Acupuncture in patients with osteoarthritis of the knee: a randomised trial

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Summary

Background **Acupuncture is widely used by patients with chronic pain although there is little evidence of its effectiveness. We investigated the efficacy of acupuncture compared with minimal acupuncture and with no acupuncture in patients with osteoarthritis of the knee.**

Methods **Patients with chronic osteoarthritis of the knee (Kellgren grade ⩽2) were randomly assigned to acupuncture (n=150), minimal acupuncture (superficial needling at non-acupuncture points; n=76), or a waiting list control (n=74). Specialised physicians, in 28 outpatient centres, administered acupuncture and minimal acupuncture in 12 sessions over 8 weeks. Patients completed standard questionnaires at baseline and after 8 weeks, 26 weeks, and 52 weeks. The primary outcome was the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index at the end of week 8 (adjusted for baseline score). All main analyses were by intention to treat.**

Results **294 patients were enrolled from March 6, 2002, to January 17, 2003; eight patients were lost to follow-up after randomisation, but were included in the final analysis. The mean baseline-adjusted WOMAC index at week 8 was 26·9 (SE 1·4) in the acupuncture group, 35·8 (1·9) in the minimal acupuncture group, and 49·6 (2·0) in the waiting list group (treatment difference acupuncture *vs* minimal acupuncture –8·8, [95% CI –13·5 to –4·2], p=0·0002; acupuncture *vs* waiting list –22·7 [–27·5 to –17·9], p<0·0001). After 52 weeks the difference between the acupuncture and minimal acupuncture groups was no longer significant (p=0·08).**

Interpretation **After 8 weeks of treatment, pain and joint function are improved more with acupuncture than with minimal acupuncture or no acupuncture in patients with osteoarthritis of the knee. However, this benefit decreases over time.**

Introduction

Osteoarthritis most frequently affects the knee joint.[1] Anti-inflammatory drugs used to treat the symptoms of this disorder are associated with various side-effects.[2] Furthermore, for patients for whom these drugs do not lead to an adequate response, replacement surgery is often recommended.[3] Patients with chronic pain are increasingly using acupuncture for pain relief.[4] There is some evidence that acupuncture can be effective in treating pain and dysfunction in patients with osteoarthritis of the knee. In a systematic review including seven randomised controlled trials with a total of 393 patients, acupuncture was more effective than sham acupuncture in reducing pain, whereas for joint function the results were inconclusive.[5] These previous studies, however, were based on small sample sizes and the follow-up period was never longer than 3 months.

We aimed to investigate the efficacy of acupuncture compared with minimal acupuncture and with no acupuncture in patients with pain and dysfunction due to osteoarthritis of the knee.

Methods

Patients

Patients were included in our study if they were aged 50–75 years, had been diagnosed with osteoarthritis according to the American College of Rheumatology criteria, had documented radiological alterations in the knee joint of grade 2 or more according to Kellgren-Lawrence criteria,[6,7] had an average pain intensity of 40 or more on a 100 mm visual analogue scale in the 7 days before baseline assessment, and if they gave written informed consent. The exclusion criteria were one or more of the following: pain in the knee caused by inflammatory, malignant, or autoimmune disease; or other reasons for pain in the knee, such as serious valgus-defective or varus-defective position. Patients were also excluded if they had had knee surgery, arthroscopy of the affected knee in the past year, chondroprotective or intra-articular injection in the past 4 months, systemic corticoid treatment or beginning of a new treatment for osteoarthritis in the past 4 weeks, local antiphlogistic treatment, acupuncture treatment during the past 12 months, or physiotherapy or other treatments for osteoarthritis knee pain (with the exception of non-steroidal anti-inflammatory drugs) during the previous 4 weeks. Additional exclusion criteria were application for pension or disability benefits, serious acute or chronic organic disease or mental disorder, pregnancy or breastfeeding, and blood coagulation disorders or coagulation-inhibiting medication other than aspirin. Most participants were recruited through reports in local newspapers; a few patients spontaneously contacted trial centres. All study participants provided written informed consent and were insured according to the German law for medical products.

Procedures

Figure 1 shows the study design. Patients were randomly assigned to a treatment group stratified by centre in a 2: 1: 1 ratio (acupuncture: minimal acupuncture: waiting list) with a centralised telephone randomisation procedure (random list generated with Samp Size 2·0). The 2: 1: 1 ratio was used to help with recruitment and increase the compliance of trial physicians. Minimal acupuncture served as a sham intervention; the additional no acupuncture waiting list control was included since minimal acupuncture might not be a physiologically inert placebo. Patients in the acupuncture and minimal acupuncture groups were unaware of their treatment allocation. The total follow-up study period per patient was 52 weeks. The study was undertaken according to common guidelines for clinical trials (Declaration of Helsinki, ICH-GCP including certification by an external audit). The study protocol was approved by the appropriate ethics review boards and has been described in detail elsewhere.[8]

Study interventions were developed in a consensus process with acupuncture experts and societies, and provided by physicians who were trained (at least 140 h) and experienced in acupuncture. Both the acupuncture and minimal acupuncture treatments consisted of 12 sessions of 30 min duration, administered over 8 weeks (usually two sessions per week for the first 4 weeks, followed by one session per week in the remaining 4 weeks). For patients with bilateral osteoarthritis in the acupuncture and the minimal acupuncture groups, both knees were needled with at least eight out of ten proposed points (at least 16 needles altogether), whereas for patients with unilateral osteoarthritis, the physician was able to choose unilateral or bilateral acupuncture. For unilateral acupuncture, the treatment had to be done with at least eight needles. Patients in the waiting list group did not receive acupuncture treatment for a period of 8 weeks, after which time they then also received acupuncture.

