnior, J.A.; Carnè, X.; Severiono Vasconelos, G.M.; Rodrigues Correa-Filho, H. "Acupuncture in Migraine Prevention. A Randomized Sham Controlled Study With 6-months Posttreatment Follow-up". *Clin J Pain* (vol. 24 – n. 2 – febrer del 2008): 98-105.
- Alecrim-Andrade, J.; Maciel-Júnior, J.A.; Cladellas, X.C.; Correa-Filho, H.R.; Machado, H.C. "Acupuncture in migraine prophylaxis: a randomized sham-controlled trial". *Cephalalgia* (2006, n. 26): 520-529.

La Subcomissió de Postgrau de la Comissió d'Afers Acadèmics,
Per delegació

Carles JAIME CARDIEL
Delegat del Rector per a Doctorat

Bellaterra (Cerdanyola del Vallès), 3 d'abril de 2008

Contra aquesta resolució, que no esgota la via administrativa, les persones interessades poden interposar recurs d'alçada davant l'Excm. i Magfc. Rector de la UAB, en el termini d'un mes, a comptar des del dia següent a la recepció d'aquesta notificació o, si s'escau, des d'un mes, a comptar des del dia següent de la seva publicació, de conformitat amb el que preveu l'article 115 de la Llei 30/1992, de 26 de novembre, de Règim Jurídic de les Administracions Públiques i del Procediment Administratiu Comú, modificada per la Llei 4/1999, de 13 de gener"

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AMBULATÓRIO DE CEFALÉIAS E ALGIAS CRANIOFACIAIS
PESQUISA: ACUPUNTURA EM MIGRÂNEA
DEPARTAMENTO DE NEUROLOGIA
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Informações sobre a pesquisa: *Avaliação da Eficácia Terapêutica da Acupuntura na Profilaxia das Crises de Migrânea*

Estamos realizando no Ambulatório de Cefaléia do Hospital das Clínicas da UNICAMP uma pesquisa para avaliar a eficácia terapêutica da Acupuntura no tratamento da migrânea (enxaqueca). A acupuntura é um tratamento médico originado na China e que consiste na colocação de finas agulhas em algumas partes do corpo para obtenção do alívio de determinados males e, neste caso, para diminuição da intensidade da dor e redução no número das crises de "enxaqueca" e duração das mesmas. O objetivo deste estudo é conseguir provar que a acupuntura é um tratamento eficaz na prevenção das crises de enxaqueca e não apresenta as contra-indicações e efeitos colaterais dos medicamentos comumente usados no tratamento desta doença. A importância deste estudo também consiste no fato de que ainda não foram encontrados medicamentos que sejam eficazes em prevenir as crises de enxaqueca em cerca de 40% das pessoas que sofrem desta doença, além do que, são muitos os pacientes que não toleram os efeitos colaterais dos medicamentos atualmente utilizados.

Serão selecionados pacientes para serem submetidos a dois tipos de tratamentos com acupuntura, sendo um deles, sem eficácia terapêutica (placebo) e o outro com eficácia. A participação na pesquisa terá caráter voluntário. Os pacientes que ingressarem no estudo terão que comparecer ao Hospital das Clínicas cerca de 20 vezes num período de 10 meses. Cada paciente será avaliado pelo médico neurologista Dr. Jayme Antunes Maciel Júnior por 4 vezes e serão feitas 16 sessões de acupuntura pela médica-acupuntora Dra. Jerusa Alecrim Andrade, além de uma avaliação inicial. Em cada sessão de acupuntura serão introduzidas pequenas agulhas em diversas partes do corpo de cada paciente, sendo que estas agulhas serão estéreis e descartáveis. Todos os dados clínicos e pessoais dos pacientes participantes da pesquisa serão mantidos em caráter confidencial. Será oferecido aos pacientes após cada sessão de acupuntura ou consulta o valor referente a 2 a 4 passagens de ônibus locais, visto que o comparecimento ao ambulatório com maior freqüência somente se dará em função da pesquisa. Durante a realização do estudo os pacientes poderão fazer uso de medicamentos analgésicos e antiinflamatórios caso apresentem crises dolorosas, sendo que uma lista com os medicamentos que poderão ser usados será entregue

por ocasião da assinatura do Consentimento Pós-Informado (documento de adesão ao estudo com assinatura do paciente participante e dos responsáveis pela pesquisa). Também será entregue uma lista com os medicamentos que não poderão ser consumidos durante o estudo, pois o seu uso alteraria o resultado da pesquisa. Esta lista deverá ser apresentada aos médicos quando o paciente tenha necessidade de fazer alguma consulta ou tratamento médico durante todo o período em que esteja no estudo. Caso o paciente tenha necessidade premente de fazer uso de algum medicamento da referida lista o fato deverá ser comunicado aos responsáveis pela pesquisa para que seja avaliada a viabilidade de permanência do participante no estudo.

