

COMMENTARY ON THE COCHRANE REVIEW OF ACUPUNCTURE FOR TENSION-TYPE HEADACHE

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ABSTRACT OF THE COCHRANE REVIEW

Background: Acupuncture is often used for tension-type headache prophylaxis but its effectiveness is still controversial. This review (along with a companion review on 'Acupuncture for migraine prophylaxis') represents an updated version of a Cochrane review originally published in Issue 1, 2001, of *The Cochrane Library*.

Objectives: To investigate whether acupuncture is a) more effective than no prophylactic treatment/routine care only; b) more effective than 'sham' (placebo) acupuncture; and c) as effective as other interventions in reducing headache frequency in patients with episodic or chronic tension-type headache.

Search Strategy: The Cochrane Pain, Palliative & Supportive Care Trials Register, CENTRAL, MEDLINE, EMBASE and the Cochrane Complementary Medicine Field Trials Register were searched to January 2008.

Selection Criteria: We included randomized trials with a post-randomization observation period of at least eight weeks that compared the clinical effects of an acupuncture intervention with a control (treatment of acute headaches only or routine care), a sham acupuncture intervention or another intervention in patients with episodic or chronic tension-type headache.

Data Collection and Analysis: Two reviewers checked eligibility; extracted

information on patients, interventions, methods and results; and assessed risk of bias and quality of the acupuncture intervention. Outcomes extracted included response (at least 50% reduction of headache frequency; outcome of primary interest), headache days, pain intensity and analgesic use.

Main Results: Eleven trials with 2317 participants (median 62, range 10 to 1265) met the inclusion criteria. Two large trials compared acupuncture to treatment of acute headaches or routine care only. Both found statistically significant and clinically relevant short-term (up to three months) benefits of acupuncture over control for response, number of headache days and pain intensity. Long-term effects (beyond three months) were not investigated. Six trials compared acupuncture with a sham acupuncture intervention, and five of the six provided data for meta-analyses. Small but statistically significant benefits of acupuncture over sham were found for response as well as for several other outcomes. Three of the four trials comparing acupuncture with physiotherapy, massage or relaxation had important methodological or reporting shortcomings. Their findings are difficult to interpret, but collectively suggest slightly better results for some outcomes in the control groups.

Conclusions: In the previous version of this review, evidence in support of acupuncture for tension-type headache was

considered insufficient. Now, with six additional trials, the authors conclude that acupuncture could be a valuable non-pharmacological tool in patients with frequent episodic or chronic tension-type headaches.

COMMENTARY ON COCHRANE REVIEW

The Cochrane reviews on acupuncture for migraine and tension-type headache (TTH) have received much attention. Indeed, they are the top two reviews highlighted on the Cochrane Web site and are among the top 10 most visited reviews on *The Cochrane Library*, as of Issue 2, 2009. Both have associated podcasts. This commentary is a closer look into the review of acupuncture for TTH. It is focused on three aspects:

- the possible redefinition of the role of acupuncture in TTH therapy
- the problem of randomized controlled trials, which, although they aim to provide objective evidence, sometimes rest on shaky and subjective fundamentals
- the possible explanations for verum acupuncture's superiority to sham acupuncture in TTH

Redefining the Role of Acupuncture in TTH Therapy

"The Cochrane Review of Acupuncture for Tension-Type Headache," by Linde et

al¹ gives, for the first time, evidence that acupuncture is effective for frequent, episodic, or chronic TTH and thus provides a valuable nonpharmacological treatment option. In the light of the data, one would expect these findings to redefine the clinical significance of acupuncture for the treatment of TTH within Western medicine. TTH is widespread; epidemiological studies show a one-year prevalence of 30% to 60% for episodic TTH and 2% to 3% for chronic TTH.² It is also hard to treat.

Tension-type headache is one of the main reasons for the consumption of analgesics worldwide, but this conventional therapy poses a dangerous problem in Western medicine. It is estimated, for example, that in Germany 80% of over-the-counter painkillers are taken by headache patients and account for 2,000 to 7,000 deaths annually, mainly due to gastrointestinal bleeding (D.O. Stichtenoth, personal communication, February 2006).³ In contrast, acupuncture is rated as a relatively safe therapy.⁴

For prophylactic treatment of chronic TTH, tricyclic antidepressants, mainly amitriptyline, are most widely used.⁵ Surprisingly, only 14 trials of this therapy, with very small samples (median 36, range 15-197), inadequate efficacy parameters, and short durations, have been performed.⁵ Ten of these are positive, but the clinical relevance of their outcomes is questionable. This contrasts to acupuncture, for which the Cochrane review lists 11 strictly selected randomized controlled trials with 2,317 participants (median 62, range 10-1,265) for TTH.² In regard to chronic TTH alone, the largest amitriptyline trial (n = 197) found that headache days were reduced from 16 to only 15 after 12 weeks of daily intake of 75 mg; 10.9% of the patients were lost during the trial due to such adverse effects as dry mouth, drowsiness, weight gain, dizziness, and constipation.⁶ The large German Acupuncture Trial (GERAC) on chronic TTH (n = 409) found a reduction from 16 to six days in the verum and from 16 to eight days in the sham group; adverse effects possibly related to acupuncture were observed in only one patient (0.002%).⁷ Nevertheless, major reviews and the guidelines of the German Society of Neurology for the Treatment of Tension-Type Headache recommend amitriptyline as the therapy of first choice.^{5,8}

In view of the data presented in the Cochrane review, one should expect that acupuncture will soon be recommended as a nonpharmacological therapy because of its high level of evidence (ie, a positive systematic review), its negligible adverse effects, and its effectiveness on the reduction of headache days in chronic TTH.

