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Acupuncture Randomized Trials (ART) in Patients with Migraine or Tension-Type Headache – Design and Protocols

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Key Words
Acupuncture · Randomized controlled trial · Migraine · Tension-type headache

Summary
Background and Objective: We report the design and essentials of the protocols of two Acupuncture Randomized Trials (ART) investigating whether acupuncture is more efficacious than no treatment and minimal acupuncture in the interval treatment of migraine and tension-type headache. **Design:** Randomized controlled multicenter trials with three treatment arms and a total observation period of 28 weeks. **Setting:** 30 practitioners and outpatient units in Germany specialized in acupuncture treatment. **Patients:** Per study 300 patients with migraine and episodic or chronic tension-type headache, respectively (diagnosis according to the criteria of the International Headache Society). **Interventions:** Patients are randomly assigned to receive either (1) semi-standardized acupuncture (150 patients), (2) standardized minimal acupuncture (75 patients), or (3) no interval treatment for 12 weeks followed by semi-standardized acupuncture (75 patients, waiting list control). Acupuncture treatment consists of 12 sessions per patient over a period of 8 weeks. **Main Outcome Measure:** Main outcome measure in the migraine trial is the difference between the number of days with headache of moderate or severe intensity during the 4 weeks before randomization and weeks 9 to 12 after randomization. In the study on tension-type headache the main outcome measure is similar to that described above, but for the number of headache days regardless of intensity. **Outlook:** The results of these two studies (available in 2004) will provide health care providers and policy makers with the information needed to make scientifically sound assessments of acupuncture therapy.

Schlüsselwörter
Akupunktur · Randomisierte klinische Studie · Migräne · Spannungskopfschmerz

Zusammenfassung
Hintergrund und Ziel: Der vorliegende Artikel beschreibt Design und essentielle Teile der Protokolle zweier randomisierter Studien («Acupuncture Randomized Trials» = ART), deren Ziel es ist, zu überprüfen, ob eine Akupunkturbehandlung bei der prophylaktischen Behandlung von Migräne bzw. Spannungskopfschmerzen wirksamer ist als eine Nichtbehandlung (Wartelistenkontrolle) bzw. eine Minimalakupunktur. **Design:** Zwei randomisierte, dreiarmige Multizenterstudien über 28 Wochen. **Prüfzentren:** 30 auf Akupunktur spezialisierte Arztpraxen und Ambulanzen in Deutschland. **Patienten:** Pro Studie 300 Patienten mit Migräne bzw. episodischen oder chronischen Spannungskopfschmerzen (Diagnose entsprechend den Kriterien der International Headache Society). **Interventionen:** Entsprechend der randomisierten Zuteilung erhalten die Patienten entweder (1) semistandardisierte Verumakupunktur (150 Patienten), (2) standardisierte Minimalakupunktur (75 Patienten) oder (3) keine prophylaktische Behandlung (75 Patienten, Wartelistengruppe). Die Patienten der Wartelistengruppe erhalten 12 Wochen nach Randomisation ebenfalls Verumakupunktur. Die Akupunkturbehandlung besteht aus 12 Sitzungen pro Patient über einen Zeitraum von 8 Wochen. **Hauptzielkriterium:** Hauptzielparameter in der Migränestudie ist die Differenz der Tage mit Kopfschmerzen mittlerer oder starker Intensität in den 4 Wochen vor Randomisation und den Wochen 9 bis 12 nach Randomisation. In der Studie zu Spannungskopfschmerzen ist der Hauptzielparameter die entsprechende Differenz der Anzahl der Kopfschmerztage jeglicher Intensität. **Ausblick:** Erste Studienergebnisse, die eine Basis für eine wissenschaftliche und gesundheitspolitische Neubeurteilung der Akupunktur bieten werden, sind im Jahr 2004 zu erwarten.