Acupuncture treatment was semi-standardised: all patients were treated with a selection of local and distant points chosen by the acupuncturists according to the principles of traditional Chinese medicine. Additional points included body acupuncture points, ear acupuncture points, and trigger points. Patients were treated by use of at least six local acupuncture points from the following selection:[9] stomach 34, 35, 36; spleen 9, 10; bladder 40; kidney 10; gall bladder 33, 34; liver 8; extraordinary points Heding, Xiyan. Additionally, physicians selected and needled at least two distant points from the following selection: spleen 4, 5, 6; stomach 6; bladder 20, 57, 58, 60, 62; kidney 3. Sterile disposable one-time needles had to be used, but physicians were able to choose the needle length and diameter. Physicians were instructed to achieve de qi (an irradiating feeling deemed to indicate effective needling) if possible, and needles were stimulated manually at least once during each session.

Minimal acupuncture treatment entailed superficial insertion of fine needles (20–40 mm in length) at predefined, distant non-acupuncture points.[8] These non-acupuncture points were not in the area of the knee, and the selection of at least eight out of ten points was left to the physician's discretion. Physicians were instructed to avoid manual stimulation of the needles and provocation of de qi in the minimal acupuncture treatment. In investigator meetings, all acupuncturists received training in the application of minimal acupuncture, which included a videotape and a brochure showing detailed information about the procedure.

Patients in the waiting list group did not receive acupuncture treatment for 8 weeks after randomisation; from week 9 they received 12 sessions of the acupuncture treatment described above. In all treatment groups, patients were allowed to treat osteoarthritis knee pain with oral non-steroidal anti-inflammatory drugs if necessary. The use of other pain treatments, such as drugs acting through the central nervous system, or corticosteroids, was not allowed.

Patients were informed about 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."

All patients completed standard questionnaires at baseline, and after 8 weeks, 26 weeks, and 52 weeks. The first questionnaire was distributed to the patients by the study physician and completed before the start of treatment (baseline). Patients sent their completed questionnaires to the study office in sealed envelopes. Follow-up questionnaires were sent to all patients by the study office. The primary outcome measure was the Western Ontario and McMasters Universities Osteoarthritis Index.[10,11] In cases of bilateral osteoarthritis, the knee defined at baseline as most

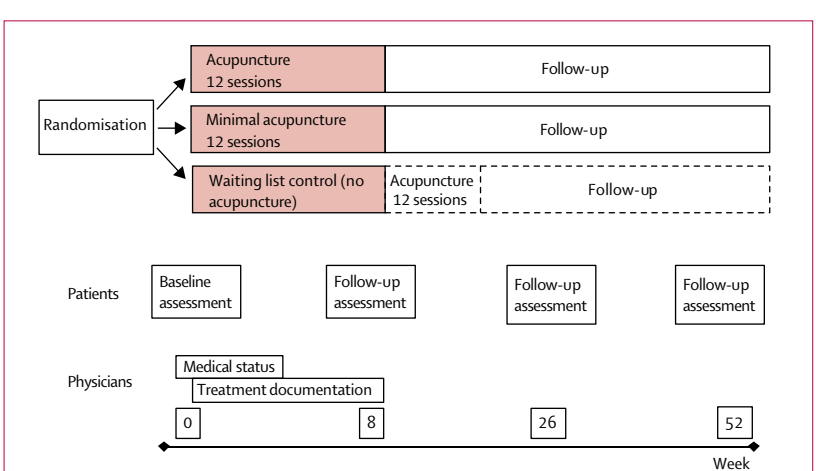

Figure 1: **Study design**

painful was the one assessed throughout the entire study. Furthermore, the patient questionnaire included a modified version of the German Society for the Study of Pain survey,[12] which uses the German version of the pain disability index;[13] a scale for assessing emotional aspects of pain (Schmerzempfindungs-Skala [SES]);[14] the depression scale (Allgemeine Depressionsskala [ADS]);[15] and the German version of the SF-36[16] (MOS36-item short form quality-of-life questionnaire) to assess health-related quality of life. Additionally, several questions on sociodemographic characteristics, numerical rating scales for pain intensity, questions about workdays lost, and global assessments were asked. The number of days with pain and medication were documented in a diary by the patients.