Os pacientes selecionados poderão entrar no estudo após a exposição verbal e escrita feita pelo médico neurologista. A participação na pesquisa será voluntária e, as pessoas que aceitem participar, poderão se retirar do estudo no momento em que desejarem. Reiteramos que não será prejudicada a continuidade do tratamento destes pacientes no Ambulatório de Cefaléia do Hospital das Clínicas da UNICAMP.

A acupuntura, como qualquer outro tratamento, apresenta vantagens e inconvenientes. Temos como vantagens ser um tratamento de efeito prolongado, o paciente não precisa ingerir nenhum medicamento, portanto não há risco de interação com outros medicamentos. Como inconvenientes, a necessidade do paciente ter que se deslocar semanalmente para receber o tratamento durante um período, a sensação de desconforto ao serem introduzidas as agulhas em diversas regiões do corpo, eventualmente, o aparecimento de pequenos hematomas no local da punção e, muito raramente, reação alérgica ao material das agulhas.

Após o término da pesquisa, cada paciente incluído no estudo receberá o tratamento que seja mais benéfico, ou seja, no caso de que a hipótese da pesquisa seja confirmada, os pacientes do grupo de acupuntura sham (placebo) terão prioridade para serem tratados com acupuntura no Ambulatório de Cefaléia.

Serão responsáveis pelo estudo o Professor Dr. Jayme Antunes Maciel Júnior e a Dra. Jerusa Alecrim Andrade. Em caso de necessidade, os pacientes participantes da pesquisa poderão contactá-los no Departamento de Neurologia da Faculdade de Ciências Médicas da UNICAMP ou nos telefones expostos adiante: na residência / consultório da Dra. Jerusa nos telefone 19-3242.1492/ 9602-2631 e do Dr.Jayme Maciel 19 32331562/ 32332247/ 9772.1607.

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UNICAMP

Termo de Consentimento Pós-Informação de Participação na Pesquisa.

Projeto : AVALIAÇÃO DA EFICÁCIA TERAPÊUTICA DA ACUPUNTURA NA PROFILAXIA DAS CRISES DE MIGRÂNEA

Responsáveis pela Pesquisa :

♠ Jayme Antunes Maciel Júnior, professor Associado do Departamento de Neurologia da Faculdade de Ciências Médicas da Universidade Estadual de Campinas.

Telefones: (19) 3233.1562 / 3788.7990 / 3788.7994 / 3233.2247

♠ Jerusa Alecrim Andrade, médica, mestre em Clínica Médica, especializada em Acupuntura há 9 anos.

Telefones: (19) 3231.3664 / 3234.4847 / 3242.1492

Dados de Identificação do Paciente

Nome: Idade:

Data de Nasc. : Documento de Identidade (RG) :

Número de Registro no HC :

Endereço :

Cidade :

CEP : Telefone :

Estamos realizando no Ambulatório de Cefaléia do Hospital de Clínicas da UNICAMP uma pesquisa para avaliar a eficácia terapêutica da Acupuntura no tratamento da migrânea (enxaqueca). A acupuntura é um tratamento médico originado na China e que consiste na colocação de finas agulhas em algumas partes do corpo para obtenção do alívio de determinados males e, neste caso, para diminuição da intensidade da dor e redução no número das crises de

"enxaqueca". O objetivo deste estudo é conseguir provar que a acupuntura é um tratamento eficaz na prevenção das crises de enxaqueca e não apresenta as contra-indicações e efeitos colaterais dos medicamentos comumente usados no tratamento desta doença. A importância deste estudo também consiste no fato de que ainda não foram encontrados medicamentos que sejam eficazes em prevenir as crises de enxaqueca em cerca de 40% das pessoas que sofrem desta doença, além do que, são muitos os pacientes que não toleram os efeitos colaterais dos medicamentos.

