Rheumatology 1999;38:346–354

A randomized trial of acupuncture as an adjunctive therapy in osteoarthritis of the knee

B. M. Berman, B. B. Singh, L. Lao, P. Langenberg[1], H. Li[2], V. Hadhazy, J. Bareta and M. Hochberg[3]

Complementary Medicine Program, University of Maryland School of Medicine, Baltimore, [1]Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, [2]1717 York Road, Lutherville and [3]Division of Rheumatology and Clinical Immunology, University of Maryland School of Medicine, Baltimore, MD, USA

Abstract

Objective. The purpose of this study was to investigate the efficacy of acupuncture as an adjunctive therapy to standard care for the relief of pain and dysfunction in elderly patients with osteoarthritis (OA) of the knee.

Methods. Seventy-three patients with symptomatic OA of the knee were randomly assigned to treatment (acupuncture) or standard care (control). Analysis was performed on last score carried forward to account for patients who dropped out before completion. Patients self-scored Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Lequesne indices at baseline and at 4, 8 and 12 weeks. Patients in the control group were offered acupuncture treatment after 12 weeks. The data for these patients are pooled with those from the original acupuncture group for within-group analysis.

Results. Patients randomized to acupuncture improved on both WOMAC and Lequesne indices compared to those who received standard treatment alone. Significant differences on total WOMAC Scale were seen at 4 and 8 weeks. There appears to be a slight decline in effect at 4 weeks after cessation of treatment (12 weeks after first treatment). No adverse effects of acupuncture were reported.

Conclusion. These data suggest that acupuncture is an effective and safe adjunctive therapy to conventional care for patients with OA of the knee.

KEY WORDS: Osteoarthritis, Knee, Acupuncture, Adjunctive therapy, Elderly.

Osteoarthritis (OA) is the most prevalent form of arthritis [1] and its most common site is the knee joint [2, 3]. Community-based studies [4–6] are increasingly emphasizing the contribution made by knee pain and knee OA to lower limb disability and reduced quality of life.

Recent guidelines for the medical management of knee OA [7] emphasize the role of patient education, weight loss, physical and occupational therapy, aerobic exercise and pharmacological therapy. Drug therapy includes non-opioid analgesics such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), topical analgesics (capsaicin cream), opioid analgesics and intra-articular steroid injection. Management of OA, however, is often ineffective and pharmacological agents, especially NSAIDs, have the potential to cause unpleasant and sometimes dangerous side-effects [8–13].

Submitted 29 June 1998; revised version accepted 18 December 1998.

Correspondence to: B. M. Berman, University of Maryland School of Medicine, Kernan Hospital Mansion, 2200 Kernan Drive, Baltimore, MD 21207-6697, USA.

If medical management fails to control a patient's symptoms adequately, knee arthroplasty may be recommended for those with severe disease. Replacement surgery can pose risks, especially in the elderly OA patients who often have co-morbid medical conditions [14]. Patients who fail medical therapy and are either not candidates for, or refuse, surgery need to be considered for complementary medical treatment.

In many Asian countries, and increasingly in western countries, acupuncture is a popular treatment for arthritis [15]. In traditional Chinese Medicine (TCM), OA is known as *Bi* syndrome and acupuncture has long been a standard treatment. A recent review of the mechanism of acupuncture analgesia [16, 17] provided an overview of the neural, humoral and biomagnetic mechanisms that may contribute to the production of acupuncture analgesia. More conventional research into the mechanism of acupuncture pain relief has diverged into two widely accepted theories: (1) activation of the gate control system [18, 19]; (2) stimulation of the release of neurochemicals in the central nervous system [20–22]. Treatments with acupuncture have been shown

to increase the production of endorphins and enkephalins [23, 24]. Transient increases in B-lipotropin and B-endorphin have been detected up to 60 min after electroacupuncture treatment [25]. Stux and Pomeranz [26] have explained acupuncture analgesia as a technique of peripheral sensory stimulation that causes a maximal activation of the endogenous opioid and non-opioid analgesic systems.

Apart from the mechanism-of-action literature on acupuncture, research into the effectiveness of acupuncture for pain has been carried out; yet, most studies have methodological flaws that cast doubt on results reported. In a recent systematic review of acupuncture and pain, Berman [27] identified only seven studies assessing the effectiveness of acupuncture for the treatment of OA. However, systematic flaws were found in these studies as well. Inadequate statistical power [28–31], failure to blind the evaluator [28–30, 32], inadequate number of acupuncture treatments to effect change according to TCM authorities [33], failure to control for concomitant therapies [28, 32] and uninvestigated patient attrition were among the major flaws.

