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Acupuncture in Patients With Osteoarthritis of the Knee or Hip

A Randomized, Controlled Trial With an Additional Nonrandomized Arm

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Objective. **To investigate the effectiveness of acupuncture in addition to routine care, compared with routine care alone, in the treatment of patients with chronic pain due to osteoarthritis (OA) of the knee or hip.**

Methods. **In a randomized, controlled trial, patients with chronic pain due to OA of the knee or hip were randomly allocated to undergo up to 15 sessions of acupuncture in a 3-month period or to a control group receiving no acupuncture. Another group of patients who did not consent to randomization underwent acupuncture treatment. All patients were allowed to receive usual medical care in addition to the study treatment. Clinical OA severity (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]) and health-related quality of life (Short Form 36) were assessed at baseline and after 3 months and 6 months.**

Results. **Of 3,633 patients (mean ± SD age 61.8 ± 10.8 years; 61% female), 357 were randomized to the acupuncture group and 355 to the control group, and 2,921 were included in the nonrandomized acupuncture group. At 3 months, the WOMAC had improved by a mean ± SEM of 17.6 ± 1.0 in the acupuncture group and 0.9 ± 1.0 in the control group (3-month scores 30.5 ± 1.0 and 47.3 ± 1.0, respectively [difference in improvement 16.7 ± 1.4; $P < 0.001$]). Similarly, quality of life improvements were more pronounced in the acupuncture group versus the control group ($P < 0.001$). Treatment success was maintained through 6 months. The changes in outcome in nonrandomized patients were comparable with those in randomized patients who received acupuncture.**

Conclusion. **These results indicate that acupuncture plus routine care is associated with marked clinical improvement in patients with chronic OA–associated pain of the knee or hip.**

Osteoarthritis (OA) has a major impact on patients' physical functioning and independent mobility (1). Common sites of OA are the knee and the hip (2). The antiinflammatory medications frequently used to treat symptoms of this condition are associated with a number of side effects (3). Furthermore, if these drugs do not lead to adequate response, replacement surgery is often recommended (4).

In recent years, patients with chronic pain have increasingly used acupuncture for relief (5). In a systematic review including 7 randomized controlled trials with a total of 393 patients, acupuncture was shown to be more effective than sham acupuncture in reducing pain, whereas the results regarding joint function were inconclusive (6). Two recent studies, one by Berman et al (7) and one by our group (8), showed some evidence that acupuncture is superior to sham acupuncture in improv-

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ing function and reducing pain in patients with OA of the knee. The main aim of all of the above-mentioned studies was to determine the efficacy of acupuncture compared with sham acupuncture. To maximize internal validity, these trials used standardized or at least semi-standardized acupuncture interventions. In contrast, in routine care a broad variety of acupuncture styles is used, and acupuncture is often administered in conjunction with other treatments. To date there has been little information about the effectiveness of acupuncture treatment provided as an adjunct to routine medical care.

In 2000 the German Federal Committee of Physicians and Health Insurers proposed that large research initiatives on the use of acupuncture for several pain syndromes could be conducted by health insurance companies (9). As one of these research initiatives, we designed the present study as a pragmatic trial to investigate the efficacy of acupuncture in addition to routine care compared with routine care alone in patients with pain due to OA of the knee or the hip. In addition, we examined whether the effects of acupuncture differ in randomized and nonrandomized patients, whether treatment effects last for a period of time after treatment is discontinued, and whether specific patient and physician characteristics are associated with particular treatment outcomes.

Based in part on the results of the present study, the German Federal Committee of Physicians and Health Insurers proposed in April 2006 that acupuncture will be reimbursed by statutory health insurance funds. Pending final decision by the German Ministry of Health, acupuncture will likely be provided as a routine medical option in the treatment of pain due to OA of the knee.

PATIENTS AND METHODS

Study design. The Acupuncture in Routine Care (ARC) study included a multicenter, randomized, controlled trial and a nonrandomized cohort. Patients who agreed to randomization were allocated to an acupuncture group (patients who received immediate acupuncture treatment) or a control group (patients who received delayed acupuncture treatment [starting 3 months after baseline]). Patients who declined to be randomized were included in a third arm and also received immediate acupuncture treatment (nonrandomized acupuncture group). The study period for each patient was 6 months: a 3-month treatment phase followed by 3 months of followup.

The ARC study is part of a large acupuncture research initiative funded by a group of statutory health insurance funds that provide coverage to ~10% of the German population. The study protocol was approved by the local ethics review boards, and the study itself was conducted according to standard guidelines (i.e., Declaration of Helsinki and Good Epidemiological Practice [10]). All study participants provided written informed consent.