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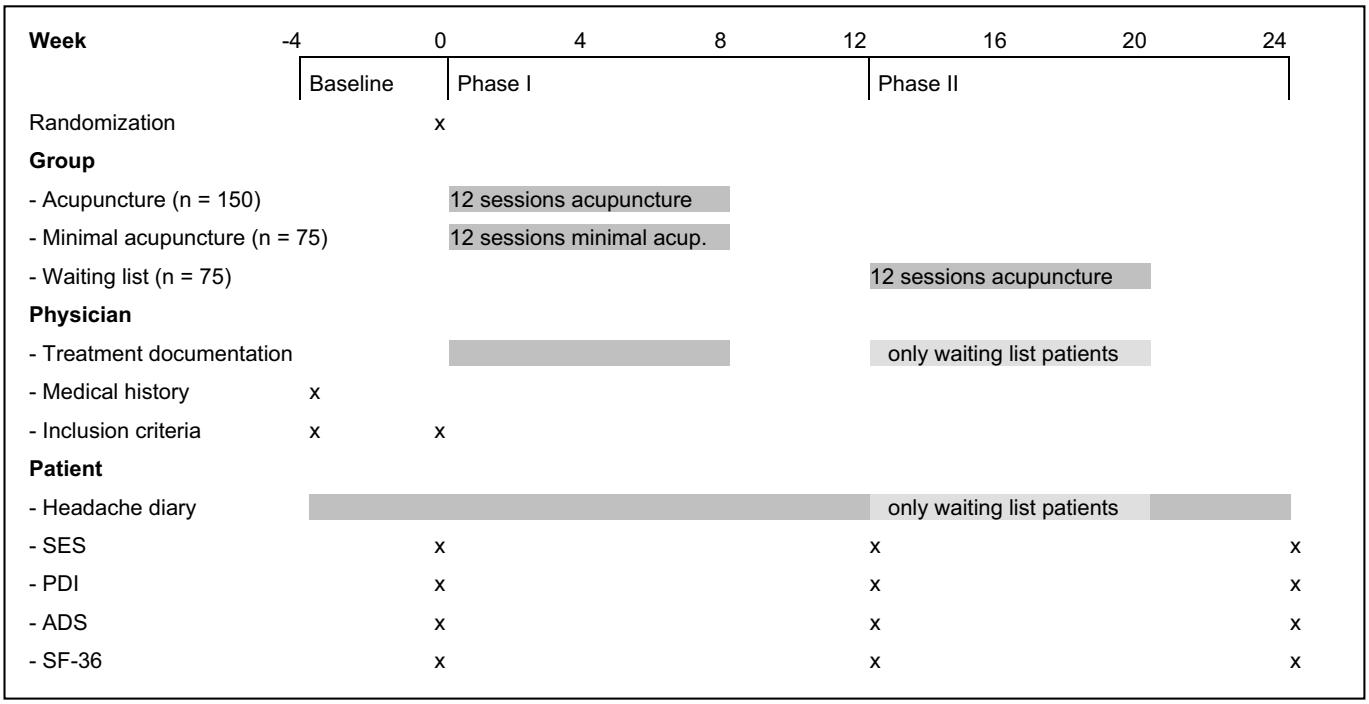

Fig. 1. Trial design, time schedule, and outcome measurements. SES = 'Schmerzempfindungs-Skala' (scale for assessing emotional aspects of pain); PDI = Pain Disability Index; ADS = 'Allgemeine Depressionsskala' (general depression scale); SF-36 = Short Form 36 to measure health-related quality of life.

Introduction

Throughout the 1990s, the costs of acupuncture therapy administered by physicians were partially covered by the German health insurance funds on an informal basis. Under increasing pressure to cut health care costs, however, the Federal Committee of Physicians and Health Insurers ('Bundesausschuss der Ärzte und Krankenkassen') decided in October 2000 that the scientific evidence supporting acupuncture was insufficient to justify routine reimbursement. Nevertheless, it recommended that special Model Projects on Acupuncture ('Modellvorhaben Akupunktur') be developed in order to determine the role of acupuncture in the treatment of certain illnesses. In particular, the Committee requested that 'sham'-controlled, randomized clinical trials be conducted on the role of acupuncture in the management of chronic headache, chronic low back pain, and chronic pain associated with osteoarthritis [1] – all conditions for which the available evidence had shown acupuncture to be a promising means of treatment. Today, the costs of acupuncture therapy can be covered by the health insurance funds for a limited period of time on a nation-wide level, provided that the treatment be administered within the framework of Model Projects which also include 'sham'-controlled, randomized trials as part of the evaluation strategy.

