Headache
© 2006 by American Headache Society
Published by Blackwell Publishing

ISSN 0017-8748
doi: 10.1111/j.1526-4610.2006.00598.x

Research Submission

Effectiveness and Tolerability of Acupuncture Compared With Metoprolol in Migraine Prophylaxis

Andrea Streng, PhD; Klaus Linde, MD; Andrea Hoppe, MD; Volker Pfaffenrath, MD; Michael Hammes, MD; Stefan Wagenpfeil, PhD; Wolfgang Weidenhammer, PhD; Dieter Melchart, MD

Objectives.—In a randomized controlled multicenter trial extending over 24 weeks, we investigated whether acupuncture is as effective and safe as metoprolol in the prophylactic treatment of migraine under conditions similar to routine care.

Methods.—One hundred fourteen migraine patients could be randomized to treatment over 12 weeks either with acupuncture (8 to 15 sessions) or metoprolol (100 to 200 mg daily). Main outcome measure was the difference in the number of migraine days between baseline and the weeks 9 to 12 after randomization (derived from a headache diary).

Results.—Two of 59 patients randomized to acupuncture withdrew prematurely from the study compared to 18 of 55 randomized to metoprolol. The number of migraine days decreased by 2.5 $\pm$ 2.9 days (baseline 5.8 $\pm$ 2.5 days) in the acupuncture group compared to 2.2 $\pm$ 2.7 days (baseline 5.8 $\pm$ 2.9 days) in the metoprolol group ($P =$ .721). The proportion of responders (reduction of migraine attacks by $\geq$50%) was 61% for acupuncture and 49% for metoprolol. Both physicians and patients reported fewer adverse effects in the acupuncture group.

Conclusions.—Due to missing the recruitment target (480 patients) and the high drop-out in the metoprolol group the results must be interpreted with caution. Still, they suggest that acupuncture might be an effective and safe treatment option for patients unwilling or unable to use drug prophylaxis.

Key words: migraine, randomized controlled trial, complementary medicine, metoprolol, acupuncture

Abbreviations: ICH-GCP International Conference on Harmonization—Good Clinical Practice, IMSE Institute of Medical Statistics and Epidemiology, o.d. oral dose, mg/d milligram per day, DMKG Deutsche Migräne- und Kopfschmerzgesellschaft (German Migraine and Headache Society), PDI Pain Disability Index, SES Schmerzempfindungsskala (scale for assessing emotional aspects of pain), ADS Allgemeine Depressionsskala (depression scale), SF-36 Short Form 36 (questionnaire to assess health-related quality of life), SPSS Statistical Package for the Social Sciences (software program), ITT intention-to-treat, PP per-protocol, ANCOVA Analysis of Covariance, Epi-Info (software program), RevMan Review Manager (software program), CI confidence interval, GP general practitioner, SD standard deviation, N or n number, IHS International Headache Society, Δ mean difference between groups, RR responder ratio, MOM main outcome measure

(*Headache* 2006;46:1492-1502)

From the Centre for Complementary Medicine Research, Department of Internal Medicine II, Technische Universität München, Munich, Germany (Drs. Streng, Linde, Hoppe, Weidenhammer, and Melchart); Neurological Practice, Munich, Germany (Dr. Pfaffenrath); Department of Neurology, Technische Universität München, Munich, Germany (Dr. Hammes); Institute of Medical Statistics and Epidemiology, Technische Universität München, Munich, Germany (Dr. Wagenpfeil); and Division of Complementary Medicine, Department of Internal Medicine, University Hospital Zurich, Switzerland (Dr. Melchart).

Address all correspondence to Dr. Andrea Streng, Centre for Complementary Medicine Research, Department of Internal Medicine II, Technische Universität München, Kaiserstr, 9, 80801 Munich, Germany.

Accepted for publication May 22, 2006.

Migraine prophylaxis with β-adrenergic receptor blockers, calcium antagonists, antiepileptic drugs, or other substances has been shown to reduce the frequency of migraine attacks. Although recommended by guidelines, the success of treatment is usually modest and tolerability often suboptimal.[1] Alternatively, acupuncture is widely used for migraine prophylaxis, but the available evidence of its effectiveness is controversial.[2] In 2001, German statutory health insurance companies initiated a model program including large-scale observational studies and randomized controlled trials in order to clarify the effectiveness of acupuncture for migraine and other chronic pain diseases as a precondition for future routine reimbursement.[3] For this, comparisons of acupuncture with sham treatment or effective standard therapies were requested.

For migraine, only 2 rigorous trials have been published thus far that compare acupuncture head-to-head with a standard drug prophylaxis,[4,5] both suggesting that acupuncture might be similarly effective. As part of the model program, we investigated whether acupuncture under conditions similar to routine care is as effective and safe as metoprolol, a frequently used first-line drug in migraine prophylaxis.[6]

METHODS

Design.—The study was a randomized, controlled, multicenter trial comparing acupuncture and metoprolol treatment, and performed according to common guidelines for clinical trials (Declaration of Helsinki, ICH-GCP). All study participants provided written, informed consent. The protocol had been approved by all relevant local ethics review boards.

Study duration per patient was 28 weeks: 4 weeks prerandomization baseline, 12 weeks treatment, and 12 weeks follow-up. After baseline, patients meeting the inclusion criteria were randomized stratified by center (block size 12 not known to trial centers) in a 1:1 ratio using a centralized telephone randomization performed by the Institute of Medical Statistics and Epidemiology at the Technische Universität München (random list generated with the software Sample Size 2.0). Patients could not be blinded to treatment, but analysis of patient's headache diaries (containing the main outcome measurement) was performed by 2 blinded evaluators.