Patients. All patients in this study were insured by one of the participating statutory health insurance funds and had contacted a participating physician due to OA pain in the knee or hip. If the patient requested acupuncture or if the physician considered acupuncture to be a suitable treatment option, the patient was informed about the study. Patients were provided with information on the study design, study procedure, and acupuncture treatment. Those who met the inclusion criteria (see below), provided informed consent, and signed an agreement for randomization were randomized using a central telephone randomization procedure. For randomization we used blocks of 10, and the random list was generated with SAS software. Patients who declined randomization were included in the nonrandomized acupuncture group. Patients were included in the study only if we received the patient consent form following randomization. Upon successful enrollment in the study, patients were sent, by standard mail, a questionnaire in which to record their baseline characteristics. Criteria for inclusion in the study were as follows: age $\geq$40 years, clinical diagnosis of OA-associated pain in the knee or hip with disease duration of $>$6 months, radiologic evidence of OA (osteophyte formation), and at least 15 days with pain in the preceding 30 days. Knee or hip pain due to inflammation or malignancy was a criterion for exclusion.

Interventions. Physicians interested in participating in the study were required to have at least an A-diploma, which represents 140 hours of certified acupuncture education. Certified acupuncture education and training programs in Germany vary widely in terms of the acupuncture style and technique that are taught.

Each patient in the randomized and nonrandomized acupuncture groups received up to 15 acupuncture sessions during the first 3 months of the study, and no acupuncture during the fourth through sixth months. Because the aim of this study was to assess the effectiveness of acupuncture in general medical practice, each patient could be treated individually (as opposed to use of a standardized protocol), and the number of needles and acupuncture points used were chosen at the physician's discretion. Only needle acupuncture (with disposable 1-time-use needles) was allowed; other forms of acupuncture treatment (e.g., laser acupuncture, electroacupuncture, moxibustion) were not permitted. In addition, only manual needle stimulation was allowed. The control group was not allowed to receive any kind of acupuncture during the first 3 months. In all 3 treatment groups, the patients were permitted to receive any additional conventional treatments as needed. In accordance with German federal regulations, the participating health insurance companies covered 100% of the acupuncture costs for patients who agreed to randomization and 90% percent of the costs for patients who participated in the study but did not agree to randomization.

Outcome measures. The patients completed standardized questionnaires, including information on sociodemographic characteristics, at baseline and after 3 months and 6 months. The primary outcome measure was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (11,12). The patients documented, at baseline,

which was the most painful joint and assessed this during the whole study period. As a secondary outcome measure, we used the percent reduction in the WOMAC index. If the WOMAC index increased in a patient during followup, the percent was calculated with respect to the maximum possible decrease and shown as a negative value. We decided to use the percent reduction rather than the absolute reduction in the WOMAC index since the latter correlated with the baseline score ($r = 0.415$) while the former showed almost no correlation ($r = 0.047$). Patients who showed an improvement of at least 50% in the WOMAC were considered to be treatment responders. All patients with missing data were counted as nonresponders.

As further secondary outcome parameters we used the Short Form 36 (SF-36) component scales (13) to assess health-related quality of life. Side effects were recorded on patient and physician questionnaires after 3 months.

Statistical analysis. Confirmatory testing of the primary and secondary outcome measures (using SPSS 11.5) was based on the intent-to-treat population, using the maximum available data set. Sensitivity analyses for the primary outcome measure were performed either by replacing missing data according to the last observation carried forward principle or by using various hot deck methods or regression-based multiple imputation. Test procedures to maintain a global significance level (α) of 5% were performed. Using covariance analysis, we tested the 2-sided null hypothesis, i.e., mean WOMAC index after 3 months of acupuncture = mean WOMAC index after 3 months in controls. Group sizes of 223 patients were required for the study to have 90% power to detect a difference of 8 points in the WOMAC index, assuming a mean of 43 score points and an SD of 26.

In order to identify factors affecting improvement in the WOMAC index and for better understanding of patient selection due to acceptance of randomization, we fitted linear mixed models for the WOMAC index to the data on all study patients. Mixed models were chosen to comply with the potential cluster structure of the data, because several patients were enrolled by the same physician. As potential regressors, we prespecified several characteristics of the physicians (age, years of professional experience, type of acupuncture diploma, hours of acupuncture training, years of acupuncture experience, experience in diagnosis in the context of traditional Chinese medicine, and percent of practice time spent performing acupuncture) and of the patients (sex, age, education level, baseline physical and mental quality of life scores, WOMAC index, duration of symptoms prior to the study, and study group to which each patient was assigned). For the final model, we selected significant variables in a stepwise backwards procedure based on likelihood ratio tests. In addition, we considered the selected regressors as potential modifiers of the acupuncture effect and added the corresponding interaction terms to the model, backwards selecting if they were significant. All reported P values are 2-sided.