In this paper, we report on the design and protocols of two such clinical trials for migraine and tension-type headache, which are part of larger acupuncture research programs (the 'Modellvorhaben der Ersatzkassen' and the 'Modellvorhaben der Techniker Krankenkasse und der dem Modellvorhaben beigetretenen Krankenkassen'). Following commonly recommended standards for headache research [2, 3], these trials investigate whether a semi-standardized acupuncture intervention is more efficacious than 1) no treatment and 2) a standardized minimal acupuncture intervention in the interval treatment of patients with migraine and tension-type headache, respectively. In another, separate paper [4], we present details on clinical trials that examine the role of acupuncture in the management of chronic low back pain and osteoarthritis of the knee.

State of Research on Acupuncture for Headache

A systematic review published in 2001 [5] identified 26 randomized controlled trials of acupuncture for the interval treatment of chronic headaches. Sixteen trials were conducted among migraine patients, 6 among patients with tension-type headache, and 4 among patients with various headaches. Sixteen trials compared acupuncture with a sham intervention, 10 with other treatments. Overall, the results suggest that acupuncture is more efficacious than sham interventions in migraine. For tension-type headache and the comparison of acupuncture with other treatments the number of trials is too small for reliable conclusions. Other limitations of these trials included small patient groups (median sample size 37), single site performance, and relevant methodological and/or reporting shortcomings [5]. Since the completion of the systematic

review several new trials have been published [6–11] which, however, did not change the overall evidence picture fundamentally.

Patients and Methods

Design

Both studies are randomized, three-armed multicenter trials comparing (1) acupuncture, (2) minimal acupuncture, and (3) a no treatment (waiting list) condition (fig. 1). Patients are blinded to treatment in the acupuncture and minimal acupuncture arms of the studies. Analysis of headache diaries will be performed by two blinded evaluators. The total observation period within the study is 28 weeks per patient. Before randomization patients enter a 4-week baseline period. After randomization, patients in the acupuncture and in the minimal acupuncture group receive 12 treatments over a period of 8 weeks; patients in the waiting list group do not receive any prophylactic headache treatment for 12 weeks. All patients are asked to document their headaches both in the baseline period and for 12 weeks after randomization. Additionally, patients in the acupuncture and in the minimal acupuncture group have to continue their headache diaries in the weeks 21 to 24 after randomization. After 12 weeks without prophylactic treatment, patients in the waiting list group receive 12 acupuncture treatments within 8 weeks and fill in headache diaries during these 8 and the following 4 weeks.

Randomization into the 3 study arms is performed centrally by the Institute of Medical Statistics and Epidemiology (IMSE) at the Technische Universität München using the software Samp Size 2.0 [12]. Participating practitioners and outpatient units are not involved in the randomization process. Patients who meet the inclusion criteria and give written and oral consent are included in the study. After a patient is included in the study, his or her physician phones IMSE, where the patient is registered. Then the physician receives information from the IMSE regarding patient allocation both via phone and fax. This procedure assures that randomization cannot be influenced by the treating physicians.

The studies are performed according to the principles of the Declaration of Helsinki (Version Edinburgh 2000, cf. http://www.wits.ac.za/bioethics/helsinki.htm) and according to common guidelines for clinical trials (ICH-GCP). The protocols have been approved by local ethics review boards in all regions where the study is being conducted. The study participants are insured according to the German law for medicinal products ('Medizinproduktegesetz').

Patients

Each study aims to recruit a total of 300 patients. Recruitment for the trials started in April 2002.