Serão selecionados pacientes para serem submetidos a dois tipos de tratamentos com acupuntura, sendo um deles, sem eficácia terapêutica (placebo) e o outro com eficácia (acupuntura "verdadeira"). A participação na pesquisa terá caráter voluntário. Os pacientes que ingressarem no estudo terão que comparecer ao Hospital das Clínicas cerca de 20 vezes num período de 10 meses. Cada paciente será avaliado pelo médico neurologista Dr. Jayme Antunes Maciel Júnior por 4 vezes e serão feitas 16 sessões de acupuntura pela médica-acupuntora Dra. Jerusa Alecrim Andrade, além de uma avaliação inicial. Em cada sessão de acupuntura serão introduzidas pequenas agulhas em diversas partes do corpo de cada paciente, sendo que estas agulhas serão estéreis e descartáveis. Será oferecido aos pacientes após cada sessão de acupuntura ou consulta o valor referente a 2 a 4 passagens de ônibus locais, visto que o comparecimento ao ambulatório com maior freqüência somente se dará em função da pesquisa. Durante a realização do estudo os pacientes poderão fazer uso de medicamentos analgésicos e antiinflamatórios caso apresentem crises dolorosas, sendo que uma lista com os medicamentos que poderão ser usados será entregue por ocasião da assinatura deste Consentimento Pós-Informado (documento de adesão ao estudo com assinatura do paciente participante e dos responsáveis pela pesquisa).

A acupuntura, como qualquer outro tratamento, apresenta vantagens e inconvenientes. Temos como vantagens ser um tratamento de efeito prolongado, o paciente não precisa ingerir nenhum medicamento, portanto não há risco de interação com outros medicamentos. Como inconvenientes, a necessidade do paciente ter que se deslocar semanalmente para receber o tratamento durante um período que neste caso será de 12 semanas, a sensação de desconforto ao serem introduzidas as agulhas em diversas regiões do corpo, eventualmente, o aparecimento de

pequenos hematomas no local da punção e, muito raramente, reação alérgica ao material das agulhas.

Com este estudo esperamos que os pacientes que sejam tratados com a acupuntura "verdadeira", obtenham uma redução no número de crises de migrânea, na duração e na intensidade das mesmas, sem que para isso seja necessário o uso de medicamentos.

No caso dos pacientes que apresentam duas ou mais crises de migrânea mensalmente, seria indicada a profilaxia medicamentosa das crises. Para o tratamento profilático das crises são usados os seguintes medicamentos: antidepressivos tricíclicos, betabloqueadores adrenérgicos (principalmente o propranolol e nadolol), valproato de sódio, bloqueadores dos canais de cálcio não seletivos (flunarizina), a metisergida, o pizotifeno, a nefazodona e a sertralina. Estas seriam as opções de tratamento caso você não ingresse nesta pesquisa.

Os pacientes que não aceitem participar da pesquisa, não terão o seu tratamento prejudicado no Ambulatório de Cefaléia do Hospital de Clínicas da Unicamp.

Os pacientes participantes da pesquisa poderão retirar-se da mesma a qualquer tempo, no entanto, solicitamos, por gentileza, que tal fato nos seja informado.

Qualquer dúvida ou problemas decorrentes da pesquisa, que porventura surja no decorrer da mesma, poderá ser solicitado um maior esclarecimento aos médicos pesquisadores, cujos telefones constam no início deste documento.

Todos os dados clínicos e pessoais dos pacientes participantes da pesquisa serão mantidos em caráter confidencial. Em caso de publicação da pesquisa, a identidade dos participantes será ocultada.

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Caso os pacientes participantes da pesquisa tenham alguma reclamação a respeito da mesma, deverá ser comunicada ao ***Comitê de Ética em Pesquisa*** da Unicamp, no telefone : 19-788.8936.

Eu,_____ ,RG_____ declaro que:

1) Li o texto contendo informações sobre a pesquisa "Avaliação da Eficácia Terapêutica da Acupuntura no Tratamento da Migrânea".
2) Recebi informações verbais e por escrito sobre a pesquisa.
3) Pude tirar minhas dúvidas com o Dr. Jayme Antunes Maciel Júnior.
4) Compreendo que minha participação no estudo é voluntária.
5) Estou ciente de que posso retirar-me da pesquisa quando queira, sem que tenha que dar explicações e sem que esta atitude repercuta no meu atendimento no Ambulatório de Cefaléia e Algias Craniofaciais do Hospital de Clínicas da UNICAMP.
   Assim sendo, anuncio minha concordância em participar desta pesquisa.

Data: ___/___/___. _____

Assinatura do paciente

_____

Assinatura do pesquisador que obteve o Consentimento

AMBULATÓRIO DE CEFALÉIAS E ALGIAS CRANIOFACIAIS
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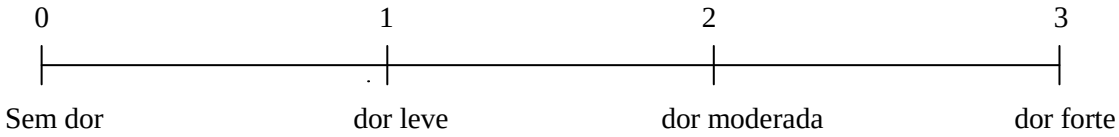
Diário de Cefaléia