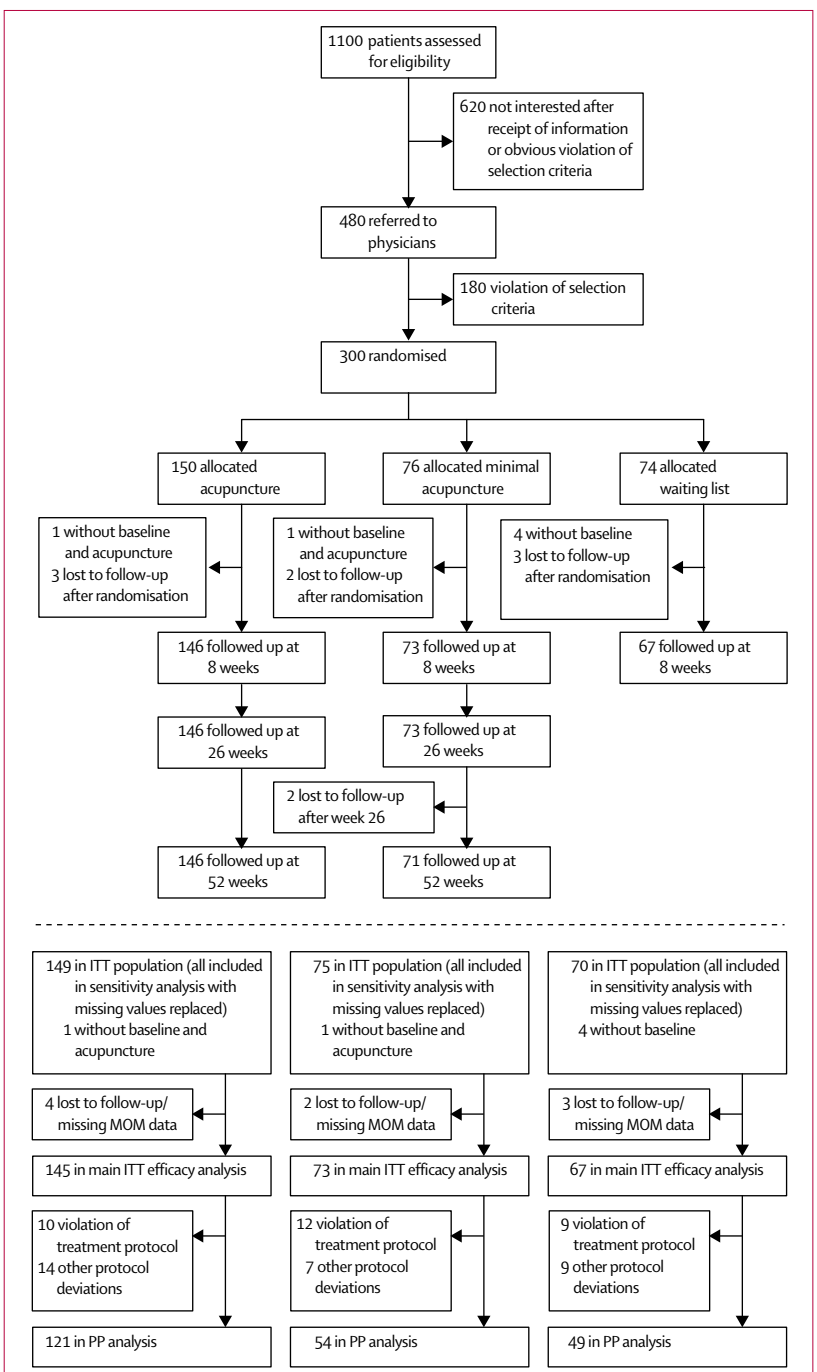

Figure 2: **Trial flow chart**
ITT=intention to treat, FU=follow-up, MOM=main outcome measure, PP=per protocol.

Blinding to treatment and the credibility of the treatment method were assessed by the patients with a credibility questionnaire[17] after the third acupuncture session. At the end of the study, patients were asked whether they thought they had received acupuncture following the principles of Chinese medicine or the other type of acupuncture. Physicians documented medical history, acupuncture treatment, serious adverse events, and side-effects for each session. Patients also reported side-effects at the end of week 8.

Statistical analysis

Confirmatory tests of the primary outcome measure (WOMAC index at the end of week 8) and all main analyses (with SPSS 11·5) were based on the intention-to-treat population and used all available data. Sensitivity analyses were done for the primary outcome measure by replacing missing data with multiple imputations and last value carried forward by use of SOLAS 3·0 (Statistical Solutions, Cork, Ireland). For multiple imputation, the propensity score method was used with the main outcome as variable to impute. Five imputed datasets were generated in addition to the last value carried forward. An analysis of covariance,[18] with the main outcome WOMAC score at the end of week 8 as the dependent variable and baseline WOMAC score and treatment group as independent variables, was undertaken as primary analysis to account for potential baseline differences. Resulting baseline-adjusted treatment effects are given together with 95% CI and corresponding p values as well as means and standard errors (SE) of the primary outcome for each treatment group. The same analysis was done for all secondary parameters at the end of week 8.

The study was powered to detect a change of eight score points on the WOMAC Index[19] between the acupuncture and minimal acupuncture groups with 80% power on the basis of a SD of 17 score points and a two-sided significance level of 5%. Exploratory analyses (two-sided t tests and χ^2 tests for pairwise comparisons of groups without adjustment for multiple testing) were done for follow-up measurements. Because the waiting list group could not be compared directly with the two other groups after 26 weeks and 52 weeks, all subsequent data from this group were only analysed descriptively. Additionally, a per protocol analysis was done including only patients with no major protocol violations by the end of week 8.