For inclusion into either study the following general criteria have to be met: age 18–65 years; duration of complaints at least 12 months; complete baseline headache diary; written informed consent. General exclusion criteria are: secondary headaches; start of headaches after age of 50 years; use of analgesics on more than 10 days per month; prophylactic headache treatment with drugs during the last 4 weeks; any acupuncture treatment during the last 12 months or at any time if performed by the participating trial physician; blood coagulation disorders or coagulation-inhibiting medication other than acetyl-salicylic acid; relevant organic or mental disorders; pregnant or lactating women; application for pension or disability benefits; alcohol or drug abuse; any research study participation during the last 6 months; inability to understand the study.

Specific inclusion criteria for the migraine trial are: a diagnosis of migraine with or without aura according to the criteria of the International Headache Society, 2 to 8 migraine attacks per month during the last 3 months and during the baseline period. Specific exclusion criteria: interval headaches or additional tension-type headache on more than 10 days per month, and inability to differentiate migraine and interval headaches.

Specific inclusion criteria for the tension-type headache trial are: a diagnosis of episodic or chronic tension-type headache according to the criteria of the International Headache Society, at least 8 headache days per month in the last 3 months and in the baseline period. Specific exclusion criterion: additional migraine attacks.

All patients are asked to complete the Kiel Headache Questionnaire [13] which has been designed to separate migraine, tension-type and other headaches. Furthermore, the Mainz Classification Scheme ('Mainzer Stadieneinteilung') [14] is used. This is a physician-based questionnaire to classify the degree of chronicity in pain patients.

Participating Physicians

Participating trial physicians were recruited in a manner designed to ensure that their qualification is at least equal to the average qualification of physicians currently accredited for providing acupuncture in the German 'Modellvorhaben Akupunktur'. Physicians were thus required to fulfil all of the following criteria: (1) acupuncture training at least equivalent to an 'A-diploma' from one of the major German acupuncture societies (140 hours of acupuncture training); (2) 50% of trial physicians had to have at least a 'B-diploma' (350 hours; about 20% of physicians accredited to provide acupuncture as part of the 'Modellvorhaben Akupunktur' and outside the trials have this qualification [15]); (3) 50% had to have experience working in clinical studies; (4) all physicians had to have at least 3 years of practical experience with acupuncture; (5) all physicians had to participate in study training sessions on the trial methods, the interventions tested, and standards for performing clinical trials (ICH-GCP). About 30 study centers are currently participating in the studies. Non-medical acupuncturists were excluded from the studies.

Interventions

The treatment strategies for acupuncture and minimal acupuncture were developed in a consensus process with experienced acupuncture experts (Hammes M, Hummelsberger J, Irnich D) representing the following two major German societies for medical acupuncture: German Medical Acupuncture Association ('Deutsche Ärztegesellschaft für Akupunktur', DÄGfA); International Society for Chinese Medicine (Societas Medicinae Sinensis, SMS). In a first step the three experts developed a proposal which was then presented to more than 30 experts from both acupuncture societies for discussion. The final strategies were defined by the three experts together with the study team and communicated to the external advisors. The final strategies were generally considered as a pragmatic compromise between the need for some standardization and the need for individualization.

Both the acupuncture and minimal acupuncture treatments consist of 12 sessions of 30 min duration, each administered over a period of 8 weeks (preferably 2 sessions in each of the first 4 weeks, followed by 1 session per week in the remaining 4 weeks). Patients in the waiting list group do not receive acupuncture treatment for a period of 12 weeks after randomization, after which they receive the acupuncture treatment described below.

Acupuncture treatment is semi-standardized (tables 1, 2): All patients have to be treated at 'basic' points bilaterally unless there are contra-indications. In addition, physicians can treat at other points based on a traditional Chinese syndrome diagnosis, personal experience, localisation of pain or symptom modalities. Recommendations of additional points (uni- or bilaterally) are made, but acupuncturists can choose other optional points (including ear acupuncture points or trigger points). The number and name of additional acupuncture points must be documented. A traditional Chinese syndrome diagnosis is requested, but not mandatory. If it is performed, the diagnosis must be documented. Needle length and diameter are not predefined but have to be documented. An irradiating needling sensation ('de qi') should be achieved if possible. Needles should be stimulated manually at least once in each session. The total number of needles must not exceed 25.