Patients.—Inclusion criteria were a diagnosis of migraine with or without aura according to the criteria of the International Headache Society;[7] 2 to 8 migraine attacks per month for the preceding 3 months and during baseline; age 18 to 65 years; migraine present for at least 12 months; completed baseline headache diary; written informed consent.

Exclusion criteria were additional interval headaches on more than 6 days per month; secondary headaches; start of headaches after age of 50 years; use of analgesics on more than 10 days per month; prophylactic migraine treatment with drugs during the 4 preceding weeks; acupuncture treatment for migraine in the 6 preceding months; blood coagulation disorders or coagulation-inhibiting medication other than acetyl-salicylic acid; previous prophylactic use of a β-blocker without success; a co-existing condition incompatible with the use of metoprolol in the study; relevant organic or mental disorders; inability to understand the study; alcohol or drug abuse; pregnancy or lactation; participation in any clinical research study in the preceding 6 months; application for pension or disability benefits; no member of a statutory health insurance company (because the metoprolol prescription was reimbursed by the statutory health insurance companies).

Participating Physicians.—Physicians had to have an acupuncture training at least equivalent to an "A-diploma" from one of the major German acupuncture societies (140 hours of acupuncture training); at least 50% had to have a "B-diploma" (350 hours); all had to participate in study training sessions on the trial methods, the interventions tested, and standards for performing clinical trials (ICH-GCP). Nonmedical acupuncturists were excluded.

Treatments.—The acupuncture intervention was not standardized in order to achieve conditions similar to routine care; only recommendations were given, developed in a consensus process with experienced acupuncture experts.[8] The acupuncture treatment consisted of at least 8 to a maximum of 15 sessions of 20 to 30 minutes duration, administered over a period of 12 weeks. "Basic" points (Gall Bladder 20, 40 or 41 or 42, Du Mai—Governing Vessel 20, Liver 3, San Jiao 3 or 5, extrapoint Taiyang) and additional points based on Traditional Chinese syndrome diagnosis,

localization of pain and symptom modalities were recommended (see[8] for details), but the physician was free to choose other points, including, eg, ear acupuncture and trigger points. Further recommendations were: the use of at least 6 needles and manual stimulation at least once during each session; achievement of "de qi" (an irradiating feeling considered to be indicative of effective needling); the use of sterile disposable single use needles. The details of treatment had to be documented for each session.

The metoprolol intervention was based on the recommendations of the German Migraine and Headache Society[6] and consisted of metoprolol 100 to 200 mg o.d. daily for 12 weeks. During the first 2 weeks of treatment, lower doses could be prescribed. Afterwards, a dose below 100 mg/day was allowed only if the regular dose resulted in adverse drug effects. The first prescription of metoprolol was at the day of randomization. During the treatment period, the patient had to visit the physician at the end of week 4, 8, and 12 in order to check for adverse drug reactions and for the next metoprolol prescription. After the treatment period, 4 weeks with gradual dose reduction were recommended. Metoprolol preparations of "zero order kinetic" were not allowed; otherwise, the preparation could be prescribed freely. The patients were reimbursed for the customary fees of each metoprolol prescription by the trial coordination center.

All patients were allowed to treat acute headaches as needed. Attack treatment should follow the guidelines of the German Migraine and Headache Society,[7] and had to be documented in the diary. After baseline, concomitant treatment should not be changed.

Outcome Measurement.—At the start of the trial, the physician documented the headache diagnosis and the specific migraine history, checked the inclusion and exclusion criteria, and performed a general physical examination. After randomization, the physician documented at each visit details of acupuncture or metoprolol treatment, serious adverse events, and adverse therapy effects.

Additionally, vital parameters of metoprolol patients were measured for safety reasons. To check the compliance, the patient was asked how often he had not followed the metoprolol prescription scheme, with the assurance that reported deviations would have no negative consequence on study participation. At the end of treatment, the physicians evaluated global treatment success and tolerability.

All patients filled in headache diaries in the 4 weeks before randomization (baseline), the 12 weeks after randomization, and in the weeks 21 to 24 after randomization. In the diary, patients recorded for each day occurrence, intensity, type, onset and duration of headaches, and use of rescue medication, if needed. Accompanying symptoms, location, and further characteristics of the headaches were recorded in order to verify the documented headache as migraine.

Furthermore, patients were asked to fill in a modified version of the pain questionnaire of the German Society for the Study of Pain[9] before treatment, after 12 and 24 weeks. The questionnaire includes questions on sociodemographic characteristics, numerical rating scales for pain intensity, questions on workdays lost, global assessments, as well as the following validated scales: the German version of the Pain Disability Index;[10] a scale for assessing emotional aspects of pain (Schmerzempfindungs-Skala SES);[11] the depression scale ADS;[12] the German version of the SF-36 to assess health-related quality of life.[13] Patients reported the occurrence of side effects at the end of week 12.

Primary outcome measure was the difference in number of days with migraine between the 4 weeks before randomization (baseline) and weeks 9 to 12 after randomization as reported by the patient in the headache diary. Predefined secondary outcomes included: number of migraine attacks, number of headache days, and days with rescue medication per 4 weeks; proportion of treatment responders; number of patients with adverse side effects; number of patients which discontinued the trial due to side effects.

Statistics.—The study was originally planned to have 80% power to reject the null-hypothesis H_0: "Acupuncture and metoprolol treatment are not equivalent," with an assumed equivalence range up to an effect size of 0.25 (ie, 1 day with migraine with standard deviation of 4 days), and a 16% drop-out rate. For these conditions, 240 patients per group were considered necessary to prove that acupuncture is at least as effective as metoprolol at the 5% significance level with 1-sided testing.