RESULTS

Patient enrollment, baseline characteristics, and treatment. From July 2001 to July 2004 a total of 3,633 patients with pain due to arthritis of the knee or the hip were recruited for the study, by 1,417 study physicians (Figure 1). A total of 712 patients accepted randomization and were allocated to the acupuncture group or the control group. Eighty patients (35 randomized to the acupuncture group, 45 to the control group) could not be included in the analysis because the study office did not receive the consent form or the patient did not receive the study intervention. The remaining 3,553 patients (322 in the randomized acupuncture group, 310 in the control group, 2,921 in the nonrandomized acupuncture group) were included in the analysis. After 3 months, data were available on 93.2% of the patients (308 in the randomized acupuncture group, 289 in the control group, 2,716 in the nonrandomized acupuncture group).

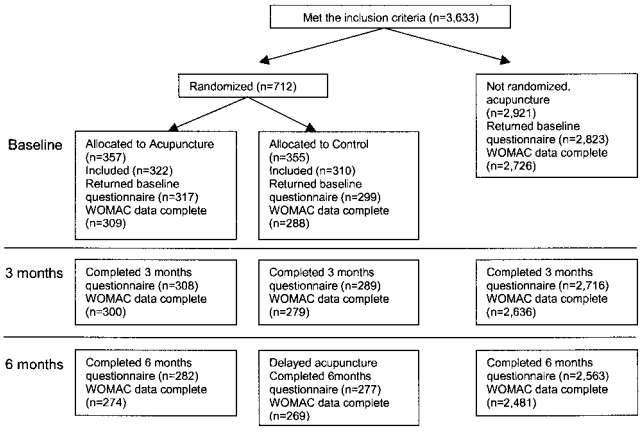

Figure 1. Flow chart of patient disposition in the trial. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

The randomized groups were comparable with regard to baseline characteristics (Table 1). In addition, with the exception of the reason for seeking acupuncture treatment, the randomized and the nonrandomized acupuncture groups showed no significant differences at baseline.

OA of the knee was present in 57.1% of the patients, OA of the hip in 14.5%, and OA of both the knee and the hip in 28.4% (Table 1). Only 11.8% of the patients had had acupuncture during the 12 months immediately prior to study entry (13.9% of those in the randomized acupuncture group, 10.0% of those in the control group, and 11.7% of those in the nonrandomized acupuncture group; $P = 0.328$). For subgroup analyses, patients were grouped according to the most painful joint (as reported at baseline and assessed throughout the study period); the evaluated joint was the knee in 2,627 patients and the hip in 926.

Table 1. Baseline characteristics of the study population*

Characteristic	Randomized patients only			Randomized and nonrandomized patients			
	Acupuncture (n = 322)	Control (n = 310)	P†	Randomized (acupuncture and control) (n = 632)	Nonrandomized (n = 2,921)	P†	Total (n = 3,553)
Female, %	56.8	63.9	0.071	60.3	61.2	0.665	61.0
Age, years	60.6 ± 10.2	61.9 ± 10.6	0.123	61.2 ± 10.4	61.9 ± 10.9	0.148	61.8 ± 10.8
>10 years of education, %	17.9	21.7	0.256	19.8	22.3	0.178	21.8
Site of osteoarthritis, no. (%)							
Hip	51 (15.8)	41 (13.2)		92 (14.6)	423 (14.5)		515 (14.5)
Knee	175 (54.3)	167 (53.9)		342 (54.1)	1,686 (57.7)		2,028 (57.1)
Hip and knee	96 (29.8)	102 (32.9)	0.618	198 (31.3)	812 (27.8)	0.064	1,010 (28.4)
Evaluated joint, no. (%)							
Hip	87 (27.0)	82 (26.5)		169 (26.7)	757 (25.9)		926 (26.1)
Knee	235 (73.0)	228 (73.5)	0.872	463 (73.3)	2,164 (74.1)	0.669	2,627 (73.9)
Reason for participating in this study‡							
Previous successful acupuncture	103 (32.0)	93 (30.0)	0.698	196 (31.0)	848 (29.0)	0.357	1,044 (29.4)
Ineffectiveness of other treatments	139 (43.2)	140 (45.2)	0.332	279 (44.1)	1,162 (39.8)	0.049	1,441 (40.6)
Wish to reduce medication	256 (79.5)	239 (77.1)	0.693	495 (78.3)	2,164 (74.1)	0.026	2,659 (74.8)
Suggestion of the physician	253 (78.6)	241 (77.7)	0.535	494 (78.2)	2,126 (72.8)	0.011	2,620 (73.7)
Disease duration, years	5.2 ± 5.9	5.3 ± 6.5	0.759	5.3 ± 6.2	5.0 ± 6.3	0.411	5.1 ± 6.3
WOMAC index	48.2 ± 23.3	48.0 ± 23.4	0.946	48.1 ± 23.4	46.8 ± 22.9	0.207	47.0 ± 23.0
WOMAC pain	48.5 ± 23.2	48.0 ± 22.4	0.799	48.3 ± 22.8	47.0 ± 22.8	0.229	47.3 ± 22.8
WOMAC stiffness	51.9 ± 29.7	51.4 ± 30.1	0.817	51.7 ± 29.8	50.4 ± 29.1	0.338	50.6 ± 29.2
WOMAC function	47.3 ± 24.5	47.7 ± 24.6	0.865	47.5 ± 24.6	46.3 ± 24.2	0.260	46.5 ± 24.3
Quality of life (SF-36)							
Physical component score	30.6 ± 8.6	30.6 ± 8.9	0.955	30.6 ± 8.7	30.6 ± 8.8	0.956	30.6 ± 8.8
Mental component score	49.9 ± 12.2	49.0 ± 12.0	0.393	49.5 ± 12.1	49.7 ± 12.0	0.685	49.7 ± 12.0