Nome do Paciente:_____ HC_____

Data da Avaliação Inicial : ____/____/____

Data de início deste Diário : ___/___/____



Janeiro 2003 / Fevereiro 2003

DIA																														
MANHÃ																														
TARDE																														
NOITE																														
MENSTRUAÇÃO																														
MEDICAMENTOS																														
Náuseas																														
Vômitos																														

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Diário de Cefaléia 1

Nome do Paciente:_____ HC_____

Data de início deste Diário: ___/___/____

2003 / 2003

DIA																											
MADRUGADA (00 - 06h)																											
MANHÃ (6-12h)																											
TARDE (12-18h)																											
NOITE (18-24h)																											
MENSTRUAÇÃO																											
MEDICAMENTOS																											
Náuseas																											
Vômitos																											
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Avaliação do Tratamento com Acupuntura

Paciente:

Data do início da Acupuntura: ...../...../.....

Data de término da Acupuntura: ...../...../.....

Número de sessões realizadas: .....

Data de resposta desta avaliação: ...../...../.....

1) Analisando o tratamento de Acupuntura que você recebeu nos últimos 3 meses em relação aos outros tratamentos de enxaqueca que você tenha se submetido anteriormente (medicamentosos ou não), você se trataria com acupuntura novamente?

□ (1) sim

□ (2) não

2) De um modo geral, como você classifica o tratamento de acupuntura que você recebeu para a prevenção das suas crises de enxaqueca?
□ Ruim

□ Regular

□ Bom

□ Muito Bom

□ Excelente

3) Você saberia nos informar qual tipo de tratamento recebeu na pesquisa?

□ (1) Acupuntura Real

□ (2) Acupuntura Placebo

□ (3) Não sabe

Cephalalgia

Abstracts of the XII Congress of the International Headache Society/*IHC* 2005

Kyoto, Japan
9–12 October 2005

Results Of 64 migraineurs in 1989, 54 had low-frequency migraine (1–14 days/year) and 10 had high-frequency migraine (>14 days/year). At follow-up, 27 migraineurs (42%) experienced remission (0 days/year), 24 (38%) had low-frequency migraine, while 13 (20%) experienced poor outcome (>14 days/year). Poor outcome was observed in 13% (7) of subjects with low frequency and 60% (6) with high frequency at baseline. Prognostic factors for poor outcome of migraine were high baseline migraine frequency and age at onset before 20 years.
Conclusion Clinical assessment of headache status at baseline and follow-up ensured high validity. Generally, the prognosis of migraine is favourable but increased focus should be directed towards the minority at risk for progression.
Keywords: migraine, prognosis, follow-up studies, epidemiology

G029

Prevalence of migraine and non-migraine headaches in female medical workers

Megumi Takeuchi, Yuko Shimizu & Makoto Iwata
Department of Neurology, Neurological Institute, Tokyo Women's Medical University, Japan

Object This study was carried out to assess the prevalence of chronic headaches in female medical workers.
Subject and methods Data on headaches were obtained through a self-administered questionnaire distributed among 1584 female employees working in four hospitals and three pharmacies, during January and May of 2003. Of the 1584 subjects, 1410 responded (89.0%). Subjects included 106 doctors, 1080 nurses, 105 pharmacists and 119 others. Subjects ranged in age from 19 to 65 with a mean age of 29.5 years.
Results Experience of chronic headache was noted in 64.5% of the subjects without significant differences between occupations. According to the International Headache Society criteria, 6.2% of the samples were classified as having migraine and 37.3% as tension headache. The age distribution of migraine was 4.9% under 30, 10.3% in their 30s, 10.6% in their 40s, and 2.1% over 50. Daily life activities or work productivity were affected in 61.4% of migraineurs. Only 14% of subjects with headaches consult a doctor or go to hospital regularly, and 60% are using OTC. Recognition of triptans was as low as 9.2% of nurses compared with 62.5% of doctors and 69.7% of pharmacists.
Conclusion Headache sufferers, even amongst medical workers, are underdiagnosed and should be encouraged to receive the proper diagnosis and better management

G030

Efficacy of acupuncture in migraine attack prophylaxis: a randomized sham-controlled trial

Jerusa Alecrim-Andrade[1,2], Jayme Antunes Maciel-Júnior[2], Xavier Carne i Cladellas[3], Heleno Rodrigues Correa-Filho[2], Helymar Costa Machado MSc[2] & Geraldo Magela Severino Vasconcelos[2]
[1]*Autonomous University of Barcelona, Barcelona, Spain,* [2]*State University of Campinas, Campinas, Brazil, and* [3]*Clinical Pharmacology Unit, Hospital Clinic, Barcelona, Spain*