Table 1. Acupuncture points used in the migraine trial

Basic points
Gall bladder (GB) 20
GB 40 or GB 41 or GB 42
Du Mai – Governing vessel (Du Mai, DU) 20
Liver (LIV) 3
San Jiao (SJ) 3 or 5
Extrapoint Taiyang
Optional points
Mainly frontal headache DU 23, extrapoint Yintang, bladder (BL) 2, GB 14, large intestine (LI) 4, stomach (ST) 4
Mainly temporal pain: SJ 20, GB 8, GB 12, ST 8
In case of retro-orbital pain: ST 8, SJ 23
Headache associated with menses: spleen (SP) 6, LIV 2, SP 10
Associated with nausea or vomiting: conception vessel (Ren-Mai, REN) 12, pericard (P) 6
Headache triggered by stress/anger: LIV 2, LIV 5
Triggered by fatigue: ST 36, REN 4

Table 2. Acupuncture points used in the tension-type headache trial

Basic points
GB 20
GB 21
LIV 3
Optional points
Mainly frontal headache: LI 4, DU 23, extrapoints Yintang and Taiyang, ST 44, GB 2
In case of headache mainly in the vertex: DU 20 or DU 23, extrapoint Si Shen Cong
In case of mainly neck pain: BL 10, BL 60 or BL 62, DU 14 or DU 19, small intestine (SI) 3 or SI 6
In case of holocephalic pain with fatigue: extrapoint Taiyang, SP 6 or 9, ST 36 or ST 40, REN 12
Complaints worse with wet or cold weather: LI 4, DU 14, GB 3, SJ 6, GB 39
Modalities wind, dampness, cold: LI 4, DU 14, SJ 6, GB 34
Modalities cold, wind: LI 4, lung (LU) 7, SJ 5, DU 14

Table 3. Minimal acupuncture points used in both trials; one 'cun' is defined according to the rules of traditional Chinese medicine as the width of the interphalangeal joint of patient's thumb

MA point 'Deltoideus'*:* in the middle of the line insertion of M. deltoideus (LI 14) and acromion
MA point 'Upper Arm'*:* 2 cun laterally (radial) of LU 3
MA point 'Forearm'*:* 1 cun ulnar of the proximal third of the line between heart (HE) 3 and HE 7
MA point 'Scapula'*:* 1 cun laterally of the lower scapular edge
MA point 'Spina Iliaca'*:* 2 cun above spina iliaca anterior superior in vertical line to the arch of left ribs
MA point 'Back I'*:* 5 cun laterally of the spine of lumbar vertebrum IV
MA point 'Back II'*:* 5 cun laterally of the spine of lumbar vertebrum V
MA point 'Upper Leg I'*:* 6 cun above the upper edge of the patella (between the spleen and stomach meridian)
MA point 'Upper Leg II'*:* 4 cun above the upper edge of the patella
MA point 'Upper Leg III'*:* 2 cun dorsally of GB 31 (avoidance of bladder meridian)

Number, duration and frequency of the sessions in the minimal acupuncture group are the same as for the acupuncture group. In each session at least 5 out of 10 points (table 3) have to be acupunctured bilaterally (at least 10 needles). Superficial insertion using fine needles (20–40 mm in length) is recommended. 'De qi' and manual stimulation of the needles should be avoided; the needles should be placed subcutaneously. All acupuncturists were trained to apply minimal acupuncture and received a videotape and a brochure showing detailed information on minimal acupuncture.

Patients in the waiting list control group do not receive any prophylactic treatment for their headaches for a period of 12 weeks after randomization. After that period they receive the acupuncture treatment described above.

All patients can treat acute headaches as needed. Attack treatment should be performed according to the guidelines of the German Migraine and Headache Society (DMKG) [16, 17]. Mild migraine attacks and tension-type headaches can be treated with acetyl-salicylic acid, naproxen, paracetamol, or ibuprofen orally. Severe migraine attacks can be treated with sumatriptan orally or subcutaneously, another triptan, or with ergotamine tatrate. Tension-type headache may also be treated by topical peppermint oil. Antiemetics can be used if needed. Non-drug interventions (such as relaxation) can be maintained if already used since at least 3 months. Attack treatment must not be modified after the baseline period. All drugs taken for acute headaches have to be documented in the headache diary.