* Except where indicated otherwise, values are the mean ± SD. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index (lower values indicate fewer symptoms); SF-36 = Short Form 36 (higher values indicate better quality of life).
† By 2-sided *t*-test or chi-square test.
‡ Patients were allowed to choose multiple answers.

Because there were no significant baseline differences between patients with OA of the knee and patients with OA of the hip, the baseline data on these subgroups are not presented separately. Patients in the acupuncture groups received a mean ± SD of 10.7 ± 3.9 acupuncture sessions (randomized acupuncture group 10.8 ± 2.1, nonrandomized acupuncture group 10.7 ± 4.0; $P = 0.647$). Most patients (76.6%) underwent 5–10 sessions, whereas 21.1% had >10 sessions and 2.2% had <5 sessions.

Comparisons between randomized groups. Changes in the WOMAC scores in both randomized groups and the nonrandomized group are depicted in Figure 2. In the primary analysis at 3 months, the WOMAC index had improved to a more pronounced degree in the acupuncture group than in the control group (mean ± SEM score at 3 months 30.5 ± 1.0 [change of 17.6 ± 1.0] in the acupuncture group, mean ± SEM score at 3 months 47.3 ± 1.0 [change of 0.9 ± 1.0] in the control group [difference in degree of change 16.7 ± 1.4]; $P < 0.001$ after adjustment for baseline values) (Table 2). This improvement was robust in the sensitivity analyses for missing data (smallest difference between acupuncture and control groups 15.6; $P < 0.001$). The proportion of responders (≥50% reduction in WOMAC index) was 34.5% in the acupuncture group, compared with 6.5% in the control group

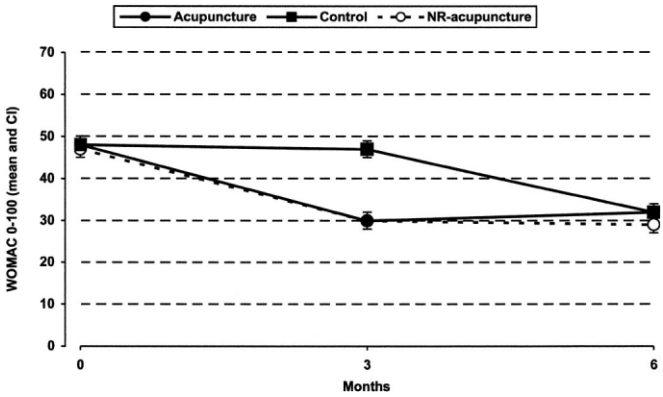

Figure 2. Scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) over time in the 3 treatment groups. NR = nonrandomized; CI = 95% confidence interval.

Table 2. Assessments of osteoarthritis symptoms (WOMAC) and quality of life (SF-36) in the randomized acupuncture and control groups at 3 months*

	Acupuncture, mean ± SEM	Control, mean ± SEM	Degree of improvement in acupuncture group − control group	
			Mean ± SEM	*P*
Arthritis symptoms				
All				
WOMAC index	30.5 ± 1.0	47.3 ± 1.0	−16.7 ± 1.4	<0.001
WOMAC pain	27.3 ± 1.0	45.7 ± 1.1	−18.4 ± 1.5	<0.001
WOMAC stiffness	33.6 ± 1.1	50.9 ± 1.2	−17.3 ± 1.7	<0.001
WOMAC function	30.8 ± 1.0	47.1 ± 1.0	−16.3 ± 1.4	<0.001
Arthritis of the knee				
WOMAC index	30.7 ± 1.1	46.4 ± 1.1	−15.7 ± 1.6	<0.001
WOMAC pain	27.7 ± 1.2	44.4 ± 1.2	−16.7 ± 1.7	<0.001
WOMAC stiffness	33.9 ± 1.4	50.5 ± 1.4	−16.7 ± 2.0	<0.001
WOMAC function	31.0 ± 1.1	46.3 ± 1.2	−15.3 ± 1.6	<0.001
Arthritis of the hip				
WOMAC index	30.1 ± 1.9	49.7 ± 2.0	−19.6 ± 2.8	<0.001
WOMAC pain	26.3 ± 2.2	49.2 ± 2.3	−22.9 ± 3.2	<0.001
WOMAC stiffness	33.1 ± 2.3	51.8 ± 2.4	−18.7 ± 3.3	<0.001
WOMAC function	30.2 ± 1.9	49.2 ± 2.0	−19.0 ± 2.8	<0.001
Quality of life				
All				
SF-36 physical component score	38.8 ± 0.5	31.2 ± 0.5	5.5 ± 0.6	<0.001
SF-36 mental component score	51.1 ± 0.5	49.4 ± 0.5	1.6 ± 0.7	0.024
Arthritis of the knee				
SF-36 physical component score	36.8 ± 0.5	31.4 ± 0.5	5.3 ± 0.7	<0.001
SF-36 mental component score	51.0 ± 0.6	49.3 ± 0.6	1.7 ± 0.8	0.048
Arthritis of the hip				
SF-36 physical component score	36.8 ± 1.0	30.8 ± 0.9	6.0 ± 1.3	<0.001
SF-36 mental component score	51.2 ± 1.0	49.7 ± 1.0	1.5 ± 1.4	0.263