	Total (n=294)	Acupuncture (n=149)	Minimal acupuncture (n=75)	Waiting list (n=70)
Women	195 (66%)	105 (70%)	49 (65%)	41 (59%)
Men	99 (34%)	44 (30%)	26 (35%)	29 (41%)
Age (years)	64·0 (6·5)	64·5 (6·4)	63·4 (6·6)	63·6 (6·7)
Body-mass index	29·0 (5·0)	29·5 (4·8)	28·8 (4·6)	28·3 (5·89)
>10 years of school	43 (16%)	16 (11%)	11 (17%)	16 (24%)
Kellgren criteria				
Kellgren 0	1 (0·3%)	0	0	1 (1%)
Kellgren 1	15 (5%)	6 (4%)	5 (7%)	4 (6%)
Kellgren 2	121 (41%)	52 (35%)	29 (39%)	40 (57%)
Kellgren 3	120 (41%)	66 (44%)	32 (43%)	22 (31%)
Kellgren 4	37 (13%)	25 (17%)	9 (12%)	3 (4%)
Duration of disease (years)	9·2 (7·9)	9·1 (8·5)	9·9 (7·6)	8·8 (6·8)
Days per month with pain	26·2 (6·5)	26·2 (6·5)	26·6 (6·4)	25·7 (6·8)
Osteoarthritis bilateral	224 (76%)	110 (74%)	58 (77%)	56 (80%)
Previous treatment				
Pharmaceutical intervention (past 6 months)	97 (33%)	43 (29%)	27 (36%)	27 (39%)
Physiotherapy (past 6 months)	45 (15%)	22 (15%)	7 (9%)	16 (23%)
Previous acupuncture treatment	23 (8%)	14 (9%)	5 (7%)	4 (6%)
Average pain (VAS)	65·3 (14·5)	64·9 (14·2)	68·5 (14·4)	62·8 (15·0)
WOMAC Index	51·4 (18·7)	50·8 (18·8)	52·5 (18·6)	51·6 (18·8)
Disability (PDI)	28·0 (13·2)	27·9 (14·2)	27·8 (13·2)	28·3 (11·3)
Physical health (SF-36)*	29·7 (7·7)	30·0 (7·4)	29·2 (8·2)	29·8 (7·9)
Mental health (SF-36)*	51·3 (12·0)	51·8 (12·1)	51·1 (11·6)	50·6 (12·1)
Pain affective (SES, *t* standard scores)	48·9 (9·1)	48·8 (9·3)	49·2 (8·7)	48·8 (9·3)
Pain sensoric (SES, *t* standard scores)	52·7 (9·9)	52·4 (9·5)	54·1 (10·8)	52·0 (10·0)
Depression (ADS, *t* standard scores)	51·2 (9·4)	51·2 (10·0)	51·3 (7·9)	51·2 (9·4)

Data are number (%) or mean (SD). WOMAC=questionnaire for assessing pain, function and stiffness due to osteoarthritis (Western Ontario and McMasters Universities Osteoarthritis Index); VAS=visual analogue scale; PDI=pain disability index; SF-36=MOS 36-item short-form quality-of-life questionnaire; SES=questionnaire for assessing the emotional aspects of pain (Schmerzempfindungsskala); ADS=depression scale (Allgemeine Depressionsskala). *Higher values indicate better status.

Table 1: **Baseline characteristics of intention-to-treat population**

Role of the funding source

The trial was initiated after a request from German health authorities (Federal Committee of Physicians and Social Health Insurance Companies, German Federal Social Insurance Authority) and sponsored by German Social Health Insurance Companies. The health authorities had requested a randomised trial that included a sham control and a follow-up period of at least 6 months. All other decisions on study design, data collection, data analysis, data interpretation, and writing of the report were the complete responsibility of the researchers. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Acupuncture	Minimal acupuncture	p
Credibility after third session	n=148	n=73	
Improvement expected	5·2 (1·1)	5·1 (0·9)	0·860
Recommendation to others	5·5 (1·0)	5·6 (0·7)	0·384
Treatment logical	5·0 (1·3)	4·8 (1·3)	0·327
Effective also for other diseases	5·6 (0·9)	5·7 (0·6)	0·601
Guess at end of week 52	n=146	n=71	0·332
"Chinese acupuncture"	96 (66%)	40 (56%)	
"The other type of acupuncture"	9 (6%)	4 (6%)	
"Don't know"	41 (28%)	27 (38%)	

Rating scale based on 0=minimum and 6=maximum agreement; data are number (%) or mean (SD).

Table 2: **Treatment credibility after the third treatment session and assessment of blinding**

Results

Between March 6, 2002, and January 17, 2003, about 1100 patients with osteoarthritis of the knee applied to

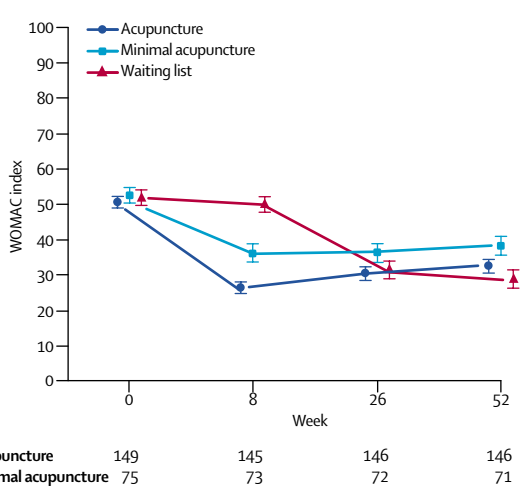

Figure 3: **Development of the mean WOMAC Index in the three treatment groups**
Vertical bars represent standard errors.

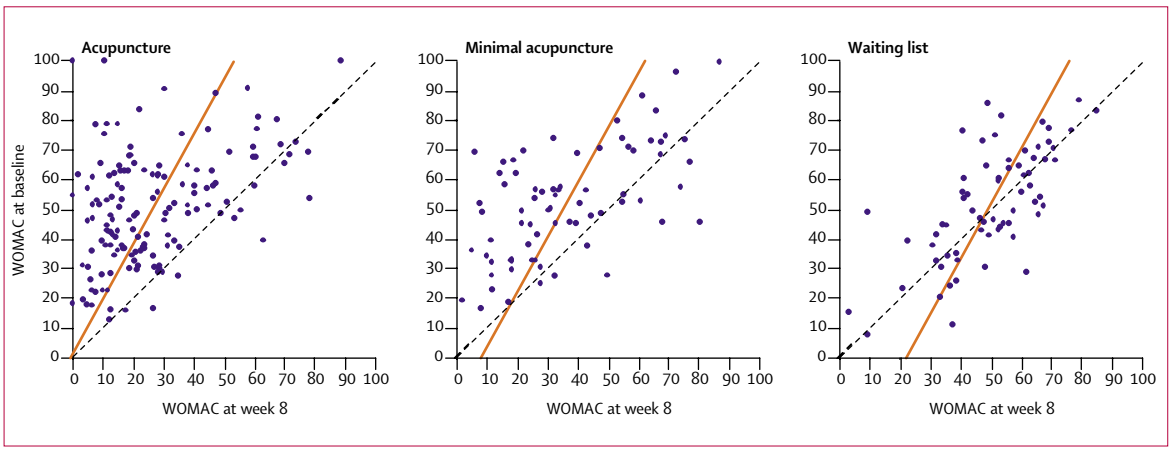

Figure 4: **Scatter plots of the WOMAC index at baseline and at week 8**
Solid lines represent parallel linear regression and dotted lines represent analysis of covariance (45° line). Patients on the 45° line have no change in WOMAC score, whereas those above and below indicate better and worse condition, respectively.