Berman *et al.* [34] reported in a pilot study that 12 patients with symptomatic knee OA who added traditional Chinese acupuncture to background therapy showed improvement in symptoms and joint function when standard outcome measures were used. The current study was designed to answer questions raised from the pilot work in anticipation of conducting a larger more definitive randomized controlled trial (RCT). The design compared acupuncture as an adjunctive therapy to standard oral medication *vs* standard medication alone, specifically to examine whether improvement seen with acupuncture treatment was biased by the natural course of the disease or by regression to the mean due to repeated outcome measurement. The rationale behind the use of acupuncture in adjunctive trials is that standard care is not fully effective in alleviating pain or slowing the progression of the disease, and acupuncture may improve outcome [35] either by potentiating the analgesic effects of medication [22] and/or slowing the disease progression [36]. This adjunctive design, however, may not totally control for the placebo effect and, therefore, cannot conclusively determine how much improvement is attributable to the acupuncture treatment *vs* the effects that stem from the entire treatment experience [37].

This intermediate clinical trial also addressed some of the methodological limitations found in prior studies by including random treatment assignment, adequate sample size, use of standard outcome measures, and a blinded independent assessor. Valid and reliable outcome measures, including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score, WOMAC pain and disability subscales, and Lequesne Algofunctional Index [38–40] were used for assessing pain and physical dysfunction. Questions concerning differences in outcome between true, sham and placebo acupuncture groups were not examined in this study, but will be considered in a large multicentre Phase III trial.

The purpose of this study was to determine whether acupuncture is a clinically effective and safe adjunctive therapy when added to conventional treatment for elderly persons with OA of the knee. The questions addressed were designed to (1) examine whether the addition of acupuncture to conventional therapy would produce relief of pain and dysfunction symptoms greater than conventional therapy alone for elderly patients with OA of the knee, (2) ascertain whether the therapy effects last for 4 weeks following termination of treatment and (3) determine whether side-effects to this therapy are reported for participants.

Methods

Sample selection generation and sample selection

Based on our pilot data, with a mean difference on the WOMAC score of −14.0 (at 8 weeks) and S.D. of 20.5, we estimated that 35 patients would be needed in each group to give 80% power to demonstrate a statistically significant improvement in total WOMAC score between the treated and control patients at 8 weeks after enrolment. Seventy-three patients with symptomatic knee OA were screened as being eligible and randomized using computer-generated assignment. Patients were recruited from the Faculty Practice of the Division of Rheumatology at the University of Maryland, and through public service advertisements in radio and print media in the greater Baltimore area. Block randomization to ensure balance within groups was carried out using opaque sealed envelopes. Computer-generated random numbers were used to select randomly block size and permutation within block. Block sizes of four or six subjects were used, e.g. if 'A' is treatment group and 'B' is control group, for blocks of four, the possible assignment orders are AABB, BBAA, ABAB, BABA, ABBA, BAAB; for blocks of six there are 20 permutations.

Six participants were lost to follow-up before the week 4 assessment, and 58 remained in the study through the follow-up at 12 weeks from baseline (Fig. 1 presents attrition numbers in a method similar to that suggested by Altman [41]). In the acupuncture group, a total of 29 patients completed 12 weeks of follow-up, and in the conventional therapy group 29 patients completed the 12 week visits. Of the 15 drop-outs, seven were in the acupuncture group and eight in the conventional therapy arm. Patients randomly assigned to the control group were given the opportunity to receive acupuncture following completion of their control assessments (partial cross-over design). Scores from all patients receiving acupuncture in the trial, regardless of original assignment, are pooled for within-group analyses.