However, only approximately one quarter of the required patients could be recruited for the trial (see results). Hence, confirmatory testing of equivalence for the primary outcome measure was not possible and exploratory testing (using the Statistical Package for the Social Sciences software program, version 11.5, SPSS Inc., Chicago, Illinois) was performed. The null-hypothesis was modified in a manner to allow the conclusion that the 2 therapies are not equivalent, if a significant difference between the 2 groups in the primary outcome measure is found. However, in case of no significant difference it was not allowed to conclude that the therapies are equivalent. Statistical testing of the main outcome measure was performed by using Student's *t*-test for independent samples (2-sided, 5% significance level), on the intention-to-treat population using all available data without replacement of missing values. In addition, exploratory testing of the originally planned equivalence test and a sensitivity analysis for the main outcome measure replacing missing data by baseline values (thus, setting differences compared with baseline to zero) was performed. Exploratory analyses (*t*-tests or χ^2 tests, 2-tailed, without adjustment for multiple testing) based on all available data without replacing missing data were done for the predefined secondary outcome measures. All data were analyzed descriptively; mean values with standard deviation (SD), 95% confidence intervals (CI), and percentages were provided.

For the analyses the following populations were defined:

- Intention-to-treat ITT: All randomized patients with a filled-in 4 weeks baseline diary, which had started treatment
- Per-protocol PP: All ITT patients excluding relevant protocol violators until week 12

In case of significant baseline differences, analyses of covariance (ANCOVA) with the baseline values as covariates were performed. For dichotomous data, relative risks and responder ratios, respectively, with 95% CI were calculated using the software programs Epi-Info and RevMan 4.2.

RESULTS

Patient Disposition.—Twenty-one study physicians from 17 trial centers in Germany recruited patients for the study; the 3 large centers recruited 50% of the patients. Recruitment of patients was stopped prematurely due to serious problems (most potential patients rejected metoprolol; unequal drop-out from the treatment groups, details see below) and a fixed timeline for the scientific evaluation of the model program.

Most participants were recruited from patients spontaneously contacting trial centers, a minority through reports in local newspapers. Between October 2002 and June 2004, approximately 900 patients expressed interest to participate in the study (Figure 1), 153 entered the baseline, and 114 were randomized. One patient randomized to metoprolol dropped out immediately after randomization and the physician did not save the baseline data. The intent-to-treat population comprised all remaining 113 patients (59 acupuncture, 54 metoprolol).

Two (3%) patients in the acupuncture group and 17 (31%) in the metoprolol group withdrew or were lost to follow-up at week 12 ($P < .001$, χ^2 test). Reasons for the high drop-out in the metoprolol group were as follows: 7 patients refused metoprolol treatment (3 immediately after randomization without metoprolol prescription, 4 at a later time), 7 had intolerable adverse side effects, and 1 showed worsening of symptoms (2 unclear). A further 5 patients (1 acupuncture, 4 metoprolol) did not fill in the headache diary in a manner which allowed the extraction of the main outcome measure. Hence, valid data for the main analysis at week 12 were available for 56 (95%) patients in the acupuncture group and 33 (61%) in the metoprolol group (Figure 1). At week 24 (follow-up), diary data were available for 54 (92%) in the acupuncture group and 33 (61%) in the metoprolol group. For the PP-analysis, 46 acupuncture patients and 26 metoprolol patients without major protocol violations were available at week 12.

Groups showed no significant differences at baseline (Table 1), except for the scale for sensoric pain of the SES.

The mean number of sessions was 13.4 ± 2.5 (mean number of needles per session 13.5 ± 5.8) in the acupuncture group, and 3.2 ± 1.1 in the metoprolol