participate in the study. Figure 2 shows the trial profile. Of 300 patients randomised six were excluded from the intention-to-treat population because no baseline data were available, and they did not receive the study intervention. All the remaining 294 patients treated in a total of 28 outpatient centres were included in the intention-to-treat population. Three patients in the acupuncture group (one planned operation, one car accident, one reason unclear) and three in the minimal acupuncture group (one moved to another town, two reason unclear) stopped the acupuncture treatment prematurely. After 8 weeks, data for the main efficacy analysis were available for 285 (97%) patients. The per-protocol analysis included 224 patients.

All patients had previously been treated with analgesics. 95 (32%) had received acupuncture in the past (8% for osteoarthritis) and 261 (88%) patients expected a substantial improvement from acupuncture treatment. Table 1 shows the baseline characteristics of patients in the three study groups.

Patients in the acupuncture group were treated with a mean of 17 (SD 8) needles and patients in the minimal acupuncture group with a mean of 12 (3) needles. The average duration of sessions was about 30 min in both groups. All patients in the acupuncture group were treated at local and distant points; additional points were used in 609 (35%) treatment sessions and trigger points in 246 (14%) treatment sessions. After three treatment sessions, patients rated the credibility of acupuncture and minimal acupuncture much the same and as very high, and at the end of the study most patients believed that they had received acupuncture following the principles of Chinese medicine (table 2).

Figure 3 shows the development of the mean WOMAC index score. The mean baseline-adjusted WOMAC index at the end of week 8 was 26·9 (SE 1·4) in the

Primary outcome	Acupuncture mean (SE)	Minimal acupuncture mean (SE)	Waiting list mean (SE)	Acupuncture vs minimal acupuncture* (95%CI)	p	Acupuncture vs waiting list * (95%CI)	p
Questionnaire							
WOMAC Index	26·9 (1·4)	35·8 (1·9)	49·6 (2·0)	−8·8 (−13·5 to −4·2)	<0·001	−22·7 (−27·5 to −17·9)	<0·001
WOMAC Pain	24·4 (1·4)	33·2 (2·0)	44·9 (2·1)	−8·8 (−13·7 to −3·9)	<0·001	−20·5 (−25·5 to −15·5)	<0·001
WOMAC Stiffness	32·7 (1·9)	42·3 (2·7)	55·0 (2·8)	−9·6 (−16·0 to −3·2)	0·003	−22·3 (−28·9 to −15·7)	<0·001
WOMAC Physical function	27·0 (1·4)	35·8 (2·0)	50·4 (2·1)	−8·9 (−13·7 to −4·0)	<0·001	−23·4 (−28·4 to −18·4)	<0·001
Disability (PDI)	16·4 (0·9)	22·2 (1·2)	27·4 (1·3)	−5·8 (−8·8 to −2·8)	<0·001	−11·0 (−14·1 to −7·9)	<0·001
Physical health (SF–36)†	36·2 (0·6)	33·1 (0·8)	31·8 (0·9)	3·1 (1·1 to 5·1)	0·003	4·4 (2·3 to 6·5)	<0·001
Mental health (SF–36)†	53·6 (0·7)	51·9 (1·0)	50·7 (1·0)	1·7 (−0·6 to 4·0)	0·137	2·9 (0·6 to 5·3)	0·016
Pain affective (SES, *t* standard scores)	42·4 (0·7)	44·1 (0·9)	45·9 (1·0)	−1·7 (−3·9 to 0·5)	0·134	−3·5 (−5·8 to −1·2)	0·003
Pain sensoric (SES, *t* standard scores)	47·3 (0·7)	48·1 (1·0)	49·8 (1·0)	−0·8 (−3·2 to 1·6)	0·494	−2·5 (−5·0 to −0·1)	0·044
Depression (ADS, *t* standard scores)	47·9 (0·8)	48·3 (1·1)	49·4 (1·1)	−0·5 (−3·1 to 2·1)	0·725	−1·5 (−4·1 to 1·1)	0·250
Days with limited function	16·3 (1·5)	21·3 (2·1)	27·4 (2·2)	−4·9 (−10·1 to 0·2)	0·059	−11·1 (−16·3 to −5·8)	<0·001
Diary							
Days with pain in week 8 (diary)	4·4 (0·2)	5·3 (0·3)	6·4 (0·3)	−1·0 (−1·6 to −0·3)	0·005	−2·1 (−2·8 to −1·4)	<0·001
Days with medication in weeks 5–8 (diary)	4·5 (0·5)	4·6 (0·6)	5·8 (0·7)	−0·1 (−1·6 to 1·5)	0·922	−1·3 (−3·0 to 0·3)	0·110

WOMAC=questionnaire for assessing pain, function, and stiffness due to osteoarthritis (Western Ontario and McMasters Universities Osteoarthritis Index); PDI=pain disability index; SF-36=MOS 36-item short-form quality-of-life questionnaire; SES=questionnaire for assessing the emotional aspects of pain (Schmerzempfindungsskala); ADS=depression scale (Allgemeine Depressionsskala). *Mean baseline-adjusted treatment difference between groups. †Higher values indicate better status