Patients are informed in respect to acupuncture and minimal acupuncture in the study as follows: 'In this study, different types of acupuncture will be compared. One type is similar to the acupuncture treatment used in China. The other type does not follow these principles, but has also been associated with positive outcomes in clinical studies.'

Outcome Measurement

All patients fill in headache diaries in the 4 weeks before randomization, the 12 weeks after randomization, and in the weeks 21 to 24 after randomization (fig. 1). In the diaries they document each day whether or not they have headache and, if it does occur, they describe its duration, intensity, laterality, disability, concomitant symptoms, and medication used. In addition, patients are asked to fill in a modified version of the pain questionnaire of the German Society for the Study of Pain (DGSS; http://www.medizin.uni-koeln.de/projekte/dgss/Schmerzfragebogen.html) before treatment, after 12 weeks, and after 24 weeks. In addition to a number of questions on sociodemographic characteristics, numerical rating scales for pain intensity, questions on workdays lost, global assessments, etc., the DGSS pain questionnaire includes the following validated instruments: 1) the German version of the Pain Disability Index (PDI) [18]; 2) a scale for assessing emotional aspects of pain ('Schmerzempfindungs-Skala' SES) [19]; 3) the depression scale ADS [20]; 4) the German version of the SF-36 to assess health-related quality of life [21].

Main outcome measure in the migraine trial is the difference in number of days with headache of moderate or severe intensity in the 4 weeks before randomization and in weeks 9 to 12 after randomization. In the tension-type headache trial the main outcome measure is similar but compares the number of headache days regardless of intensity. Secondary outcome measures derived from the headache diaries include: Headache days (of moderate or severe intensity as well as regardless of intensity) and their differences to baseline during weeks 1 to 4, 5 to 8, and 21 to 24 after randomization, headache hours in 4-week periods, headache scores, mean pain intensity, number of days with accompanying symptoms, days with impaired function, days with medication, and number of responders (at least 50% reduction in the main outcome measure). In the migraine trial the number of migraine days, number of migraine attacks and responders

(at least 50% reduction in migraine days and attacks) will also be evaluated. Further secondary outcome measures are the changes in the items and scales included in the pain questionnaires.

In order to test the blinding to treatment, patients fill in a questionnaire after the third acupuncture session to assess the credibility of the respective treatment methods [22]. At the end of the study, patients are asked whether they think that they have received acupuncture following the principles of Chinese medicine or the other type of acupuncture. For each session, physicians are asked to report whether side effects or adverse effects occur. In addition, the patients are asked to report side effects in the above-mentioned questionnaires both at the end of 12 and 24 weeks after randomization (fig. 1). Drop-outs and withdrawals and the respective reasons are documented.

Statistics

Analyses will be performed for two populations: 1) an intention to treat population with all patients randomized (missing data will be replaced with baseline values); 2) a per protocol population including only patients without major protocol deviations. All data will be analyzed descriptively. Confirmatory testing of the main outcome measure and all main analyses will be based on the intention to treat population. A priori ordered one-sided (due to the available evidence suggesting a positive effect [5]) null hypotheses to be tested are $H_{0,1}$: acupuncture = waiting list, $H_{0,2}$: acupuncture = minimal acupuncture. For each hypothesis Student's t-test and $\alpha = 5\%$ will be used, thus testing in a first step whether acupuncture is more efficacious than no treatment, and in a second step whether acupuncture is more efficacious than minimal acupuncture. The studies are powered to detect a difference of 2 days with moderate or severe headache with a standard deviation of 5 days (thus an effect size of 0.4) with 80% power. The waiting list control group will be included in the main analysis only until week 12 after randomization.