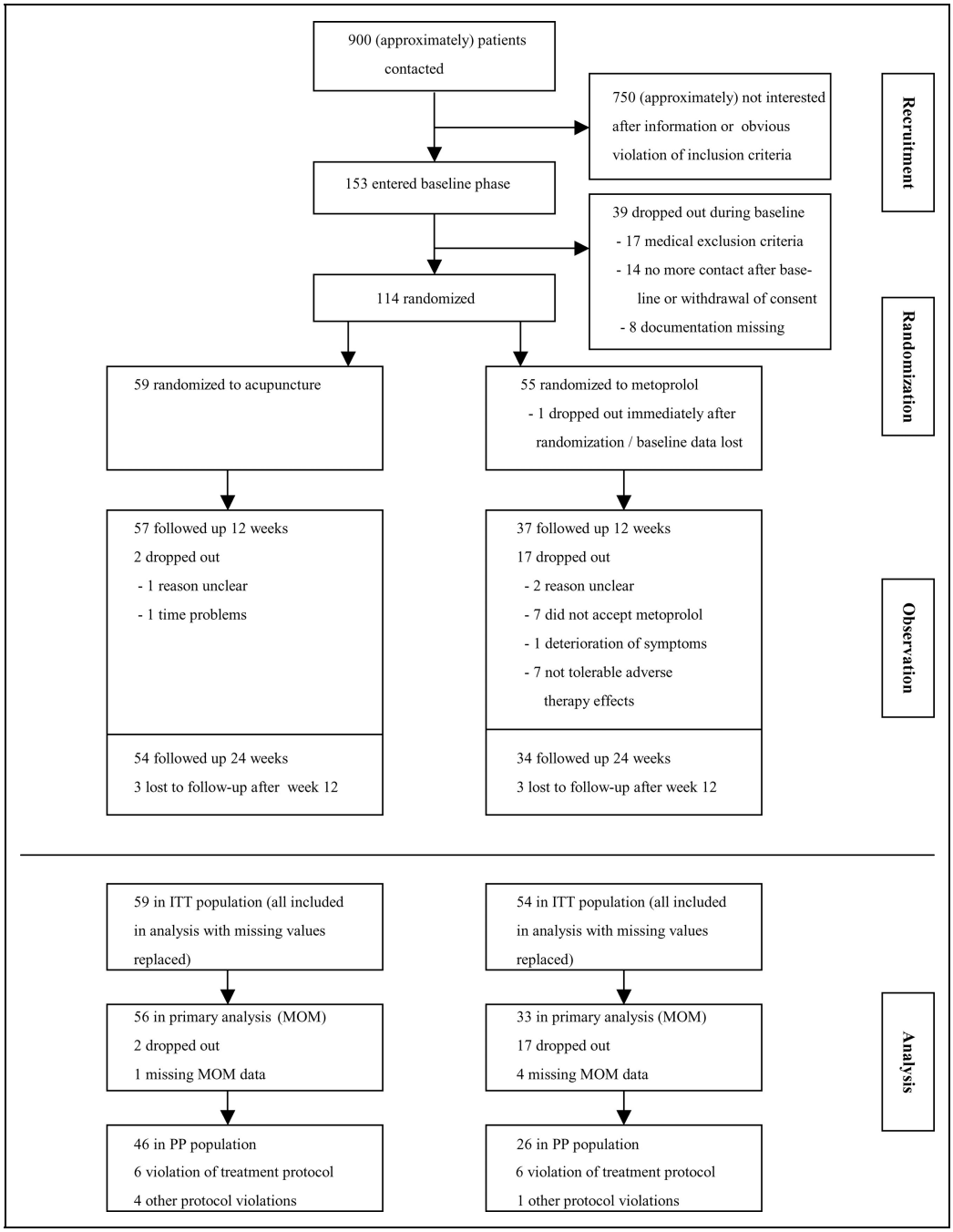

Fig 1.—Trial flow chart (ITT = intention to treat; MOM = main outcome measure; PP = per protocol).

group. With few exceptions, the physicians complied with the rules for metoprolol treatment. During the first 4 weeks, the maintenance dose of 100 to 200 mg/day was reached by 42 (82%) patients. After the control visit at start of week 5, 25 (68%) of the 37 patients remaining after drop-out continued with the requested maintenance dose, and after the control visit at start of week 9, 24 (69%) of 35 patients. The main reason for doses <100 mg/day after week 4 was that a dose reduction had been necessary due to adverse side effects. In addition to the 17 patients that dropped out of the trial completely, 5 patients stopped the metoprolol treatment after some time but continued the diary and the pain questionnaire (2 intolerable

Table 1.—Baseline Characteristics. Values Are Absolute Numbers (Column Percentages) or Means (Standard Deviations)

	N	Acupuncture Mean (SD)/n (%)	N	Metoprolol Mean (SD)/n (%)
Female	59	52 (88%)	54	48 (89%)
Age (years)	59	40.0 (11.4)	54	40.3 (10.7)
Body mass index	57	22.8 (3.6)	45	24.3 (4.2)
Diagnosis according to IHS criteria*	59		54	
Migraine without aura		53 (90%)		48 (89%)
Migraine with aura		10 (17%)		9 (17%)
Duration of disease (years)	59	14.5 (9.9)	54	17.3 (10.8)
Previous acupuncture (for any condition)	59	28 (48%)	54	32 (59%)
No medical prophylaxis according to guidelines (during previous 3 years)	59	54 (92%)	54	49 (91%)
Days with migraine	59	5.8 (2.5)	54	5.8 (2.9)
Days with headache	59	8.0 (3.4)	54	7.3 (2.7)
Number of migraine attacks	59	3.0 (1.4)	54	2.9 (1.3)
Days with rescue medication	59	5.5 (3.2)	54	5.2 (2.8)
Attack medication (baseline phase)				
Triptans	59	24 (41%)	54	30 (57%)
Ergotamines	59	1 (2%)	54	1 (2%)
Analgesics	59	45 (76%)	54	47 (87%)
Combinations	59	11 (19%)	54	7 (13%)
Pain affective (SES, t standard scores)	58	56.2 (8.1)	46	59.0 (7.5)
Pain sensoric (SES, t standard scores)	57	54.8 (7.1)	44	59.0 (9.1)
Disability (PDI)	58	34.7 (18.1)	46	37.5 (18.2)
Physical health (SF-36)†	56	42.6 (7.7)	46	41.1 (8.5)
Mental health (SF-36)†	56	45.7 (11.8)	46	46.8 (10.4)
Depression (ADS, t standard scores)	54	49.9 (9.4)	43	51.4 (7.4)
Average pain (rating scale 0 to 10)	57	5.9 (2.1)	46	6.4 (1.7)

*6% of the patients had both migraine with and without aura.
†Higher values indicate better status.
IHS = International Headache Society; SES = questionnaire for assessing the emotional aspects of pain (Schmerzempfindungsskala); PDI = Pain Disability Index; ADS = depression scale (Allgemeine Depressionsskala).

side effects, 1 did not accept metoprolol any longer, 2 other reasons). Compliance of drug intake as reported by the patients was good; only 3 (9%) of the 33 patients included in the main analysis had forgotten drug intake on more than 10 days during 12 weeks of treatment.

Primary and Secondary Outcomes.—Between baseline and week 9 to 12 the number of days with migraine decreased by 2.5 ± 2.9 days in the acupuncture group compared to 2.2 ± 2.7 days in the metoprolol group (difference acupuncture vs. metoprolol 0.2 days, 95% CI −1.0 to 1.5 days, $P = .721$; 2-sided exploratory testing, intent-to-treat population with all available diary data without replacement of missing values; see Figure 2). The results tended to be in favor of acupuncture if a sensitivity analysis was performed with missing values replaced (ie, difference in migraine days was assumed to be zero). The PP analysis confirmed the results from the main analysis.