* Estimated means and *P* values were derived from covariance analyses with adjustment for baseline values. See Table 1 for definitions and explanations.

($P < 0.001$). Subgroup analyses showed very similar results in patients with OA pain in the knee and patients with OA pain in the hip (Table 2).

The 3-month improvement (percent reduction) in the WOMAC index and its 3 subscales was significantly more pronounced in the acupuncture group than in the control group, in the total study population as well as in the hip OA patients and the knee OA patients analyzed separately (Table 3). Similar results were found for quality of life as assessed by both SF-36 component scores, with the mental component score in hip OA patients being the only exception (Table 3). There were no differences between the acupuncture and control groups with regard to the proportion of patients prescribed medication due to OA during the 3 months following randomization (36.2% of patients in the acupuncture group, 35.8% of controls).

Comparisons between the randomized and nonrandomized acupuncture groups. At 3 months, improvement was similar in the nonrandomized acupuncture group and the randomized acupuncture group (mean ± SEM WOMAC score 30.3 ± 0.4 [change of 17.8 ± 0.4] in the nonrandomized group, compared with a score of 30.5 ± 1.0 [change of 17.6 ± 1.0] in the randomized group [difference in degree of change −0.2]; 95% confidence interval −2.4, −2.0, $P = 0.845$). The proportion of responders was 35.7% in the nonrandomized acupuncture group, compared with 34.5% in the randomized acupuncture group ($P = 0.660$). There were no significant differences between patients in the randomized and the nonrandomized acupuncture groups in the 3-month improvement from baseline, in any of the parameters assessed (Table 3).

Factors affecting the WOMAC score at 3 months. There were several confounding factors affecting the 3-month WOMAC index. By multivariate analysis, the improvement in the WOMAC index was significantly ($P < 0.001$) more pronounced in patients of younger age, with higher baseline physical or mental quality of life, and with higher baseline WOMAC indexes, consistently over all treatment groups and independent of treatment. Patients in all treatment groups (including

Table 3. Changes from baseline to 3 months in assessments of osteoarthritis symptoms and quality of life in the 3 treatment groups*