Objective To evaluate acupuncture efficacy in preventing migraine attacks.
Methods Sixty-two migraine patients were randomized to the real or sham acupuncture groups. Both groups were treated with 16 acupuncture sessions in 12 weeks. Treatment was individualized in the real acupuncture group following the Traditional Chinese Medicine (TCM) principles and minimal acupuncture was used in the sham acupuncture group not respecting the TCM rules.
Results The first primary endpoints adopted, the percentage of patients with reduction ≥ 50% in their migraine attack frequency, showed no difference between groups. The second, the total of migraine days, showed that real acupuncture group improved with a statistically significant difference in all treatment periods ($P = 0.013$). Serious secondary parameters evaluated showed the improvement of the real acupuncture group with statistically significant difference, such as: the total duration of migraine pain in hours per 4-week headache diary (0.009); average duration of a migraine attack ($P = 0.017$); number of attacks ($P = 0.014$). There were no statistically significant differences between groups when the average headache severity, rate of rescue medication used as well as nausea and vomiting frequency were evaluated. Nevertheless, both groups improved in almost all parameters. No serious adverse events were reported.
Conclusion Individualized acupuncture should be an interesting option to reduce migraine attacks.
Keywords: acupuncture, migraine, prophylaxis, randomized controlled trial, efficacy

G031

The long- lasting effects of acupuncture treatment for migraine prophylaxis: 44 weeks' post-treatment follow-up

Jerusa Alecrim-Andrade[1,2], Jayme Antunes Maciel-Júnior[2], Xavier Carne i Cladellas[3], Heleno Rodrigues Correa-Filho[2], Helymar Costa Machado MSc[2] & Geraldo Magela Severino Vasconcelos[2]
[1]*Autonomous University of Barcelona, Barcelona, Spain,* [2]*State University of Campinas, Campinas, Brazil, and* [3]*Clinical Pharmacology Unit, Hospital Clinic, Barcelona, Spain*

Objective The objective of this present trial was to evaluate the long-lasting effects of acupuncture treatment for migraine prophylaxis.
Methods Sixty-two migraine patients were randomized to the real or sham acupuncture groups and treated with 16 acupuncture sessions for 12 weeks. Treatment was individualized in the real acupuncture group and minimal standard acupuncture was used in the sham acupuncture group. The post-treatment follow-up was done for 44 weeks with headache diaries.

GO30

Efficacy of acupuncture in migraine attacks prophylaxis: A randomized sham controlled trial

Jerusa Alecrim-Andrade*[1,2]; Jayme Antunes Maciel-Júnior [2]; Xavier Carnè i Cladellas [3]; Heleno Rodrigues Correa-Filho [2]; Helymar Costa Machado[2] ; Geraldo Magela Severino Vasconcelos [2].

[1]Autonomous University of Barcelona, Barcelona, Spain,[2] State University of Campinas, Campinas, Brazil, [3]Clinical Pharmacology Unit, Hospital Clinic, Barcelona, Spain.

jalecrim@uol.com.br

Introduction

Acupuncture could be defined as a practice when needles were inserted in the body to treat a large kind of signs, symptoms and diseases. Despite the acupuncture's role to prevent migraine attacks is not yet clearly established, it is widely used for migraine sufferers. Trials results are controversial. One of the great troubles to reach this aim is a consequence of the acupuncture theory basis and practice are not homogeneous in any part of the world.

Objective

To evaluate the efficacy of the sort of acupuncture - individualized treatment based on the Traditional Chinese Medicine (TCM) principles - to prevent migraine attacks.

Design

Sixty-two migraine patients were randomized to the real or sham acupuncture groups. Both groups were treated with 16 acupuncture sessions in twelve weeks. Treatment was individualized in the real acupuncture group following the TCM principles. Minimal acupuncture was used in the sham acupuncture group. In this trial, minimal acupuncture was done in the acupuncture points not strictly related to headache treatment in the literature, not respecting the TCM rules, as well as, the insertion of the needles were very superficial, with the needle almost falling out.

Results

The first primary endpoint adopted was the percentage of patients with reduction ≥50% in their migraine attacks frequency and showed no difference between groups. The second, the total of migraine days, showed that real acupuncture group improved with statistical significant difference in all treatment period (p=0.013). Serious secondary parameters evaluated showed the improvement of the real acupuncture group with statistical significant difference, such as: the total duration of migraine pain in hours per diary (0.009), average duration of a migraine attack (p=0.017), attacks number (p=0.014). There were no statistical significant differences between groups when the average headache severity, rate of rescue medication used as well as nausea and vomiting frequency were evaluated. Nevertheless, both groups improved in almost all parameters. No serious adverse events were reported.