The proportion of responders (reduction of migraine attacks by at least 50%) for patients with available diary data without replacement of missing values was 61% in the acupuncture group and 49% in the metoprolol group ($P = .261$). Also for other secondary outcome measures from the diary there were no significant differences between the acupuncture and metoprolol group until week 12. However, acupuncture patients fared significantly better for several parameters from the pain questionnaire (Table 2).

The improvements observed in both groups persisted during the follow-up. Results in the acupuncture group tended to be slightly better than in the

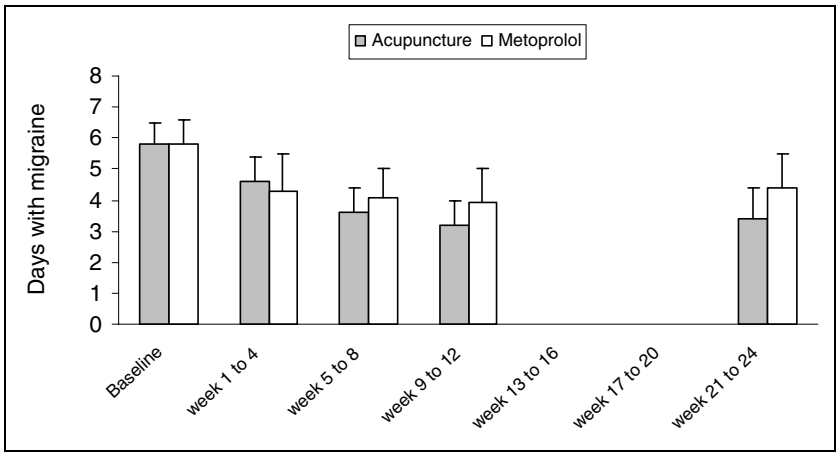

Fig 2.—Number of days (means and 95% CI) with migraine.

metoprolol group; for migraine attacks and several parameters from the pain questionnaire the differences were significant (Table 3).

Global assessment by patients after 12 weeks was evaluated as "very good" or "good" by 37 (70%) of 53 acupuncture patients and by 15 (45%) of 33 metoprolol patients, and after 24 weeks by 56% and 26%, respectively. Physicians assessed global treatment success at end of week 12 as significantly better in the acupuncture group.

Safety and Tolerability.—For 2 patients a hospital stay for surgery considered unrelated to study

Table 2.—Secondary Outcomes at Week 9 to 12 (Diary) and End of Week 12 (Questionnaire), Respectively

	Acupuncture Mean (SD)/n (%)	Metoprolol Mean (SD)/n (%)	Acupuncture versus Metoprolol; Δ (95% CI)/RR (95% CI)	*P*
Headache diary weeks 9 to 12				
Days with migraine	3.2 (3.0)	3.9 (3.1)	−0.7 (−2.0; 0.7)	.309
Days with headache	4.5 (3.6)	4.6 (3.1)	−0.1 (−1.6; 1.4)	.892
Number of migraine attacks	1.6 (1.5)	1.9 (1.5)	−0.3 (−0.9; −0.4)	.373
Days with rescue medication	3.4 (3.2)	3.6 (2.5)	−0.2 (−1.5; 1.1)	.724
≥50% reduction migraine attacks*	34 (61%)	16 (49%)	1.25 (0.83; 1.89)	.261
≥50% reduction days with migraine*	31 (55%)	16 (49%)	1.14 (0.75; 1.74)	.530
Questionnaire end of week 12				
Pain affective (SES, t standard scores)	46.0 (10.5)	52.5 (12.1)	−6.5 (−11.4; −1.6)	.032
Pain sensoric (SES, t standard scores)	50.8 (9.1)	55.9 (12.4)	−5.1 (−9.7; −0.5)	.089
Disability (PDI)	14.4 (15.8)	22.8 (17.6)	−8.3 (−15.6; −1.1)	.025
Physical health (SF-36)†	48.3 (7.4)	44.5 (8.8)	3.8 (0.3; 7.3)	.034
Mental health (SF-36)†	50.1 (9.0)	50.1 (7.6)	−0.1 (−3.8; 3.7)	.979
Depression (ADS, t standard scores)	45.7 (7.9)	47.5 (8.6)	−1.8 (−5.6; 2.0)	.350
Average pain (rating scale 0 to 10)	3.1 (2.1)	4.4 (2.0)	−1.4 (−2.3; −0.4)	.005

Exploratory *P*-values from two-sided t-tests or χ^2 test; for SES from ANCOVA with baseline values as covariates; percentages are column percentages; Δ = mean difference between groups; RR = responder ratio (proportion responders acupuncture/proportion responders metoprolol).

*Responder proportions were calculated considering all patients with available data (n acupuncture group = 56, metoprolol group = 33).

†Higher values indicate better status.

Minor discrepancies between differences calculated from group means presented in the table and Δ are due to rounding.

SES = questionnaire for assessing the emotional aspects of pain (Schmerzempfindungsskala); PDI = Pain Disability Index; ADS = depression scale (Allgemeine Depressionsskala).