Discussion

Together with studies in other 'Modellvorhaben Akupunktur' [23] (model projects on acupuncture) the planned trials described in this and the following paper [4] are likely to have a major impact on the decision whether acupuncture will be reimbursed by social health insurance companies in Germany. Compared with most trials of acupuncture currently available [24] our studies are performed with a much larger number of acupuncturists and include a much larger number of patients. The Federal Committee of Physicians and Health Insurers in Germany has requested reports on results of these studies in January 2004. By this date a final report on the migraine trial should be available, and the results of the study in tension-type headache patients will be available later that year.

A major issue in the planning phase of the studies presented here and in the following paper [4] was the choice of control groups. The Federal Committee has explicitly asked that the trials include 'sham' or 'placebo' controls to investigate whether the effects of acupuncture are 'specific'. However, the concepts of placebo, and its specific and unspecific effects in relation to complex physical interventions such as acupuncture are unclear. How is 'specific' defined in relation to acupuncture? Do only the effects due to correct localization of points have an influence, or do other aspects such as skin penetration, correct insertion depth, triggering of 'de qi', stimulation, number, frequency and duration of sessions also play a part? We have performed a systematic review (submitted for publication) of sham-controlled trials of acupuncture. Similar to an older review of the topic [25] we found that a multiplicity of different sham techniques are used and that the differences between 'true' and 'sham' interventions vary greatly between studies. This might explain in part the obvious heterogeneity of results between different acupuncture trials [24]. We decided to use a 'minimal' acupuncture [26] intervention as control which differs from the 'full' acupuncture intervention in point location, needling depth, avoidance of 'de qi' and of manual stimulation. Similar interventions have been used in a variety of trials [24]. As this trial is aimed to help in the decision process whether acupuncture should be reimbursed, a pragmatic comparison between an acupuncture 'lege artis' and a form which is clearly suboptimal according to acupuncture theory seems adequate. For example, we decided not to use 'placebo' needles [27] for practical (difficult to use in hairy areas, at the head, hands and feet; costs; handling in a multicenter trial) and conceptual reasons (much more physician-patient contact than in routine practice). Furthermore, it is unclear whether placebo needles should be used at the correct site (testing only whether skin penetration makes a difference) or at incorrect sites (testing skin penetration and localization). To quantify the 'unspecific' effects of minimal acupuncture we included a waiting list control group.

We deliberately avoid the expressions 'placebo' and 'sham' in our trial. In contact with patients the expression 'minimal acupuncture' is also avoided to ensure blinding and to increase compliance. In available trials the response rates of the control groups were high [5], suggesting that the various sham interventions had considerable 'unspecific' effects. It should be noted that our studies are only performed to clarify whether acupuncture is truly more efficacious than minimal or other sham acupuncture interventions. However, according to common simplified ways of interpretation our minimal acupuncture intervention would be considered by many as a 'placebo control.' Therefore, we found ourselves in an ethical dilemma on how to inform patients. Such a dilemma is likely to be the rule in acupuncture trials but it is rarely made explicit.

A relevant proportion of acupuncture trials uses sham interventions which are easily distinguishable from 'true' acupuncture. For example, a recent trial published in a major journal used an inactive laser acupuncture pen [28]. Many trials inform patients that two treatment modalities are compared without suggesting that one is a 'placebo' (results of a survey submitted for publication). This clearly lowers the likelihood of unblinding as patients are more likely to find the control intervention credible, but remains a major ethical issue. We chose a way of information which mentions that one treatment option does not meet all elements of traditional acupuncture but we do not mention that many would consider this – wrongly in our opinion – a placebo. All ethics committees approved our patient information leaflet without reservation and we believe it is adequate for the situation. However, there is urgent need for

earnest discussion of this subject in acupuncture research as well as in non-drug research in general.

The protocols of the planned studies have been developed in a consensus process involving acupuncturists, neurologists, methodologists, and statisticians. The methods of the trials take into account the particular problems of acupuncture research as well as recommendations for drug trials in the prophylaxis of migraine and tension-type headache [2, 3]. Further general aspects and issues specific to the trials for low-back pain and osteoarthritis of the knee are discussed in the following paper [4]. We hope that the results of these trials will represent a major step forward in the scientific evaluation of the effectiveness of acupuncture for headache.

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