	Randomized groups				Randomized and nonrandomized acupuncture groups		
			Degree of % reduction in acupuncture group − control group			Degree of % reduction in nonrandomized group − randomized group	
	Acupuncture, mean (95% CI) % reduction	Control, mean (95% CI) % reduction	Mean (95% CI)	P†	Nonrandomized, mean (95% CI) % reduction	Mean (95% CI)	P†
Arthritis symptoms							
All							
WOMAC index	37.3 (33.1, 41.5)	2.8 (−0.5, 6.2)	34.5 (29.0, 39.9)	<0.001	38.2 (36.9, 39.6)	0.9 (−3.4, 5.2)	0.670
WOMAC pain	43.7 (39.5, 47.9)	6.2 (2.4, 10.0)	37.5 (31.8, 43.1)	<0.001	42.6 (41.2, 44.1)	−1.0 (−5.6, 3.5)	0.650
WOMAC stiffness	31.7 (27.2, 36.2)	1.5 (−2.9, 5.8)	30.2 (23.9, 36.4)	<0.001	31.2 (29.6, 32.8)	−0.5 (−5.4, 4.4)	0.846
WOMAC function	35.8 (31.5, 40.2)	2.5 (−0.9, 5.8)	33.4 (27.8, 38.9)	<0.001	36.6 (35.3, 38.0)	0.8 (−3.6, 5.1)	0.719
Arthritis of the knee							
WOMAC index	36.9 (31.9, 41.8)	4.0 (0.2, 7.8)	32.9 (26.6, 39.1)	<0.001	39.0 (37.4, 40.6)	2.1 (−3.0, 7.2)	0.414
WOMAC pain	42.8 (37.9, 47.7)	8.2 (4.0, 12.5)	34.6 (28.0, 41.1)	<0.001	43.1 (41.4, 44.8)	0.3 (−5.0, 5.7)	0.902
WOMAC stiffness	30.8 (25.4, 36.2)	2.2 (−3.0, 7.3)	28.6 (21.2, 36.0)	<0.001	31.1 (29.2, 32.9)	0.3 (−5.6, 6.2)	0.928
WOMAC function	35.2 (30.1, 40.3)	3.1 (−0.7, 6.9)	32.1 (25.7, 38.5)	<0.001	37.5 (35.9, 39.1)	2.3 (−2.8, 7.5)	0.379
Arthritis of the hip							
WOMAC index	38.4 (30.1, 46.7)	−0.2 (−7.6, 7.2)	38.6 (27.5, 49.8)	<0.001	36.1 (33.4, 38.7)	−2.4 (−10.4, 5.7)	0.564
WOMAC pain	46.0 (37.9, 54.2)	0.7 (−7.5, 8.9)	45.3 (33.8, 56.8)	<0.001	41.3 (38.5, 44.1)	−4.8 (−13.3, 3.7)	0.269
WOMAC stiffness	34.0 (25.6, 42.4)	−0.3 (−8.8, 8.2)	34.3 (22.5, 46.2)	<0.001	31.5 (28.6, 34.5)	−2.5 (−11.4, 6.5)	0.588
WOMAC function	37.5 (29.2, 45.8)	0.7 (−6.7, 8.2)	36.8 (25.6, 47.9)	<0.001	34.1 (31.5, 36.7)	−3.4 (−11.4, 4.7)	0.408
Quality of life							
All							
SF-36 physical component score	6.1 (5.0, 7.1)	0.6 (−0.2, 1.4)	5.5 (4.1, 6.8)	<0.001	5.9 (5.6, 6.3)	−0.1 (−1.2, 1.0)	0.848
SF-36 mental component score	1.3 (0.2, 2.4)	−0.3 (−1.3, 0.8)	1.6 (0.0, 3.1)	0.045	1.8 (1.5, 2.2)	0.5 (−0.6, 1.7)	0.359
Arthritis of the knee							
SF-36 physical component score	6.1 (4.9, 7.2)	0.8 (−0.2, 1.8)	5.2 (3.7, 6.8)	<0.001	6.3 (5.9, 6.7)	0.2 (−1.0, 1.5)	0.727
SF-36 mental component score	1.4 (0.1, 2.7)	−0.4 (−1.7, 0.8)	1.8 (0.0, 3.6)	0.046	1.6 (1.1, 2.0)	0.2 (−1.1, 1.5)	0.763
Arthritis of the hip							
SF-36 physical component score	6.1 (3.8, 8.3)	−0.0 (−1.6, 1.6)	6.1 (3.3, 8.8)	<0.001	5.0 (4.4, 5.7)	−1.0 (−3.0, 1.0)	0.315
SF-36 mental component score	1.1 (−1.1, 3.2)	0.2 (−1.9, 2.3)	0.9 (−2.1, 3.8)	0.562	2.5 (1.8, 3.2)	1.4 (−0.7, 3.6)	0.193

* 95% CI = 95% confidence interval (see Table 1 for other definitions and explanations).
† By 2-sided exploratory *t*-test.

those who did not receive acupuncture) had better scores on the WOMAC when the percent of the physician's routine practice time spent performing acupuncture was higher ($P = 0.025$). Even after controlling for physician acupuncture experience in the model, the patients' WOMAC indexes differed significantly between physicians ($P = 0.029$).

As noted above, treatment responses were not significantly different between the randomized and the nonrandomized patients who underwent acupuncture. After adjustment, the additional percent reduction in the WOMAC index due to acupuncture was estimated to be 35.8% (difference in the randomized acupuncture group versus the control group) (95% confidence interval 31.2%, −40.5%), which was slightly higher than the unadjusted estimate.

No acupuncture effect modifiers could be identified. The physician's acupuncture qualification (hours of training, years of experience) had no significant influence on the effect of the treatment.

Durability of acupuncture effects over 6 months. The 6-month followup results in the 3 treatment groups are shown in Table 4. At 6 months (3 months after completion of acupuncture treatment), the differences from baseline in the WOMAC and SF-36 scores of patients in the randomized and nonrandomized acupuncture groups were only slightly lower than they had been at 3 months. The proportion of patients showing a response at 6 months was 31.7% in the randomized acupuncture group and 32.8% in the nonrandomized group ($P = 0.674$).