Table 3.—Secondary Outcomes at Week 21 to 24 (Diary) and End of Week 24 (Questionnaire), Respectively

	Acupuncture Mean (SD)/n (%)	Metoprolol Mean (SD)/n (%)	Acupuncture versus Metoprolol Δ (95% CI)/RR (95% CI)	*P*
Headache diary weeks 21 to 24				
Days with migraine	3.4 (3.5)	4.4 (3.0)	−1.0 (−2.5; 0.5)	.179
Days with headache	4.5 (3.9)	5.1 (2.7)	−0.6 (−2.1; 1.0)	.474
Number of migraine attacks	1.5 (1.3)	2.4 (1.5)	−0.9 (−1.5; −0.3)	.003
Days with rescue medication	3.3 (3.0)	3.9 (2.4)	−0.7 (−1.9; 0.6)	.275
≥50% reduction migraine attacks*	35 (65%)	12 (36%)	1.78 (1.09; 2.92)	.010
≥50% reduction days with migraine*	29 (54%)	13 (39%)	1.36 (0.83; 2.23)	.195
Questionnaire end of week 24				
Pain affective (SES, t standard scores)	46.5 (11.4)	52.3 (9.7)	−5.8 (−10.4; −1.1)	.027
Pain sensoric (SES, t standard scores)	49.7 (9.4)	56.5 (10.1)	−6.7 (−10.9; −2.5)	.003
Disability (PDI)	14.3 (17.2)	24.9 (18.7)	−10.6 (−18.4; −2.8)	.008
Physical health (SF-36)†	47.0 (7.1)	43.6 (8.1)	3.4 (0.2; 6.7)	.041
Mental health (SF-36)†	48.9 (11.1)	48.4 (10.9)	0.5 (−4.3; 5.3)	.833
Depression (ADS, t standard scores)	46.1 (11.3)	47.7 (11.5)	−1.6 (−6.6; 3.3)	.520
Average pain (rating scale 0 to 10)	3.5 (2.4)	5.1 (2.3)	−1.6 (−2.7; −0.6)	.002

Exploratory *P*-values from 2-sided t-tests or χ^2 test; for SES from ANCOVA with baseline values as covariates; percentages are column percentages; Δ = mean difference between groups; RR = responder ratio (proportion responders acupuncture/proportion responders metoprolol).

*Responder proportions were calculated considering all patients with available data (n acupuncture group = 54, metoprolol group = 33).

†Higher values indicate better status.

Minor discrepancies between differences calculated from group means presented in the table and Δ are due to rounding.

SES = questionnaire for assessing the emotional aspects of pain (Schmerzempfindungsskala); PDI = Pain Disability Index; ADS = depression scale (Allgemeine Depressionsskala).

condition and intervention was reported as serious adverse event. Both patients continued the trial.

The physicians reported no adverse therapy effects of "strong" intensity for the acupuncture group, but 7 well-known side-effects of metoprolol in 6 patients from the metoprolol group. All effects were completely reversible. Thirteen "mild" adverse therapy effects were documented in 9 (15%) of 59 acupuncture patients with at least 1 treatment, and 36 in 28 (55%) of 51 patients who had received metoprolol. In the pain questionnaire, fewer patients reported side effects (12% and 35%, respectively; $P < .001$). Due to adverse effects, no acupuncture patient dropped out or ended treatment, but 7 metoprolol patients dropped out completely, 2 stopped treatment but continued diary and questionnaires, and in 11 the dose had to be reduced.

COMMENT

This study was originally planned as an equivalence trial with a total of 480 patients. However, recruitment was stopped prematurely due to recruitment problems (the majority of eligible patients did not accept the possibility of being randomized to metoprolol treatment) and the high drop-out in the metoprolol group. Therefore, only exploratory analyses could be performed and the results of our trial must be interpreted with caution. In these analyses of our data acupuncture was similarly effective and better tolerated than metoprolol. The improvements persisted during the follow-up in both groups, with a tendency to favor acupuncture.

The aim of this study was to compare acupuncture and a standard drug treatment under conditions similar to routine care. Due to the failure to meet our recruitment target our findings cannot be interpreted in a confirmatory manner. However, with a sample size of 113 patients our study is still larger than many other trials of interval treatments for migraine. Can our findings in this patient sample be considered internally valid and are they relevant for a broader group of migraineurs?

The protocol was based on the recommendations of the International Headache Society's subcommittee on clinical trials[14] and on standards for performing clinical trials (ICH-GCP). Randomization was strictly concealed and diary evaluation was performed by blinded raters. The validity of our results is supported by the consistency of findings as judged by a variety of instruments including a headache diary and validated questionnaires on quality of life, disability, and emotional aspects of pain.

However, the migraine patients in our study are probably not representative of those seeking care in the average neurological practice. Approximately 50% of the participants had received acupuncture treatment for migraine before, and 95% of the patients in the acupuncture group expected a definite improvement of their complaints. The large number of eligible patients refusing consent or dropping out after being allocated to metoprolol further indicates that the majority of patients approached for recruitment had a highly positive attitude towards acupuncture. There is some evidence for acute pain that positive expectations have an impact on pain relief.[15,16] In our study, improvements regarding the rather "descriptive" parameters from the headache diary were similar in both groups, whereas several "affective" parameters from the pain questionnaire showed significantly better results for acupuncture. Apparently, the acupuncture patients subjectively "felt" healthier after treatment than the patients with metoprolol prophylaxis. The high response rate of 61% observed after acupuncture treatment in this trial might not be achieved in patients being more skeptical about this therapy. Still, experiences from ongoing reimbursement programs in Germany show that a large number of patients seek acupuncture treatment. From July 2001 to December 2004 more than 2 million patients (2.5% of the total German population) with chronic pain have been treated with acupuncture; about a third of these had migraine or tension-type headache. The results of a large observational study embedded in the reimbursement program suggest that the response rate for acupuncture under conditions of routine practice is similar to that observed in our randomized trial.[17] Therefore, while our findings are probably not generalizable to all migraine sufferers, they could well apply to an important subgroup.