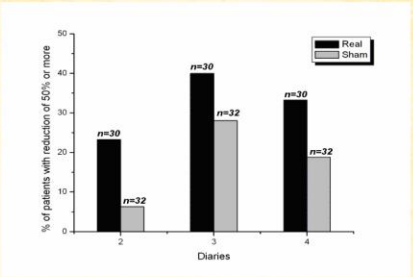

Figure 1 Percentage of responders (reduction ≥50% in migraine attacks frequency) in each diary (4-weeks each one) compared with the baseline period (Diary 1) in the Real and the Sham acupuncture groups. Diary 2 = week 1 to 4 of the treatment, Diary 3 = week 5 to 8 of the treatment, Diary 4 = week 9 to 12 of the treatment.

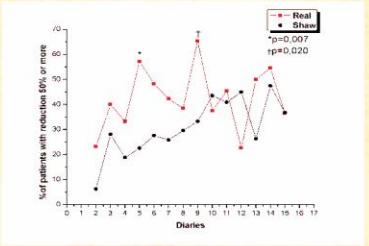

Figure 2 Duration mean of each attack in hours per diary (4-weeks each one). Diary 1 = the baseline period, Diary 2 = week 1 to 4 of the treatment, Diary 3 = week 5 to 8 of the treatment, Diary 4 = week 9 to 12 of the treatment. The p value is referred to the differences between groups.

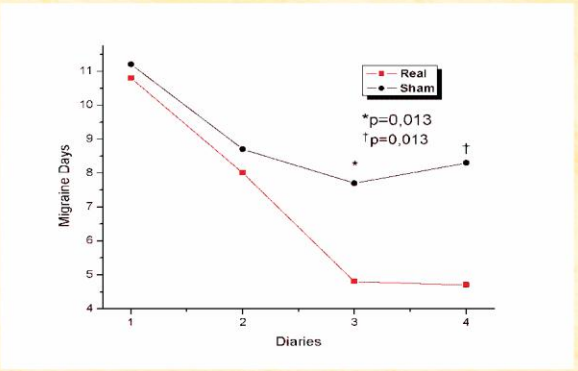

Figure 3 Total of migraine days in each diary (4 weeks) in the Real and the Sham acupuncture groups. Diary 1 = the baseline period, Diary 2 = week 1 to 4 of the treatment, Diary 3 = week 5 to 8 of the treatment, Diary 4 = week 9 to 12 of the treatment. The p value is referred to the differences between groups.

Discussion

Results showed that statistical significant differences between groups appeared in almost all pain parameters evaluated from the 4 to 12th weeks of the treatment (3rd and 4th diaries). The real acupuncture group improved more than sham group.

Control group is another great problem to acupuncture protocols. The most of sham acupuncture used in trials are not an "inert placebo". In the present trial, analysis within each group compared with the baseline period demonstrated that improvement happened in both groups with statistical significant differences in all treatment period measured (2nd, 3rd and 4th diaries). Nevertheless, it is important to highlight that the percentage of responders in this trial was in the expected response range for active and placebo groups in clinical essays testing drugs for migraine prophylaxis.

Conclusions

The present trial suggested that the individualized acupuncture following TCM principles should be an option to prevent migraine attacks. Trials with prophylactic drugs for migraine showed that their effects are often first noted at four weeks. The acupuncture effects seems to start faster than when prophylactic drugs are used.

References

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This trial was developed at the UNICAMP Clinical Hospital, into the Headache Clinic of the Neurology Department of the State University of Campinas, Brazil and was supported by a grant from the State of São Paulo Foundation Research (FAPESP - 00/09985-0).

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[1]*Autonomous University of Barcelona, Barcelona, Spain,* [2]*State University of Campinas, Campinas, Brazil, and* [3]*Clinical Pharmacology Unit, Hospital Clinic, Barcelona, Spain*

Objective The objective of this present trial was to evaluate the long-lasting effects of acupuncture treatment for migraine prophylaxis.
Methods Sixty-two migraine patients were randomized to the real or sham acupuncture groups and treated with 16 acupuncture sessions for 12 weeks. Treatment was individualized in the real acupuncture group and minimal standard acupuncture was used in the sham acupuncture group. The post-treatment follow-up was done for 44 weeks with headache diaries.

Results Fifty-three patients concluded follow-up for 20 weeks and only 41 completed 44 weeks. However, no additional change was observed between groups from the end of the treatment to the end of the follow-up period. The improvement observed in almost all parameters evaluated during the treatment period in both groups was preserved for all follow-up periods with little and expected variations. There were no statistically significant differences between groups in primary and secondary parameters evaluated ($P > 0.05$).