Inclusion and exclusion criteria

The inclusion criteria for the study were: (1) diagnosis of OA of the knee (ACR criteria applied) [42] of at least 6 months duration; (2) at least moderate pain in the knee for most days in the last month; (3) aged 50 yr or above; (4) taking analgesic or anti-inflammatory agents for control of pain for at least 1 month; (5) documented

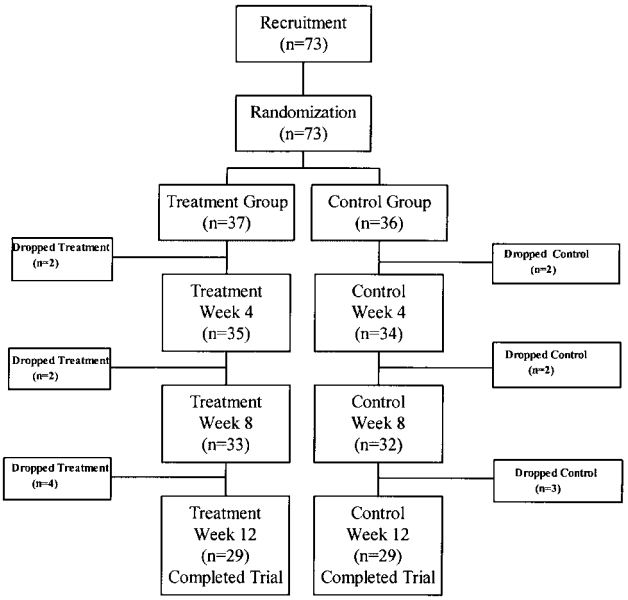

FIG. 1. Flow chart of randomization and withdrawal at each follow-up time-point; baseline, week 4, week 8 and week 12.

radiographic changes of OA (Kellgren–Lawrence grade of 2 or more); (6) signed informed consent. The exclusion criteria were: (1) intra-articular corticosteroid injection into the knee(s) within 4 weeks immediately preceding entry into study; (2) severe chronic or uncontrolled concomitant illness (e.g. coronary artery disease); (3) history or clinical indications of bleeding diathesis, including current use of anticoagulants.

Acupuncture treatment protocol

Those participants who were originally assigned to the acupuncture treatment group and those who crossed over from the control group received acupuncture biweekly for 8 weeks. Patients were asked to remain on their baseline analgesic/anti-inflammatory regimens as well and not to begin any new physiotherapy or exercise programmes.

Selection of acupuncture points was based on the TCM theory for treating *Bi* syndrome, which uses local and distal points on channels that traverse the area of pain [11, 12]. The following local acupuncture points were used: Yanglinquan (GB 34), Yinlinquan (Sp 9), Zusanli (St 36), Dubi (St 35) and the extra point Xiyan. The distal points used were Kunlun (UB 60), Xuanzhong (GB 39), Sanyinjiao (Sp 6) and Taixi (Kid 3) (Fig. 2).

The skin was sterilized with alcohol according to the standard protocol of the National Commission for the Certification of Acupuncture and Oriental Medicine (NCCAOM), and acupuncture needles (1 inch, 34 gauge, 0.22-mm-diameter needle) were inserted to standard depths (0.4–0.6 inches). The De Qi sensation was verified by the patient. Two electrodes were attached to the needles at local point Dubi (St 35) and Xiyan (extra point). Electrical stimulation with 2.5–4 Hz, square pulses of 1.0 ms duration was used for 20 min.

Standard care comparison

The conventional therapy arm participants were asked to remain on their current level of oral therapy throughout the trial. They were also offered the option to receive acupuncture therapy following assessment at 12 weeks. Assessments were identical in frequency to those for participants in the acupuncture group.

Assessments

Following the signing of an informed consent document, the patients at baseline (week 0) were examined by a rheumatologist, during which a general physical examination was performed, a standing bilateral knee radiograph of the tibiofemoral joints was taken and scored using the Kellgren–Lawrence scale, and a detailed rheumatological examination was performed. Age, gender, race, marital status and general medical history were also recorded.

Patients were then asked to record their responses to the WOMAC and Lequesne scales [38–40]. The WOMAC is a validated, multidimensional self-report scale used to assess pain, stiffness and physical function for OA of the knee [36]. The Lequesne scale is designed to measure patient status at different stages of OA and has particular value in assessing OA in weight-bearing joints [40]. At the time that baseline assessments were made, the rheumatologist was blinded to the participant group assignment. No assessments are reported here which occurred when the rheumatologist was not blinded, as these measures were for screening purposes only. Bellamy *et al.* [38] have found that changes in rheumatological examination scores are poor outcome measures, and therefore they were not monitored throughout the trial. Patient scores were ascertained at weeks 0, 4, 8 and 12 during the randomized trial (between-group data collection period). In addition, those patients who received acupuncture treatment following the completion of their tenure in the control group (12 weeks) are referred to as cross-overs for the within-group analyses.