Randomized Controlled Trials

With a 70% weight, the GERAC trial dominated the Cochrane review in regard to the comparison of verum to sham acupuncture.² Although the GERAC trial was negative for the verum versus sham acupuncture, it is precisely its data, which in the Cochrane meta-analysis led to the small but significant difference between true and sham acupuncture. This apparent contradiction warrants a closer look. In GERAC, a rigorous trial conforming to the standards of good clinical practice, the data had to be analyzed as defined in the study protocol. The stated predefined outcome measure was the proportion of patients with at least 50% reduction at six months, but patients with a protocol violation, for example, those who changed from one analgesic to another, were classified as nonresponders.⁷ Thus only 33% in the verum and 27% in the sham group were counted as responders. "This reclassification might be worthwhile for certain reasons, [but] it is very uncommon in trials on tension-type headache," as Linde et al state.² Since in the Cochrane review the predefined outcome criterion was the "usual" one, or at least a 50% reduction of headache days, the GERAC trial showed 66% responders in the verum and 55% responders in the sham group. In other words, changing the method of analysis from that of the specific study protocol of GERAC to that of the meta-analysis shifts the outcome of the comparison between verum and sham acupuncture from negative to positive, from no difference to a significant difference. For the author of this commentary, this is a striking example of how the outcome of a trial is dependent not only on the tested intervention, but may be equally dependent on the definition of the primary endpoints and the predefined method of data analysis. It is interesting to note that the selection of endpoints and procedures of statistical analysis are merely based on subjective

"expert" decisions prior to the trial. Putting these thoughts together, one arrives at the conclusion that at the end of the day huge, multimillion Euro trials that aim at the utmost scientific objectivity rest on subjective fundamentals that have the power to change their outcomes from negative to positive.

Verum Acupuncture Versus Sham Acupuncture

The Cochrane review found a small but significant difference between verum and sham acupuncture. Although this might not be of high clinical relevance, it is relevant when accepting or dismissing a therapeutic procedure being paid for by a national healthcare system. Other reviews on acupuncture, for example, for migraine,⁹ low back pain,¹⁰ or osteoarthritis,¹¹ do not reveal significant differences between sham and verum acupuncture. Although in low back pain or osteoarthritis trials sham acupuncture points were located mainly in the same region as the verum points, sham points in the large German TTH studies, GERAC and Acupuncture Randomized Trials (ART), had to be located far from the head, on the shoulder, the arm, the thigh, and the legs.^{12,13} This leads to the hypothesis that the further away the sham points are from the verum, the greater the difference may be. This hypothesis is also supported by the different outcomes of the GERAC and the ART studies on osteoarthritis.^{14,15} Although in the negative GERAC study the sham points were located relatively close to the verum points, in the positive ART osteoarthritis study they were located farther away from the affected knee and leg. These observations raise the question of whether acupuncture points are really as small as described in the common textbooks. Or rather, are they larger sites or areas? This issue may have considerable impact on future acupuncture trials and should be the subject of further investigation.

REFERENCES

1. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. Acupuncture for tension-type headache. *Cochrane Database Syst Rev*. 2009;1:CD007587.
2. Schwartz BS, Stewart WF, Simon D, Lipton RB. Epidemiology of tension-type headache. *JAMA*. 1998;279:381-383.

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3. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med.* 1999;340:1888-1899.
 4. Witt CM, Pach D, Brinkhaus B, et al. Safety of acupuncture: results of a prospective observational study with 229,230 patients and introduction of a medical information and consent form. *Forsch Komplementmed.* 2009;16:91-97.
 5. Fumal A, Schoenen J. Tension-type headache: current research and clinical management. *Lancet Neurol.* 2008;7:70-83.
 6. Pfaffenrath V, Diener HC, Isler H, et al. Effectiveness and tolerance of amitriptyline oxide in chronic tension headache—a multicenter double-blind study versus amitriptyline versus placebo [in German]. *Nervenarzt.* 1993;64:114-120.
 7. Endres HG, Bowing G, Diener HC, et al. Acupuncture for tension-type headache: a multicentre, sham-controlled, patient-and observer-blinded, randomised trial. *J Headache Pain.* 2007;8:306-314.
 8. Diener HC, Norman P, eds. *Leitlinien für Diagnostik und Therapie in der Neurologie.* 4th ed. Stuttgart, Germany: Georg Thieme Verlag Stuttgart; 2008.
 9. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. Acupuncture for migraine prophylaxis. *Cochrane Database Syst Rev.* 2009;1:CD001218.
 10. Yuan J, Purepong N, Kerr DP, Park J, Bradbury I, McDonough S. Effectiveness of acupuncture for low back pain: a systematic review. *Spine.* 2008;33:E887-E900.
 11. Manheimer E, Linde K, Lao L, Bouter LM, Berman BM. Meta-analysis: acupuncture for osteoarthritis of the knee. *Ann Intern Med.* 2007;146:868-877.
 12. Melchart D, Linde K, Streng A, et al. Acupuncture Randomized Trials (ART) in patients with migraine or tension-type headache—design and protocols. *Forsch Komplementarmed Klass Naturheilkd.* 2003;10:179-184.
 13. Molsberger AF, Boewing G, Diener HC, et al. Designing an acupuncture study: the nationwide, randomized, controlled, German acupuncture trials on migraine and tension-type headache. *J Altern Complement Med.* 2006;12:237-245.
 14. Scharf HP, Mansmann U, Streitberger K, et al. Acupuncture and osteoarthritis: a three-armed randomized trial. *Ann Intern Med.* 2006;145:12-20.
 15. Witt C, Brinkhaus B, Jena S, et al. Acupuncture in patients with osteoarthritis of the knee: a randomised trial. *Lancet.* 2005;366:136-143.

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