Table 3: **Primary and secondary outcomes at the end of week 8**

	At 26 weeks				At 52 weeks			
	Acupuncture mean (SD)	Minimal acupuncture mean (SD)	Acupuncture *vs* minimal acupuncture* (95%CI)	p	Acupuncture mean (SD)	Minimal acupuncture mean (SD)	Acupuncture *vs* minimal acupuncture* (95%CI)	p
Questionnaire								
WOMAC Index	30·4 (21·3)	36·3 (22·3)	−5·8 (−12·0 to 0·3)	0·063	32·7 (22·4)	38·4 (22·6)	−5·7 (−12·1 to 0·7)	0·080
WOMAC Pain	28·9 (22·7)	33·8 (22·3)	−4·8 (−11·2 to 1·6)	0·137	30·0 (23·5)	33·5 (21·3)	−3·5 (−10·0 to 3·0)	0·285
WOMAC Stiffness	34·7 (25·3)	40·3 (26·1)	−5·6 (−12·8 to 1·7)	0·131	37·4 (25·2)	47·1 (28·0)	−9·7 (−17·1 to −2·2)	0·011
WOMAC Physical function	30·4 (21·4)	36·5 (23·2)	−6·2 (−12·4 to 0·1)	0·053	33·0 (23·0)	38·9 (23·8)	−5·9 (−12·5 to 0·7)	0·081
Disability (PDI)	18·6 (13·0)	22·8 (15·3)	−4·2 (−8·3 to −0·0)	0·048	20·0 (14·0)	23·6 (15·0)	−3·6 (−7·7 to 0·5)	0·089
Physical health (SF–36)†	35·1 (8·8)	33·0 (10·0)	2·1 (−0·5 to 4·8)	0·111	35·0 (10·0)	32·8 (9·5)	2·2 (−0·6 to 5·1)	0·120
Mental health (SF–36)†	52·6 (11·5)	51·7 (11·2)	0·9 (−2·3 to 4·2)	0·580	52·9 (11·0)	51·1 (11·7)	1·9 (−1·3 to 5·1)	0·254
Pain affective (SES, *t* standard scores)	41·3 (9·3)	43·4 (9·4)	−2·1 (−4·8 to 0·6)	0·120	42·5 (10·2)	44·1 (10·4)	−1·6 (−4·6 to 1·4)	0·291
Pain sensoric (SES, *t* standard scores)	46·0 (9·2)	48·0 (9·3)	−2·0 (−4·6 to 0·6)	0·138	47·7 (11·3)	48·4 (10·5)	−0·7 (−3·9 to 2·4)	0·643
Depression (ADS, *t* standard scores)	48·2 (9·9)	48·7 (9·3)	−0·5 (−3·6 to 2·5)	0·730	48·6 (10·2)	49·8 (10·1)	−1·2 (−4·3 to 1·8)	0·430
Days with limited function	41·8 (45·6)	61·1 (61·7)	−19·4 (−35·5 to −3·2)	0·019	41·1 (56·5)	67·8 (71·7)	−26·7 (−46·0 to −7·5)	0·007

WOMAC=Western Ontario and McMasters Universities Osteoarthritis Index; PDI=pain disability index; SF-36=MOS 36-item short-form quality-of-life questionnaire; SES=Schmerzempfindungsskala; ADS=Allgemeine Depressionsskala. *Mean difference between groups; minor discrepancies between differences calculated from group means presented in the table are due to rounding. †Higher values indicate better status.

Table 4: **Secondary outcomes after 26 weeks and 52 weeks**

acupuncture group compared with 35·8 (1·9) in the minimal acupuncture group and 49·6 (2·0) in the waiting list group (treatment difference: acupuncture *vs* minimal acupuncture −8·8 [95% CI −13·5 to −4·2], p=0·0002; acupuncture *vs* waiting list −22·7 [−27·5 to −17·9], p<0·0001). Figure 4 shows the treatment effect for individual patients categorised with respect to treatment group. The results were very similar if missing values were replaced and if baseline values were entered in the analysis of covariance as covariates. Additionally, the per-protocol analysis showed closely similar results.

Patients who received acupuncture had significantly better results for almost all secondary outcome measures than did those in the minimal acupuncture and waiting list groups. The proportion of responders (patients with a decrease of at least 50% in their WOMAC index score) was 52% in the acupuncture group compared with 28% in the minimal acupuncture group and 3% in the waiting list group (all patients with no data were counted as non-responders). On all WOMAC subscales (pain, stiffness, and physical function), the acupuncture group showed significant improvements compared with the minimal acupuncture and the waiting list groups (table 3). When weeks 1 and 8 were compared, the mean number of days per week with intake of analgesics decreased in the acupuncture group (from 1·4 [2·2] to 0·9 [2·0]) and in the minimal acupuncture group (from 1·5 [2·6] to 1·1 [2·3]), whereas in the waiting list control group this number remained closely similar (1·8 [2·3] *vs* 1·9 [2·6]). Additionally, the percentage of patients using analgesics in the acupuncture and minimal acupuncture groups decreased between weeks 1 and 8 (from 42% to 22% and from 38% to 23%, respectively), whereas in the waiting list group there was only a small change (from 52% to 45%). The improvements recorded after 8 weeks in the acupuncture and minimal acupuncture groups persisted during the follow-up period, although the differences between the groups were no longer significant after 26 or 52 weeks (p=0·063 and 0·080 from exploratory analyses; table 4). The patients in the waiting list group who received acupuncture between weeks 9 and 16 showed improvements after treatment that were similar to those reported in the original acupuncture group (WOMAC index decreased from 51·6 [18·8] to 31·6 [20·6]).