Analysis

Between groups. Analyses were performed on the 73 participants who were randomized for the intention-to-treat (ITT) analysis using a 'last score carried forward technique' (assuming no change for non-completers). The 'last score carried forward technique' is a conservative means of applying ITT methodology. In it, the last value recorded before dropping out was carried forward to each missing time period. The assumption is that a patient's scores at the time of removal from the study will neither increase nor decrease from that point. Six of the 15 non-completers left the study before the 4 week measurement period. A separate analysis was also performed on the 58 completers. Only patients who were compliant through 12 weeks were included in these data analyses. Longitudinal linear regression analyses (repeated measures analysis of variance) were used to test for differential effects of acupuncture compared with placebo on outcome score patterns over time and to

ACUPUNCTURE POINT	INDICATION
Yanglinquan (GB 34)	Weakness, numbness and pain of the lower extremities, swelling and pain of the knee
Yinlinquan (Sp 9)	Abdominal pain and distension, diarrhoea, edema, jaundice, dysuria, pain in the knee
Zhusanli (St 36)	Gastric pain, aching of the knee joint and leg, emaciation due to general deficiency
Dubi (St 35)	Pain, numbness and motor impairment of the knee
Xiyan	Knee pain, weakness of the lower extremities
Kunlun (UB 60)	Headache, neck rigidity, pain in the shoulder, back and arm, swelling and pain of the heel
Xuanzhong (GB 39)	Muscular atrophy of the lower limbs, spastic pain of the leg
Sanyinjiao (Sp 6)	Abdominal pain, oedema, paralysis and pain of the lower extremities, muscular atrophy
Taixi (Kid 3)	Pain in lower back, insomnia, impotence

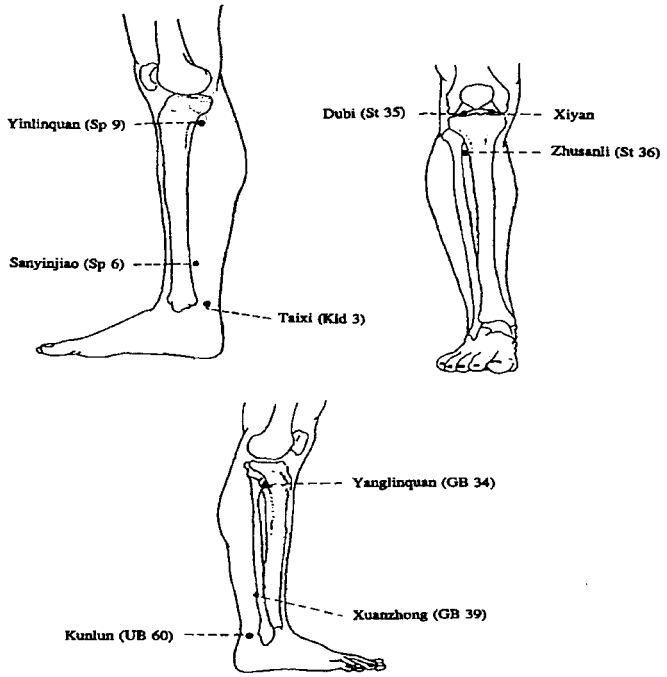

FIG. 2. The acupuncture points. The diagrams are adapted with modifications from *Chinese acupuncture and moxibustion*, 1st edn, by X. Cheng. Foreign Language Press, Beijing, 1887.

examine changes over time within treatment group. Residual analyses were completed to confirm approximate normality of the error distributions.

T-tests were used to compare groups at each time point when significant interactions of group with time were observed.

Within group: acupuncture. The within-group analysis patients are those who received acupuncture for OA of the knee as part of the initial treatment group during the randomized trial and those initially in the control group who were offered acupuncture once their control period was finished and are referred to as cross-overs in

this paper. Baseline measures for the within-group analysis are reported on 62 patients. Participants with missing values were dropped from the analysis; sample sizes for the within-group analysis points are 60 for 4 weeks, 58 for 8 weeks and 52 for 12 weeks. Repeated measures analyses were used to examine mean differences in outcome scores between baseline and subsequent assessment points at 4, 8 and 12 weeks. Thus, patients served as their own controls. All analyses were completed using SPSS for Windows, Version 6.1.