Delayed acupuncture. No significant differences were found in treatment results when patients who received immediate acupuncture and those who received delayed acupuncture (i.e., patients randomized to the control group, who began 3-month acupuncture treat-

Table 4. Changes from baseline to 6 months in assessments of osteoarthritis symptoms and quality of life in the 3 treatment groups*

	Randomized groups				Randomized and nonrandomized acupuncture groups		
	Acupuncture, mean (95% CI) % reduction	Control, mean (95% CI) % reduction†	Degree of % reduction in acupuncture group − control group		Nonrandomized, mean (95% CI) % reduction	Degree of % reduction in nonrandomized group − randomized group	
			Mean (95% CI)	P‡		Mean (95% CI)	P‡
Arthritis symptoms							
All							
WOMAC index	32.6 (27.9, 37.4)	34.6 (30.0, 39.1)	−2.0 (−8.5, 4.6)	0.561	35.8 (34.2, 37.4)	3.2 (−1.8, 8.1)	0.213
WOMAC pain	37.6 (32.6, 42.6)	42.3 (37.6, 47.0)	−4.7 (−11.6, 2.2)	0.180	41.1 (39.5, 42.8)	3.6 (−1.6, 8.7)	0.176
WOMAC stiffness	25.6 (20.2, 31.0)	23.8 (18.4, 29.1)	1.8 (−5.8, 9.4)	0.636	28.0 (26.3, 29.8)	2.4 (−3.3, 8.1)	0.402
WOMAC function	31.1 (26.1, 36.1)	32.4 (27.8, 36.9)	−1.3 (−8.0, 5.4)	0.705	34.4 (32.8, 35.9)	3.3 (−1.8, 8.3)	0.205
Arthritis of the knee							
WOMAC index	31.7 (26.1, 37.3)	36.1 (30.7, 41.5)	−4.4 (−12.1, 3.3)	0.264	36.6 (34.8, 38.5)	5.0 (−0.9, 10.8)	0.097
WOMAC pain	35.8 (30.0, 41.7)	42.7 (37.2, 48.3)	−6.9 (−14.9, 1.1)	0.090	41.8 (39.9, 43.7)	5.9 (−0.1, 12.0)	0.055
WOMAC stiffness	25.2 (18.6, 31.8)	26.8 (20.4, 33.1)	−1.6 (−10.7, 7.5)	0.736	28.5 (26.4, 30.5)	3.2 (−3.5, 10.0)	0.347
WOMAC function	30.2 (24.4, 35.9)	33.9 (28.4, 39.4)	−3.7 (−11.7, 4.2)	0.353	35.2 (33.3, 37.0)	5.0 (−0.9, 11.0)	0.097
Arthritis of the hip							
WOMAC index	35.1 (25.7, 44.5)	30.1 (21.5, 38.7)	5.0 (−7.7, 17.8)	0.436	33.4 (30.4, 36.5)	−1.6 (−11.1, 7.8)	0.732
WOMAC pain	42.1 (32.2, 52.1)	40.9 (31.8, 50.0)	1.3 (−12.2, 14.7)	0.853	39.4 (36.2, 42.6)	−2.7 (−12.7, 7.2)	0.590
WOMAC stiffness	26.6 (17.3, 36.0)	15.0 (5.1, 24.9)	11.6 (−1.9, 25.1)	0.090	26.9 (23.5, 30.3)	0.3 (−10.1, 10.7)	0.961
WOMAC function	33.5 (23.4, 43.6)	28.2 (20.1, 36.3)	5.3 (−7.6, 18.2)	0.420	32.1 (28.9, 35.2)	−1.4 (−11.1, 8.3)	0.772
Quality of life							
All							
SF-36 physical component score	5.4 (4.2, 6.6)	5.6 (4.5, 6.8)	−0.2 (−1.9, 1.5)	0.808	5.9 (5.5, 6.2)	0.4 (−0.8, 1.7)	0.501
SF-36 mental component score	−0.0 (−1.4, 1.3)	0.9 (−0.4, 2.2)	−0.9 (−2.8, 0.9)	0.335	1.1 (0.7, 1.6)	1.2 (−0.2, 2.6)	0.106
Arthritis of the knee							
SF-36 physical component score	5.2 (3.8, 6.6)	5.9 (4.5, 7.3)	−0.6 (−2.6, 1.3)	0.518	6.1 (5.6, 6.6)	0.9 (−0.6, 2.3)	0.245
SF-36 mental component score	0.0 (−1.6, 1.7)	0.3 (−1.3, 1.8)	−0.2 (−2.5, 2.0)	0.831	0.8 (0.3, 1.3)	0.8 (−0.9, 2.4)	0.363
Arthritis of the hip							
SF-36 physical component score	5.9 (3.4, 8.4)	4.9 (2.6, 7.2)	1.0 (−2.4, 4.3)	0.568	5.1 (4.4, 5.9)	−0.7 (−3.2, 1.7)	0.550
SF-36 mental component score	−0.2 (−2.4, 2.0)	2.6 (0.1, 5.2)	−2.8 (−6.2, 0.5)	0.099	2.0 (1.2, 2.9)	2.2 (−0.4, 4.8)	0.094

* 95% CI = 95% confidence interval (see Table 1 for other definitions and explanations).
† Control group received acupuncture starting at 3 months.
‡ By 2-sided exploratory *t*-test.

ment after not receiving acupuncture for the first 3 months of the study) were compared. Following delayed acupuncture, the improvement in WOMAC and SF-36 scores seen in control patients at 6 months was comparable with the improvement observed after 3 months in patients who had been randomized to receive immediate acupuncture therapy (Tables 3 and 4).