During the 26 weeks after randomisation, a total of nine serious adverse events (three acupuncture, two minimal acupuncture, four waiting list) were documented. One patient from the minimal acupuncture group died from myocardial infarction. All cases were admitted to hospital and regarded as unrelated to the study condition or the intervention. 24 side-effects were reported by 20 (14%) patients in the acupuncture group (18 small haematoma or bleeding and six other side-effects, such as needling pain), and 16 side-effects by 13 (18%) patients (p=0·410) in the minimal acupuncture group (nine small haematoma or bleeding, one case of local inflammation at the needling site, and six other side-effects).

Discussion

In this study, patients with osteoarthritis of the knee who received acupuncture had significantly less pain and better function after 8 weeks than did patients who received minimal acupuncture or no acupuncture. After 26 and 52 weeks, exploratory analysis indicated that the differences between acupuncture and minimal acupuncture were no longer significant.

The present study is, to date, one of the largest and most rigorous trials of the efficacy of acupuncture available. Its strengths include a prepublished protocol,[8] interventions based on expert consensus by qualified and experienced medical acupuncturists, assessment of the credibility of interventions, outcome measurements as recommended in guidelines for trials on osteoarthritis,[20,21] and very high follow-up rates. One

potential limitation of the study is that participants were recruited primarily through newspaper articles and might not be representative of all patients with osteoarthritis of the knee. Also, due to the nature of the intervention, it was not possible to blind acupuncturists to treatment. However, the primary outcome measure and all secondary outcome measures were assessed by the patients themselves. Acupuncture and minimal acupuncture are not strictly indistinguishable. One could, therefore, argue that our results might have been biased by a lack of sufficient blinding. Although this bias cannot be ruled out, a major bias seems unlikely to us for two reasons. First, patients were informed in a manner suggesting that two different types of acupuncture treatment were compared, not mentioning terms such as "placebo" or "sham". Similar strategies of informed consent have been used in most previous acupuncture trials.[22] Second, both acupuncture and minimal acupuncture were thought to be highly credible and most patients believed that they had received the Chinese acupuncture.

Compared with both waiting list control and minimal acupuncture, the effect of acupuncture on the WOMAC scale after 8 weeks is clinically important.[22] Significant differences were also evident for secondary outcomes. The differences between the acupuncture and the minimal acupuncture groups can probably not be explained by the intake of analgesics, which was much the same in both groups. Days with intake of analgesics did not differ between the acupuncture and minimal acupuncture groups, but differences cannot be ruled out completely because only days with intake of analgesics and not the exact number of pills or the dosage of analgesics was assessed. Exploratory analysis at 26 and 52 weeks' follow-up indicated that differences between acupuncture and minimal acupuncture were no longer significant. Because the waiting list patients received acupuncture after 8 weeks, whether the benefit of acupuncture over no treatment is still clinically relevant in the long term is difficult to assess. In any case, our results suggest that a single course of acupuncture treatment has only limited long-term point-specific effects.

In this study, the side-effects of acupuncture were of only minor severity. Several large surveys have also provided evidence that acupuncture is a relatively safe treatment.[23–25] Non-steroidal anti-inflammatory drugs, which are the most common pharmaceutical treatment in patients with osteoarthritis, are well known for producing severe side-effects, such as gastrointestinal bleeding, causing many deaths.[2] A reduction in the use of non-steroidal anti-inflammatory drugs might be a potential secondary benefit of acupuncture treatment.

Our results lend support to the findings of three previous smaller trials that compared acupuncture with a no-treatment control, two of which were randomised[26,27] and one was not.[28] Four published trials have compared acupuncture and sham acupuncture interventions.[29–32] In three of these trials,[30–32] pain improved significantly after treatment with acupuncture compared with sham acupuncture, whereas only one trial[32] reported a difference for function. In the trial that showed no difference between acupuncture and sham acupuncture,[29] acupuncture treatment was administered over a short period (three times a week for 3 weeks). One method of sham acupuncture is the minimum sham method (superficial needling at distant non-acupuncture points), which tries to keep to a minimum the non-specific needling effects.[33] In our study, and in both trials with positive results, sham acupuncture was administered as minimum sham. In the third trial with neutral results, sham acupuncture was administered superficially, but near to the real acupuncture points. This procedure could have produced more analgesic effects than the method used in the other trials. The differences in findings with respect to function might be due to low statistical power in the early trials, use of different measurement instruments, or the possibility that our form of acupuncture treatment (using more local acupuncture points) was more effective in improving physical function in patients with osteoarthritis of the knee.

Most previous studies have included only a short-term follow-up. Only in the study by Molsberger and colleagues[30] was follow-up assessed at 3 months, yielding results that were similar to those immediately after treatment completion. However, in our study the outcome differences between acupuncture and minimal acupuncture treatment decreased during the 12-month follow-up period.

In conclusion, acupuncture treatment had significant and clinically relevant short-term effects when compared to minimal acupuncture or no acupuncture treatment in patients with osteoarthritis of the knee. We now need to assess the long-term effects of acupuncture, both in comparison to sham interventions and to standard treatment.

Contributors

All authors participated in developing the study design and protocol and in revising the manuscript. Specific tasks and responsibilities were: general trial coordination (C Witt, B Brinkhaus; A Streng, K Linde), monitoring coordination (C Witt, B Brinkhaus), statistical analysis and expertise (S Jena, S Wagenpfeil), orthopaedic expertise (H U Walther), acupuncture interventions (J Hummelsberger), general medical and scientific responsibility (S N Willich, D Melchart), randomisation centre (S Wagenpfeil).

