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Does the Choice of Placebo Determine the Results of Clinical Studies on Acupuncture?

A Meta-Analysis of 100 Clinical Trials

Key Words

Acupuncture · Clinical trials · Sham acupuncture · Placebo · Meta-analysis · Research methodology

Summary

Objective: To establish whether the choice of the placebo treatment used may influence the outcomes of clinical trials on acupuncture or not. **Design:** A meta-analysis of outcomes according to the choice of the placebo. Attention was focused on the placebo design of 117 clinical, controlled trials found after an extensive search. Studies comparing acupuncture to no treatment or a reference treatment were discarded from the analysis. A set of 90 publications could be classified into one of two groups: i) Clinical studies with sham acupuncture as placebo, which consists of needling outside the meridian, but near to classical acupoints. This group of 45 trials was classified as energetic placebo model (EPM). ii) 45 studies using a placebo treatment consisting of needling within a segmental zone far enough away from the active points were classified as neurophysiological or metameric placebo model (MPM). In both groups of studies the proportions of significant results and the distribution of outcomes characterized by nonsignificant results with improvements greater than 35% in both groups of patients were assessed by the chi-square test. **Results:** The proportion of meaningful results was significantly higher in the MPM group [73.33% (33/45)], while only 33.33% (15/45) of such results were found in the EPM group ($p < 0.03$). In the EPM group 24/30 studies showed nonsignificant results with improvements greater than 35% in both groups of patients, while in the MPM group only 20% (6/30) of studies with this outcome could be observed ($p < 0.05$). **Conclusion:** Studies using EPM as placebo failed more frequently to show any differences between real acupuncture and placebo treatment than those using MPM as placebo. On the other hand, sham acupuncture appears almost as active as 'real' acupuncture. These results suggest that the design and the way of performing the placebo procedure determine the outcome, i. e. success or failure of a clinical trial in obtaining differences among the patients groups, in case they actually exist.

Schlüsselwörter

Akupunktur · Klinische Studien · Unechte Akupunktur · Placebo · Metaanalyse · Forschungsmethodik

Zusammenfassung

Bestimmt die Art der Placebo-Akupunktur die Ergebnisse klinischer Studien? Eine Metaanalyse 100 klinischer Studien

Ziel: Zu zeigen, ob die Wahl der Placebo-Behandlung das Ergebnis klinischer Studien zur Akupunktur beeinflusst. **Design:** Eine Metaanalyse der Ergebnisse bei verschiedener Form des Placebos. Die Aufmerksamkeit galt der Form des Placebos in 117 kontrollierten klinischen Studien, die nach einer umfassenden Suche gefunden wurden. Studien, die Patienten mit Akupunkturbehandlung mit solchen, die nicht behandelt wurden oder eine Referenzbehandlung erhielten, verglichen, wurden von der Analyse ausgeschlossen. 90 Publikationen konnten in jeweils eine von zwei Gruppen aufgeteilt werden: 1) Klinische Studien, die als Placebo falsche Akupunktur benutzten, d. h. die Anbringung von Nadeln ausserhalb des Meridians, aber nahe an den klassischen Aku-Punkten. Diese Gruppe von 45 Studien wurde als energetisches Placebo-Modell (EPM) klassifiziert. 2) Weitere 45 Studien, die als Placebo-Behandlung das Anbringen von Nadeln innerhalb der Segmentzone, weit genug entfernt von den aktiven Punkten, benutzten, wurden als neurophysiologisches oder metamerisches Placebo-Modell (MPM) klassifiziert. In beiden Gruppen von Studien wurde der Anteil von signifikanten Ergebnissen und die Verteilung von Ergebnissen, die durch nichtsignifikante Resultate mit Verbesserungen von mehr als 35% charakterisiert waren, mit Hilfe des Chi-Quadrat-Tests ermittelt. **Ergebnisse:** Der Anteil an klinisch bedeutsamen Ergebnissen war in der MPM-Gruppe mit 73,33% (33/45) signifikant höher, während nur 33,33% (15/45) derartiger Resultate in der EPM-Gruppe gefunden wurden ($p < 0,03$). In der EPM-Gruppe liessen sich in 24/30 Studien nichtsignifikante Resultate mit einer Verbesserung von mehr als 35% in beiden Patientengruppen nachweisen, während in der MPM-Gruppe nur 20% (6/30) der Studien mit einem solchen Resultat gefunden wurden ($p < 0,05$). **Schlussfolgerung:** In Studien, die EPM als Placebo verwendeten, konnte in den meisten Fällen kein Unterschied zwischen richtiger Akupunkturbehandlung und Placebo-Behandlung nachgewiesen werden, im Gegensatz zu solchen, die MPM als Placebo benutzten. Andererseits scheint die falsche Akupunktur beinahe so wirkungsvoll wie die richtige Akupunktur zu sein. Diese Ergebnisse zeigen, dass die Art und Weise der Placebo-Prozedur das Ergebnis, d. h. den Erfolg oder das Versagen einer klinischen Studie beim Nachweis von Unterschieden zwischen den Patientengruppen, bestimmt, vorausgesetzt, dass solche Unterschiede tatsächlich existieren.