About a third of the patients randomized to metoprolol did not complete the study. As our study was not blinded and the daily dose of metoprolol exceeded 100 mg only in a minority of the patients it could be speculated that the effect of drug prophylaxis in comparison to acupuncture was underestimated. However, the response rate of 49% in the metoprolol group in our study is well comparable with results from other trials on first-line drugs for migraine prophylaxis.[1,18-20] Furthermore, our way of analyzing the data (not replacing missing values but only including patients with valid data) would be normally considered to favor the metoprolol group as patients completing the study are more likely to be responders than patients who withdraw. Use of rescue medication was similar in both groups, making an influence of effective co-interventions unlikely.

Our study confirms the results from the 2 rigorous published trials comparing acupuncture with metoprolol[4] or flunarizine[5] suggesting that acupuncture might be similarly effective. A further large trial with head to head comparison of acupuncture and standard drug treatment is currently underway.[21] A recent large, pragmatic trial from the UK has shown that patients receiving acupuncture in addition to GP care did significantly better than patients receiving GP care alone at little additional cost.[22,23] Preliminary results of a large, pragmatic trial from Germany seem to confirm these findings.[24]

While there is increasing evidence suggesting that acupuncture is more effective than no treatment and appears to be similarly effective as interval treatment with standard drugs it is unclear how these beneficial effects are achieved. In addition to our trial presented here and the observational study cited above we also performed a trial on migraine patients comparing acupuncture to minimal acupuncture (a sort of sham acupuncture with superficial needling at distant nonacupuncture points) and no treatment.[25] While there was a marked effect over no treatment, minimal acupuncture proved as effective as true acupuncture. This finding is somewhat in contrast with those of the majority of older, smaller studies.[2] But overall, the

evidence suggests that the correct location of needles is (if relevant at all) only one factor among others. Physiological effects of repeated, mild painful stimuli by needling[26-28] as well as particularly potent "placebo" effects associated "specifically" with the whole setting of acupuncture might (also) be responsible for the relevant clinical effects. A particularly important factor regarding the routine care situation could be the increased patient—physician contact (in our study, on average 13 visits for acupuncture compared to 3 visits for metoprolol).

However, a recent meta-analysis of double-blind migraine trials on drug prophylaxis showed an average responder rate of 46% for active treatment and of 24% for placebo.[29] One aim of that study was to estimate the extent of placebo response for open-label prophylactic migraine trials. The authors concluded that if the percentage of responders in such a trial is above 35 to 40%, the chance that the effect appears to be a placebo response seems small.

Final aspects to be mentioned are safety and compliance. Several large surveys have shown that acupuncture is well tolerated and that serious complications are rare events.[30,31] In our study only minor adverse effects were reported for acupuncture and no acupuncture patient withdrew due to adverse effects. This compares favorably to our findings for metoprolol and to trials on treatment with other drugs.[20,32] Apart from patients' preferences, tolerability and safety of treatment are considered key factors to maximize compliance, an important principle of preventive therapy.[18,33]

In conclusion, the results of our exploratory analyses must be interpreted with caution. Still, despite a number of shortcomings this trial adds to the growing body of evidence that acupuncture might be an effective and safe treatment option and, thus, could be a helpful tool for the interval treatment of migraine, particularly in patients unwilling or unable to use drug prophylaxis.

Acknowledgment: The study was funded by the following German social health insurance funds: Deutsche Angestellten-Krankenkasse (DAK), Hamburg; Barmer Ersatzkasse (BEK), Wuppertal; Kaufmännische Krankenkasse (KKH), Hannover; Hamburg-Münchener Krankenkasse (HaMü), Hamburg; Hanseatische Krankenkasse (HEK), Hamburg; Gmünder Ersatzkasse (GEK), Schwäbisch Gmünd; HZK Krankenkasse für Bau- und Holzberufe, Hamburg; Brühler Ersatzkasse, Solingen; Krankenkasse Eintracht Heusenstamm (KEH), Heusenstamm; Buchdrucker Krankenkasse (BK), Hannover. We would like to thank Joseph Hummelsberger, MD, and Dominik Irnich, MD, for developing the acupuncture treatment recommendations together with Michael Hammes and for their input at various levels of the protocol development. We thank all participating study physicians, as well as Susanne Jürgens, MSc, Cornelia Aigner, MSc, Susanne Hofmann, MD, Markus Kowasch, MD, and Jolin Fischer, MD, for monitoring the trial centers, and all students involved in trial organization.
Conflict of Interest: None

REFERENCES

1. Gray RN, Goslin RE, McCrory DC, Eberlein K, Tulsky J, Hasselblad V. Drug treatment for the prevention of migraine headache. Technical Review 2.3. Duke University, Durham, NC. Center for Clinical Health Policy Research; Agency for Health Care Policy and Research, Rockville, MD.
2. Melchart D, Linde K, Fischer P, et al. Acupuncture for recurrent headaches: A systematic review of randomized controlled trials. *Cephalalgia*. 1999;19:779-786.
3. Melchart D, Streng A, Reitmayr S, Hoppe A, Weidenhammer W, Linde K. Programm zur Evaluation der Patientenversorgung mit Akupunktur (PEP-AC)—die wissenschaftliche Begleitung des Modellvorhabens der Ersatzkassen (Program to evaluate acupuncture in the German health care system [PEP-AC]—the scientific concept of the program of a group of statutory sickness funds). *Z ärztl Fortbild Qual Gesundhwes*. 2004;98:471-473.
4. Hesse J, Mogelvang B, Simonsen H. Acupuncture versus metoprolol in migraine prophylaxis: A randomized trial of trigger point inactivation. *J Intern Med*. 1994;235:451-456.
5. Allais G, De Lorenzo C, Quirico P, et al. Acupuncture in the prophylactic treatment of migraine without aura: A comparison with flunarizine. *Headache*. 2002;42:855-861.
6. Diener HC, Brune K, Gerber WD, Göbel H, Pfaffenrath V. Behandlung der Migräneattacke und Migräneprophylaxe. *Dtsch Ärztebl* 1997;94:C2277-C2283.