Conclusion The real and sham acupuncture groups maintained the effects reached in the treatment period. Therefore, acupuncture has long-lasting effects; nevertheless, there were no differences between groups.

Keywords: acupuncture, migraine, prophylaxis, randomized controlled trial, efficacy

G032

The prevalence of *Helicobacter pylori* and CagA-positive strains in patients with chronic headache

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Objective To explore the correlation of *Helicobacter pylori* (Hp) infection with the pathophysiology of chronic headache, we evaluated the presence of Hp infection in patients with migraine (MIG) in patients with tension-type headache (TH) and in headache-free control subjects (CTL). We also evaluated CagA-positive strains in Hp-positive patients and CTL subjects.

Methods ELISA was used to determine the presence of Hp infection in 168 patients with MIG, 77 patients with TH, and in 163 CTL. Specific serological IgG against CagA in infected subjects were detected using ELISA.

Results The prevalence of Hp infection was 40% in patients with MIG, 43% in patients with TH and 28% in CTL subjects. The prevalence of Hp infection was significantly higher in the patients with MIG than in CTL subjects ($P < 0.05$). Classifying the prevalence of Hp infection into groups according to age in MIG patients and CTL subjects who were under 40 years of age, the prevalence of Hp infection was significantly higher in patients with MIG than in CTL subjects ($P < 0.05$). We evaluated CagA-positive strains in Hp-positive patients. No significant differences in CagA-positive strains were found between samples.

Conclusion Our results show a direct correlation between Hp infection and migraine, especially in younger patients.

Keywords: migraine, tension-type headache, *Helicobacter pylori*, CagA

G033

The effect of preventive treatment with topiramate in chronic migraine psychiatric comorbidity

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Introduction Psychiatric comorbidity in chronic migraine (CM) is one of the most important management issues. Anxiety and depression can be found in up to 75% of cases. Little is known about the effect of migraine preventive treatment in comorbid disorders.

Objectives To analyse the effect of chronic migraine prevention with topiramate in psychiatric comorbidity.

Methods Sixty-four patients were enrolled in the study. Fifty patients completed criteria for analysis. An intention-to-treat method was used for the analysis. All patients met diagnostic criteria for chronic migraine according to the IHS-2004. Eighty-four percent of patients had at least one DSM-IV diagnosis, 76% anxiety, 50% mood disorders. Trait-state anxiety, HAM-anxiety, HAM-depression and Beck scores were used at baseline, titration and follow-up visits.

Results Frequency, intensity and duration of migraine attacks were significantly reduced. Mood and anxiety scales significantly reduced ($P < 0.001$) with topiramate treatment (median dose 100 mg), when comparing the initial visit with month 1, 2 and 3 data. The effect was already significant ($P < 0.001$) at the first month of treatment.

Discussion/conclusion Patients with chronic migraine and psychiatric comorbidity treated with topiramate reduced significantly their anxiety and depression levels in addition to their migraine attacks.

G034

Epidemiology of chronic daily headache in Koreans—the Korean Migraine Study

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Background Chronic daily headache (CDH) refers to a frequent headache syndrome (≥15 days/month). Although CDH has a great impact on the quality of life, little has been reported on Korean people.

Objective To investigate the prevalence of CDH and its causative factors in the general population in Korea.

Methods The Korean Migraine Study is the first government-supported epidemiological survey of headache disorders in the Korean population. A door-to-door survey was conducted by direct interviews among people aged between 15 and 65 years. Stratified systematic household sampling was performed and 2038 subjects (1032 men, 1006 women) were recruited. We used a standardized questionnaire using the algorithm based on the ICHD-II. Demographic, clinical and risk factors were surveyed.

Results The prevalence of CDH was 1.47% (M 0.97%, F 1.99%) and increased with age in both genders with the peak rate (7.78%) in women aged in the 60s. Most CDH subjects

GO31

The long- lasting effects of acupuncture treatment for migraine prophylaxis: 44 weeks post-treatment follow-up

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Introduction

Migraine is a considerable socioeconomic burden, with a high cost to its sufferers. In western countries 1-year migraine prevalence in adults varies from 6% to 18%. These factors had increased the need to improve our understanding of the best treatment for this condition. Migraine prophylaxis could be enriched by using natural processes and other clinical interventions. Patients with migraine had looked for these approaches on the lasts years. Some trials had identified that acupuncture has effects in migraine attacks prevention. The long-lasting effects had been referred too.

Objective

The objective of this present trial was to evaluate the long-lasting effects after the acupuncture treatment in migraine prophylaxis.