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Introduction

In the last quarter of the century, basic and clinic acupuncture research has notoriously increased. It can be assumed that basic mechanisms of acupuncture have been sufficiently established; nevertheless, its clinic validation is still incipient. Many projects came to contradictory conclusions by mere methodological defects which diminished the quality of publications [1, 2]. For example, two meta-analyses on acupuncture for chronic pain yielded contradictory results [3, 4]. For these reasons, some authors even arrive at the conclusion to doubt if is it possible to evaluate acupunctural effects through procedures such as controlled clinical studies according to Western rules [5, 6].

Independently of the design's quality, three large groups of difficulties inherent to acupuncture have been identified: i) absence of practical and clear rules for the selection of acupuntural treatment to be applied to the experimental group, which must observe acupunture's therapeutic principles and, at the same time, must be comparable for each subject within the group [7, 8], ii) difficulties related to the form of masking used to maintain the groups' comparability during the trial, and iii) lack of definition of a placebo procedure specially adapted to acupuncture. This last aspect seems of great relevance, since discrepancies in the definition of an ideal placebo for acupuncture probably constitutes the most important source of shortcomings of clinical acupuncture trials, since it leads to contradictory outcomes [9]. Two large trends exist in placebo design [1, 2], one that follows the traditional energetic model that consists in putting the placebo needles close to active points or real acupuncture, but outside of the channel; the other one is based on a neurophysiological point of view, because, in some way, it takes into account the underlying neurological structure and the functional behavior of metameres or, simply, it takes care not to activate the diffuse noxious inhibitory control [10].

The impact of imagination, beliefs, and emotions in healing processes has been recognized for a long time [11, 12]. Since the 1950s, it has been established that placebo effects oscillate between 30 and 35% through the employment of different pharmaceutical forms such as injections, tablets, capsules, pills, ointments, etc. [13]. The therapeutical effect of any treatment is the result of the addition of its therapeutic effect plus its placebo effect plus the effect of patient-therapeut interaction. Thus, the placebo action is a mixture of self-suggestion and hetero-suggestion with their psychological and sociocultural components, the effects of which are, indeed, impredictable [14]. The impredictability of the placebo effect seems to make it necessary to design placebo-controlled trials for the majority of clinical studies [15].

As evidence indicate that the selection of a placebo procedure in acupuncture clinical trials constitutes an important source of results' distortion that originates controversy and frustration, the goal of the present work is to answer the question whether the results of the acupuncture clinical trials are determined by the design and execution of the placebo procedure or not.

Material and Methods

Data were obtained through a MEDLINE online search from 1975 until 1989, combined with searches in MEDLINE CD ROM and Montpellier University's ACUBASE from 1989 until 1995 (key words: acupuncture, clinical trial, sham acupuncture, therapy, treatment). Furthermore, it was searched within bibliographical references of important reviews.

Making abstraction of the other methodological aspects, attention was focused exclusively on placebo design of clinical trials. In agreement to the placebo model used, publications were classified in two groups: one group of publications with energetic placebo model (EPM) and one group of publications with neurophysiological or metameric placebo model (MPM). Procedures that obviated needle insertion were discarded in order to avoid biasing the goal of this work to establish if trial results are different when nociceptive stimulation of the skin is executed within or outside of dermatome where the 'real acupuncture point' is located.

As EPM those procedures were classified, in which as untruthful treatment the application of needles outside the classical meridian points, nearby the real acupuncture points, was employed. The so-called sham acupuncture is based on the assumption that needles applied ouside the meridian will not have any effect, because they are not able to modify energy flow within the channels and, thus, cannot reestablish the energetic balance.

As MPM those procedures were considered consisting of an insertion of needles in a quite different dermatome, far enough away from active points used in the experimental group. It takes into account the body's metameric architecture and metameric functional behavior.

Both groups of publications were compared with regard to i) the proportion of significant results and ii) the distribution of nonsignificant results accompanied by a trend to a remarkable improvement of symptoms in both groups of patients. In studies showing these kinds of results, the proportion of subjects with improvement of some of the judgement criteria was assessed, if possible, in order to establish whether within the compared groups symptoms' relief was significantly greater than 35% or not; i. e. an effect superior to the expected value explainable through mere placebo effect.

Statistical Analysis

The proportion of significant results in both groups (EPM and MPM) was compared. Null hypothesis: Both placebo models are equivalent to such a degree that a similar proportion of good results is obtained in both groups of publications. The statistical significance was established through the chi-square test.

In both groups (EPM and MPM) the proportions of nonsignificant results distribution associated with an improvement of symptomatology superior than 35% in patients treated as well as in control patients were compared. Null hypothesis: As both placebo models are equivalent, the proportion of studies with this kind of results is similar within both groups. The statistical significance was established through the chi-square test.

Results

Search conditions were fulfilled by 127 clinical trials. Four large trends in clinical trials' design were observed: i) clinical studies using EPM 35.43% (45/127), ii) clinical studies using MPM 35.43% (45/127), iii) acupuncture compared with a reference treatment 21.26% (27/127), and iv) acupuncture compared with a group without treatment 7.87% (10/127). Articles in which the latter two study designs had been applied were discarded for this study.

