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EDITORIAL

Acupuncture for the treatment of headaches: more than sticking needles into humans?

Trial design for the conduct of clinical trials in the prophylactic treatment of migraine and tension-type headache (TTH) is of utmost importance. For this particular reason the International Headache Society published guidelines for the planning and conduct of clinical trials (1), which were adopted to a certain degree by the European authorities (European Medicines Agency) as a guidance paper. The most important aspects of clinical trials in headache prevention are randomization, blinding, the use of placebos and patient numbers based on proper power calculations. These guidelines were developed for drug trials, but also apply in principle to trials investigating non-drug treatment such as behavioural therapy or acupuncture. Until recently, the field of acupuncture trials has been at a stage were drug trials were 15 years ago: most trials had a poor trial design and were underpowered. A meta-analysis published in 1999 came to the conclusion that there was not enough evidence from randomized studies that acupuncture is effective in the prophylaxis of migraine or TTH (2). Despite this poor evidence, acupuncture was the most frequently used method to treat primary headaches in many European countries. Many acupuncture specialists argued that is would be impossible to perform randomized trials with acupuncture because therapy has to be individualized and because blinding was thought to be not feasible.

The situation changed dramatically when the German government decided to support large-scale clinical trials to prove or disprove the efficacy of acupuncture for migraine, TTH, low-back pain and chronic joint pain due to arthrosis. These studies had to be financed from the premiums of the mandatory sick funds. Two independent research groups applied for the funding, and both were successful. This offered the unique opportunity to perform prospective trials with different trial designs at the same time in the same population. In this editorial, I will concentrate only on the results of the headache trials. Both consortia decided to perform large-scale open trials in order to gain an impression of the effect of size on the improvement of headache frequency and possible adverse events (AEs) in the setting of everyday clinical practice. Both consortia also decided to perform randomized, single blinded studies. The first study in migraine included 302 patients (3) with migraine who were randomized in a group of patients who were treated with acupuncture, a group receiving sham acupuncture and a group of patients assigned to a waiting list for 3 months and treated by acupuncture afterwards. In summary, the study showed an equivalent responder rate for real and sham acupuncture of about 50%. The responder rate in the waiting list group was only 15% and represents the well-known effect of regression to the mean. This very elegant study showed that large-scale trials in acupuncture are feasible and indicated that efficacy is based on needling *per se* and not so much on the 'philosophical' concepts of classical acupuncture.

These results were basically replicated in a second randomized trial (4, 5). This trial assessed the efficacy of a part-standardized verum acupuncture procedure, in accordance with the rules of traditional Chinese medicine, compared with that of part-standardized sham acupuncture and standard migraine prophylaxis with β-blockers, calcium-channel blockers, or antiepileptic drugs in the reduction of migraine days 26 weeks after the start of treatment. The prospective, randomized, multicentre, double-blind, parallel-group, controlled, clinical trial recruited patients who had two to six migraine attacks per month, who were randomly assigned verum acupuncture ($n = 313$), sham acupuncture ($n = 339$) or standard therapy ($n = 308$). The primary outcome showed a mean reduction of 2.3 days in the verum acupuncture group, 1.5 days in the sham acupuncture group and 2.1 days in the standard therapy group. The proportion of responders, defined as patients with a reduction of migraine days by $\geq 50\%$, 26 weeks after randomization, was 47% in the verum group, 39% in the sham acupuncture group and 40% in the standard group.

In conclusion, the two trials reached identical results with different populations and trial design. The most important result was that acupuncture is as effective as drug therapy, but that that sham acupuncture is as effective as 'real' acupuncture (6). Unfortunately, Germany decided that acupuncture

would not be reimbursed. My interpretation would have been that acupuncture should be offered to patients who do not respond to prophylactic treatment with drugs, terminate drug treatment because of AEs or have contraindications to drug treatment.

The trials in TTH were more difficult to perform. One of the trials aimed to randomize patients with TTH to real acupuncture, sham acupuncture and treatment with a tricyclic antidepressant. It turned out that most patients that were randomized to drug treatment dropped out immediately after randomization because they expected to be randomized to acupuncture (7). Another trial again showed no difference between real and sham acupuncture. This trial also had a control group of patients on a waiting list (8).

In this issue of *Cephalalgia* a large-scale study is published using the 'population-based' approach (Jena et al.). Despite the fact that I have major design issues with the study, my view is that studies like this have to be published in high-ranked journals to promote discussion on trial design in non-drug trials. The trial included 15,056 headache patients, 11,874 of whom were treated in open fashion with acupuncture in addition to standard care. The percent reduction of headache days per month across 6 months was about 45% in the non-randomized patients. A similar result was observed in 1613 patients who were randomized to acupuncture in contrast to 1569 patients in the control group. The decrease of headache days at 3 months was from 8.4 to 4.7 in the acupuncture group and from 8.1 to 7.5 in the control group. Patients in the control group were not treated by acupuncture. The authors have performed the largest trial to date on the efficacy of acupuncture in primary headache and have shown that patients who are randomized in the context of a clinical trial achieve the same level of improvement with acupuncture as those treated in routine clinical practice.

My major concerns with this study are as follows.

1. The study groups mixed patients with migraine, TTH and a combination of both. The *a priori* hypothesis obviously was that all three groups would show a similar reaction to acupuncture. If one considers the different genetics and pathophysiology of both conditions, this *a priori* assumption is not justified. I admit that the treatment effect was identical in both groups of primary headaches. The experience of the trial in TTH by Endres et al. (7), however, indicates that expectation, the most important driver of a placebo effect, was different in patients with TTH compared with those with migraine.
2. The study was randomized, but not blinded. Real acupuncture was not compared with a sham procedure. This results in uncertainty as to what the basis of the improvement was. How much of the effect was due to a possible biological action of acupuncture and how much was due to a placebo effect?

What are the consequences of this large-scale study?

1. Studies investigating non-medical treatment have to follow the same principles as studies performed to investigate the efficacy of drugs. They have to be performed as randomized, blinded studies.
2. Studies investigating acupuncture need to use sham acupuncture and use a control group with an established preventive therapy, e.g. β-blockers or neuromodulators in migraine and tricyclic drugs in TTH.

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