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Conflict of interest statement

We declare that we have no conflict of interest.

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References

1 Creamer P, Hochberg MC. Osteoarthritis. *Lancet* 1997; **350:** 503–09.

2 Tramer MR, Moore RA, Reynolds DJ, McQuay HJ. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. *Pain* 2000; **85:** 169–82.

3 Anon. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum* 2000; **43:** 1905–15.

4 Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* 1998; **280:** 1569–75.

5 Ezzo J, Hadhazy V, Birch S, et al. Acupuncture for osteoarthritis of the knee: a systematic review. *Arthritis Rheum* 2001; **44:** 819–25.

6 Kellgren JH. Radiolocical Assessment of Osteo-Arthrosis. *Ann Rheum Dis* 1957; **16:** 494–502.

7 Kessler S, Guenther KP, Puhl W. Scoring prevalence and severity in gonarthritis: the suitability of the Kellgren & Lawrence scale. *Clin Rheumatol* 1998; **17:** 205–09.

8 Brinkhaus B, Becker-Witt C, Jena S, et al. Acupuncture Randomized Trials (ART) in patients with chronic low back pain and osteoarthritis of the knee: design and protocols. *Forsch Komplementarmed Klass Naturheilkd* 2003; **10:** 185–91.

9 Deadman P, Al-Khafaji M. A manual of acupuncture. Sussex, UK: Journal of Chinese Medicine Publications, 2001.

10 Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988; **15:** 1833–40.

11 Stucki G, Meier D, Stucki S, et al. Evaluation of a German version of WOMAC (Western Ontario and McMaster Universities) Arthrosis Index. *Z Rheumatol* 1996; **55:** 40–49.

12 Nagel B, Gerbershagen HU, Lindena G, Pfingsten M. Entwickling und empirische Überprüfung des Deutschen Schmerzfragebogens der DGSS. *Schmerz* 2002; **16:** 263–70.

13 Dillmann U, Nilges P, Saile H, Gerbershagen HU. Behinderungseinschätzung bei chronischen Schmerzpatienten. *Schmerz* 1994; 100–10.

14 Geissner ESA. Die Schmerzempfindungsskala (SES). Göttingen: Hogrefe, 1996.

15 Hautzinger M, Bailer M. Allgemeine Depressionsskala (ADS). Die deutsche Version des CES-D. Weinheim: Beltz, 1993.

16 Bullinger M, Kirchberger I. SF-36 Fragebogen zum Gesundheitszustand. Göttingen: Hogrefe, 1998.

17 Vincent C. Credibility assessments in trials of acupuncture. *Complement Med Res* 1990; **4:** 8–11.

18 Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. *BMJ* 2001; **323:** 1123–24.

19 Berman BM, Singh BB, Lao L, et al. A randomized trial of acupuncture as an adjunctive therapy in osteoarthritis of the knee. *Rheumatology (Oxford)* 1999; **38:** 346–54.

20 Altman R, Brandt K, Hochberg M, et al. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. *Osteoarthritis Cartilage* 1996; **4:** 217–43.

21 Bellamy N, Kirwan J, Boers M, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. *J Rheumatol* 1997; **24:** 799–802.

22 Linde K, Dincer F. How informed is consent in sham-controlled trials of acupuncture? *J Altern Complement Med* 2004; **10:** 379–85.

23 White AR, Hayhoe S, Hart A, Ernst E. Survey of Adverse events following Acupuncture (SAFA): a prospective study of 32 000 consultations. Department of Complementary Medicine, University of Exeter, Exeter, UK, 2001: 1–20.

24 Melchart D, Weidenhammer W, Streng A, et al. Prospective investigation of adverse effects of acupuncture in 97733 patients. *Arch Intern Med* 2004; **164:** 104–05.

25 Yamashita H, Tsukayama H, Hori N, Kimura T, Tanno Y. Incidence of adverse reactions associated with acupuncture. *J Altern Complement Med* 2000; **6:** 345–50.

26 Berman BM, Singh BB, Lao L, et al. A randomized trial of acupuncture as an adjunctive therapy in osteoarthritis of the knee. *Rheumatology (Oxford)* 1999; **38:** 346–54.

27 Christensen BV, Luhl IU, Vilbek H, Bulow HH, Dreijer NC, Rasmussen HF. Acupuncture treatment of severe knee osteoarthrosis: a long-term study. *Acta Anaesthesiol Scand* 1992; **36:** 519–25.

28 Tillu A, Tillu S, Vowler S. Effect of acupuncture on knee function in advanced osteoarthritis of the knee: a prospective, non-randomised controlled study. *Acupunct Med* 2002; **20:** 19–21.

29 Takeda W, Wessel J. Acupuncture for the treatment of pain of osteoarthritic knees. *Arthritis Care Res* 1994; **7:** 118–22.

30 Molsberger A, Böwing G, Jensen KU, Lorek M. Schmerztherapie mit Akupunktur bei Gonarthrose. *Der Schmerz* 1994; **8:** 37–42.

31 Petrou P, Winkler V, Genti G, Balint G. Double blind trial to evaluate the effect of acupuncture treatment on knee osteoarthritis. *Scand J Acupunct* 1988; **3:** 112–15.

32 Sangdee C, Teekachunhatean S, Sananpanich K, et al. Electroacupuncture versus diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. *BMC Complement Altern Med* 2002; **2:** 3.

33 Vincent C, Lewith G. Placebo controls for acupuncture studies. *J R Soc Med* 1995; **88:** 199–202.