Side effects. In 5.2% of the patients (n = 184), a total of 219 side effects were reported after the patients had acupuncture (66% minor local bleeding or hematoma, 5% pain at the site of needle insertion, 4% vegetative symptoms, and 25% other). No life-threatening side effects were reported.

DISCUSSION

Patients with chronic pain due to OA of the knee or the hip who were treated with acupuncture in addition to routine care showed significant improvements in symptoms and quality of life compared with patients who received routine care alone. In patients who consented to randomization, treatment outcomes after acupuncture were similar to those in patients who declined randomization. Physician characteristics, such as the level of formal acupuncture training or certification, did not influence treatment outcomes.

The present study is by far one of the largest randomized trials of acupuncture to date, including 5% of physicians specializing in acupuncture and a full 1% of all primary care physicians in Germany. The aim of the study was to evaluate acupuncture in a manner that would reflect as closely as possible the conditions of daily medical practice (needle acupuncture and manual stimulation) and maximize external validity. We used recommended outcome parameters to evaluate patients with OA of the knee or the hip (14,15). Although the study had high followup rates, we used conservative

methods to deal with missing data. The additional inclusion of patients who declined randomization allowed us to investigate any potential selection effects.

Obviously, such an approach has methodologic limitations. In this study, neither providers nor patients were blinded with regard to treatment. Although the main outcome was determined based on patient assessment, bias due to lack of blinding cannot be ruled out. To minimize social acceptability bias, all questionnaires were sent directly from and to the coordinating research institute. Because the specifics of both acupuncture treatment and any concomitant interventions were left to the discretion of the physician, treatment regimens varied greatly among patients in our study. Inclusion criteria were broad, which resulted in a heterogeneous patient sample and, possibly, some diagnostic misclassification. While these issues might be considered limitations from an experimental perspective, the study design was chosen to reflect general medical practice. Subgroup analyses in this study showed that the benefit obtained with acupuncture treatment was comparable in patients with OA at different sites, whereas a recent study with naproxen showed a greater reduction of pain in patients with knee OA than in those with hip OA (16).

Patient self-selection in randomized trials of knee OA could be a relevant problem (17). In our study, approximately four-fifths of the eligible patients refused randomization in spite of a (minor) financial incentive, even though the 50% chance of a 3-month delay before starting acupuncture treatment (following an average disease duration of 5 years) presented only a slight disadvantage. These patients were included in the nonrandomized acupuncture group. However, there were no significant differences with respect to either baseline characteristics or treatment outcomes between randomized and nonrandomized patients. Further support for the observation that randomized trials and nonrandomized observational studies could yield similar results is derived from other publications (18). In other study settings in which randomization creates a greater disadvantage (e.g., studies in which control patients receive sham acupuncture), this could be different. Therefore, to control for selection bias, the use of study designs that also include nonrandomized patients appears to be desirable. Both in randomized and in nonrandomized patients in the present study, the improvements in the WOMAC index were clinically relevant (19). A further important finding is that improvements seen immediately after completion of 3 months of acupuncture treatment were sustained for at least another 3 months.

Our results confirm the findings of 3 previous smaller trials (2 randomized [20,21] and 1 nonrandomized [22]) that compared results in patients receiving acupuncture with results in patients in a waiting-list control group receiving no treatment. Compared with the findings of our recent sham-controlled study (8), improvements in the WOMAC index and the responder rates in the present study were slightly smaller.

Our finding that the physician's formal qualifications and years of acupuncture experience had no significant influence on treatment outcome could be interpreted as a further indication that formal acupuncture training of the clinician has only a limited role in treatment effect. However, these results should be interpreted with caution, because the indicators used in the present study might not adequately reflect the quality of treatment delivered by the physician.

Results of this study provide further evidence that acupuncture is a safe intervention. This is consistent with the findings of previous large surveys (23–25). When interpreting these findings, however, it must be kept in mind that all acupuncture procedures in the present study were administered by physicians.

In conclusion, the present results show that, in patients with chronic pain due to OA of the knee or hip who were receiving routine primary care, addition of acupuncture to the treatment regimen resulted in a clinically relevant and persistent benefit. Acupuncture should be considered as a treatment option for patients with knee or hip OA–associated chronic pain.

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