7. International Headache Society. ICH-10 guide for headaches. *Cephalalgia*. 1997;17(suppl 19):1-82.
8. Melchart D, Linde K, Streng A, et al. Acupuncture randomized trials (ART) in patients with migraine or tension-type headache—design and protocols. *Forsch Komplementärmed Klass Naturheilkd*. 2003;10:179-184.
9. Nagel B, Gerbershagen HU, Lindena G, Pfingsten M. Entwicklung und empirische Überprüfung des Deutschen Schmerzfragebogens der DGSS. *Schmerz* 2002;16:263-270.
10. Dillmann U, Nilges P, Saile E, Gerbershagen HU. Behinderungseinschätzung bei chronischen Schmerzpatienten. *Schmerz*. 1994;8:100-110.
11. Geissner E. Die Schmerzempfindungsskala (SES). Göttingen, Germany: Hogrefe; 1996.
12. Hautzinger M, Bailer M. Allgemeine Depressionsskala (ADS). Die deutsche Version des CES-D. Weinheim, Germany: Beltz; 1993.
13. Bullinger M, Kirchberger I. SF-36 Fragebogen zum Gesundheitszustand. Göttingen, Germany: Hogrefe: 1998.
14. International Headache Society Clinical Trials Subcommittee. Guidelines for controlled trials of drugs in migraine: Second edition. *Cephalalgia*. 2000;20:765-786.
15. Wager TD, Rilling JK, Smith EE, et al. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science*. 2004;303:1162-1167.
16. Bausell RB, Lao L, Bergman S, Lee WL, Berman BM. Is acupuncture analgesia an expectancy effect? Preliminary evidence based on participants' perceived assignments in two placebo-controlled trials. *Eval Health Prof*. 2005;28:9-26.
17. Melchart D, Weidenhammer W, Streng A, Hoppe A, Pfaffenrath V, Linde K. Acupuncture for chronic headaches—an epidemiological study. *Headache*. (accepted).
18. Silberstein SD, Goadsby PJ. Migraine: Preventive treatment. *Cephalalgia*. 2002;22:491-512.
19. Linde K, Rossnagel K. Propranolol for migraine prophylaxis (Cochrane Review). In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd; 2004.
20. Diener HC, Matias-Guiu J, Hartung E, et al. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: A comparison with propranolol 160 mg daily. *Cephalalgia*. 2002;22:209-221.
21. Molsberger A, Diener HC, Krämer J, et al. GERAC-Akupunktur-Studien—Modellvorhaben zur Beurteilung der Wirksamkeit [GERAC acupuncture trials—a program to assess effectiveness]. *Dtsch Ärztebl*. 2002;99:A1819-A1824.
22. Vickers AJ, Rees RW, Zollmann CE, et al. Acupuncture for chronic headache in primary care: Large, pragmatic, randomised trial. *BMJ*. 2004;328:744-746.
23. Wonderling D, Vickers AJ, Grieve R, McCarney R. Cost effectiveness analysis of a randomised trial of acupuncture for chronic headache in primary care. *BMJ*. 2004;328:747-749.
24. Jena S, Becker-Witt C, Brinkhaus B, Selim D, Willich SN. Effectiveness of acupuncture treatment for headache— the Acupuncture in Routine Care Study (ARC Headache). *Focus Alternative Complementary Ther*. 2004;9(suppl 1):17.
25. Linde K, Streng A, Jürgens S, et al. Acupuncture for patiens with migraine. A randomized controlled trial. *JAMA*. 2005;293:2118-2125.
26. Irnich D, Beyer A. Neurobiologische Grundlagen der Akupunkturanalgesie. *Schmerz*. 2002;16:93-102.
27. Sandkühler J. The organization and function of endogenous antinociceptive systems. *Prog Neurobiol*. 1996;50:49-81.
28. Bäcker M, Hammes M, Sander D, et al. Changes of cerebrovascular response to visual stimulation in migraineurs after repetitive sessions of somatosensory stimulation (acupuncture): A pilot study. *Headache*. 2004;44:95-101.
29. Van der Kuy P-HM, Lohmann JJHM. A quantification of the placebo response in migraine prophylaxis. *Cephalalgia*. 2002;22:265-270.
30. Ernst E, White AR. Prospective studies of the safety of acupuncture: A systematic review. *Am J Med*. 2001;110:481-485.
31. Melchart D, Weidenhammer W, Streng A, et al. Prospective investigation of adverse effects of acupuncture in 97,733 patients. *Arch Intern Med*. 2004;164:104-105.
32. Brandes JL, Saper JR, Diamond M, et al. Topiramate for migraine prevention. A randomized controlled trial. *JAMA*. 2004;291:965-973.
33. Diener HC, Pfaffenrath V, Schnitker J, Friede M, Henneicke-von Zepelin HH on behalf of the Investigators. Efficacy and safety of 6.25 mg t.i.d. feverfew CO2-extract (MIG-99) in migraine prevention—a randomized, double-blind, multicentre, placebo-controlled study. *Cephalalgia*. 2005;25:1031-1041.