Design

Sixty-two migraine patients were randomized to the real or sham acupuncture groups. Both groups were treated with 16 acupuncture sessions in twelve weeks. Treatment was individualized in the real acupuncture group following the Traditional Chinese Medicine (TCM) principles. Minimal acupuncture was used in the sham acupuncture group not respecting the TCM rules. In this trial, minimal acupuncture was done in the acupuncture points not strictly related to headache treatment in the literature, as well as, the insertion of the needles were very superficial, with the needle almost falling out. The follow-up was done for 56 weeks with headache diaries (4-weeks each diary).

Results

Fifty-three patients (85.5%) concluded 20-weeks of the follow-up after treatment period and forty-one (66,1%) completed 44-weeks of the follow-up after treatment period. No additional change was observed between groups from the end of the treatment to the final of the follow-up period. Therefore no statistical significant differences appeared between groups in primary and secondary parameters evaluated (p>0.05). However, a slight improvement within each group was observed and preserved in almost all pain parameters evaluated from the final of the treatment up to the late follow-up period.

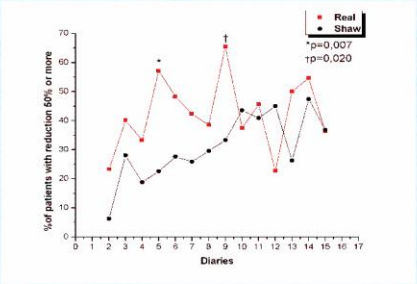

Figure 1 Percentage of responders (reduction ≥50% in migraine attacks frequency) in each diary (4 weeks) compared with the baseline period (Diary 1) in the Real and the Sham acupuncture groups. Diaries 2, 3 and 4 correspond to the treatment period (12 weeks). Diaries 5-15 correspond to the follow-up period (1st to 44th week after treatment). In this figure the p value is referred to the differences between groups.

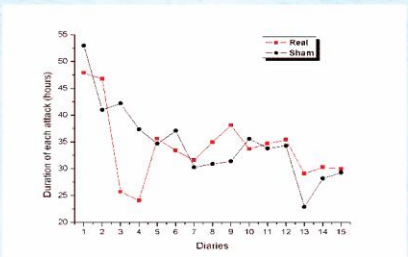

Figure 2 Mean duration of migraine attacks in each diary (4 weeks) in the Real and the Sham acupuncture groups. Diary 1 corresponds to baseline period (4 weeks). Diaries 2, 3 and 4 correspond to the treatment period (12 weeks). Diaries 5-15 correspond to the follow-up period (1st to 44th week after treatment).

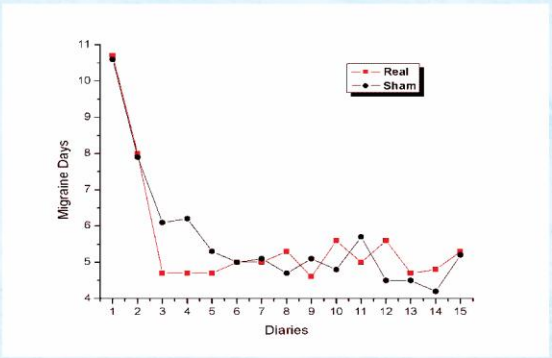

Figure3 Total of migraine days in each diary (4 weeks) in the Real and the Sham acupuncture groups. Diary 1 = baseline period (4 weeks), diaries 2, 3 and 4 correspond to the treatment period (12 weeks) and diaries 5-15 correspond to the follow-up period (1st to 44th week after treatment).

Discussion

Improvement happened in both groups in the treatment period; however the high one with the statistical significant difference was in the real acupuncture group. After the final of the treatment period the results had decreased slightly in the real acupuncture group and increased in the sham acupuncture group. The consequence of these changes was the disappearance of the statistical significant differences between groups.

The improvement rates of the both groups after the treatment period appointed that both types of acupuncture might play a role in migraine prophylaxis due to similar approach from physicians' role and context. Nevertheless no differences were observed between groups when analysis of the complete follow-up period was done together (treatment and post-treatment follow-up).

Few and expected variations appeared between diaries within each group (Figures 1, 2 and 3). It may be a result of the natural history of the illness.

Conclusions

Effects reached for both groups after the final of the treatment period up to the last week of the follow-up period were over of the expected results to the placebo in trials with drugs for migraine prophylaxis. These effects were maintained up to 44-weeks after the treatment period. Therefore, acupuncture has long-lasting effects. Nevertheless there were no differences between groups.

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This trial was developed at the UNICAMP Clinical Hospital, into the Headache Clinic of the Neurology Department of the State University of Campinas, Brazil and was supported by a grant from the State of São Paulo Foundation Research