In the EPM group significant differences were observed in 33.33% (15/45); while in the MPM group significant differences were observed in 73.33% (33/45) of cases. The chi-square test showed a

meaningful difference ($p < 0.05$) between both groups in such a way that the EPM fails more frequently in showing differences than the MPM. On the other hand, in studies using EPM, significantly more frequent outcomes with nonsignificant results associated with remarkable relief of patients were observed (in the EPM group: 80% (24/30) and in the MPM group: 20% (6/30); $p < 0.05$), showing that sham acupuncture is almost as active as 'real' acupuncture and, therefore, that those clinical trials are not able to distinguish between real and false placebos.

Discussion

The results of this study are consistent with the hypothesis that the design and the way of performing the placebo procedure do determine the results of clinical trials in acupuncture research, i. e. the placebo design determines the outcome (success or failure of a clinical trial in obtaining significant differences among the compared groups). It appears that needle application out of meridian but within the same dermatoma has a similar effect to that obtained with stimulation of a classic point due to the body's metameric architecture. Therefore, the needling outside meridians appears to be an untruthful placebo because its effects are very similar to the effects of needling the real acupuncture point, particularly if the selected placebo site belongs to the same metamere. On the other hand, it seems that placing placebo needles outside the patient's affected metamere does not act on the subject symptoms and should constitute a real placebo.

Difficulties in developing a suitable placebo for acupuncture had been identified a long time ago [1–2]. Of course, from the energetic paradigm point of view it was logic to presume that needling outside meridians sufficed because this procedure was supposedly unable to interfere with the energetic flow and so incapable to have any effect on health. For this reason sham acupuncture was considered as the 'ideal placebo' for clinical researchers of acupuncture, and, without doubt, it also became an important source of confusion and controversies. Thus, in their rigorous pioneer clinical study Gaw et al. [16] compared real and sham acupuncture in patients with osteoarthritic pain at several body regions. Placebo consisted in needling extrameridian points nearby the real acupoints. The results showed a meaningful improvement of pain and joint mobility in both groups, without meaningful differences between them. Since then and in a consistent way, the trials comparing acupuncture with sham acupuncture have very often yielded similar results. On the other hand, if placebo conditions without puncture were employed, acupuncture clinical trials showed positive results more frequently [2]. Equally, some researchers disavowing body metameric structure have used distilled water or lidocaine injection as placebo, ignoring that skin disturbance produced by needling is high enough to activate metameres' regulatory responses [17]. Currently, it is well established that injecting anesthetics or distilled water into skin has an effect at least as potent as dry needling [18, 19]. On the other hand, Duplan et al. [20] did obtain significant differences using sham acupuncture as placebo in acute sciatic pain; however, by putting the placebo needles outside of meridian at lumbar region (L4–L5), they applied them by random in a quite different dermatoma (D12–L1), which possibly explains the success of sham acupuncture in this case. Similarly, Luu et al. [21] obtained in asthmatic patients measured by spirometry (1 s maximum expiratory volume) a highly significant difference between both groups by inserting needles in the lower limbs as placebo points, a location far enough from the lung metamere.

Nevertheless, if researchers continue developing studies with sham acupuncture as placebo without taking into account the body's metameric structure, they are involuntarily sabotaging the results of their own acupuncture clinical trials, as in a recent study by Takeda and Wessel [22] who compared acupuncture and sham acupuncture for the treatment of knee pain and, like Gaw et al. [16] 19 years before, concluded once again that acupuncture is equivalent to placebo; another kind of type II error (false-negative result).

These difficulties with placebo acupuncture had been interpreted in several ways: i) both treatments produce their effects through placebo factors, ii) placebo acupuncture is an equally effective specific treatment, the location of the points being irrelevant [2], iii) small differences exist between real acupuncture and the untruthful acupuncture, but they are difficult to detect, because it would be necessary to test an unusually large number of subjects in both groups with particularly sensitive statistic instruments to be able to appoint them [23, 24]. However, the results of the present meta-analysis suggest that effects produced by needling a point outside the meridian but within the affected metamere are very close to those obtained by needling the real acupoint, as it already had been observed by Chien-Ping et al. [25] in 1974. Therefore, in order to avoid type II errors, it might be much more practical and simpler taking into consideration the metameric structure of the body and applicating placebo needles in separate zones, at least three or four segments beyond the dermatome where the real acupuncture needles are applied.

It was suggested elsewhere [26] that ideal 'placebo zones' are located at sites where voluminous muscles separate the skin from important neurovascular bundles, for example in deltoid and gluteal regions. These 'placebo zones' were recently validated by Lux et al [27]. These authors applied as real acupuncture needling one point within the gastric dermatome (BL 21) and a distal one (ST 36), while the sham acupuncture was carried out by needling outside meridians on the deltoid muscle and in the gluteus maximus muscle and, although additionally stimulated the needles electrically, they did not observe any influence of placebo manipulation on gastric acid secretion.

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