Results

RCT: intention-to-treat analysis for all study enrollees

The 73 participants were randomly assigned to treatment group with 36 assigned to the acupuncture group and 37 to the standard care group. The acupuncture group was 91% White, 5.7% Hispanic and 2.9% Black. The standard care group was 74.3% White, 11.4% Hispanic and 14.3% Black. There was a 1:1 ratio of males to females in the acupuncture group; the comparison group had 28% males and 72% females. There were no differences in mean baseline scores (WOMAC total, pain and disability) based on race or sex. Patients were on average 65 yr old at entry to the study (range 49–86). There were no significant differences between groups at baseline on body mass index, disease duration, age, WOMAC total, WOMAC disability, WOMAC pain and Lequesne score (Table 1).

However, a comparison of the 58 study participants (completers) to those who did not complete the full 12 week protocol (Table 1) showed that those who dropped out had a higher mean score on the WOMAC total (*t*-test: $P = 0.05$), had experienced OA longer (*t*-test: $P = 0.04$) and were younger (*t*-test: $P = 0.05$) than those who completed the protocol.

Longitudinal (repeated measures) linear regression analysis

A repeated measures analysis was completed to compare the treatment and comparison groups on changes in WOMAC and Lequesne scores over time. There were highly significant overall differences in patterns of change over time on all outcome scores, based on the group by time interactions ($P < 0.001$). Thus, it was necessary to compare treatment groups on scores at each time period using *t*-tests. For all time periods except baseline, there were significant differences between groups for all outcome scores ($P < 0.001$). Using separate repeated measures analyses to assess time trends within each group, the scores showed significantly different trends in the two groups, with decreases in the acupuncture group over time which were not seen in the comparison group (Table 2). In the acupuncture group, the total WOMAC scores decreased by $\sim$34% at week 4 and showed a 42% decrease from baseline at week 8. There was a slight increase in the WOMAC totals at 12 weeks, after treatment had been stopped for 4 weeks; however, it was still a 35% improvement over mean baseline score. There was no significant change in the controls from baseline to 4, 8 or 12 weeks. The differences in the two groups can be seen graphically in Fig. 3. The decrease in WOMAC scores for the acupuncture group was observed to have similar patterns for both the pain and disability subscales. Pain scores appeared to decrease at a slightly higher rate. There was a 34% decrease at 4 weeks, 44% at 8 weeks and a maintained 42% decrease in pain at 12 weeks post-acupuncture.

The Lequesne scale also showed a significant decrease in severity in the acupuncture group and not in the control group at 4 weeks, 8 weeks and during the 4 weeks post-acupuncture. There was a 14% decrease at 4 weeks, 25% decrease at 8 weeks and a maintenance of improvement of 20% at 4 weeks post-acupuncture.

TABLE 1. Acupuncture and control group: race, gender, age and disease duration with baseline standardized assessments for total randomized group and completers *vs* drop-outs ($n = 73$)

	Total randomized groups		Completers *vs* drop-outs		
	Acupuncture	Control	Completers	Drop-outs	P[a]
n	36	37	58	15	
Age	65.7 ± 7.95	65.5 ± 9.13	66.6 ± 8.83	61.8 ± 5.89	0.05
Sex					
Male	51.4%	27.8%	39.6%	40.0%	0.98
Female	48.6%	72.2%	60.4%	60.0%	
Race					
White	91.7%	74.3%	82.8%	73.3%	0.08
Non-White	8.3%	25.7%	17.2%	26.7%	
Disease duration	7.5 ± 7.46	6.9 ± 4.64	6.0 ± 4.33	11.7 ± 9.62	0.04
BMI	32.0 ± 7.47	31.9 ± 4.66	32.0 ± 5.80	32.7 ± 7.61	0.67
WOMAC total	48.4 ± 16.12	51.4 ± 12.25	48.3 ± 12.87	55.5 ± 18.34	0.08
WOMAC pain	9.6 ± 3.25	9.9 ± 2.83	9.3 ± 2.75	11.1 ± 3.73	0.05
WOMAC disability	34.3 ± 12.13	34.4 ± 9.15	34.4 ± 9.74	39.1 ± 13.74	0.13
Lequesne	11.7 ± 3.45	12.3 ± 3.54	11.6 ± 3.41	13.3 ± 3.51	0.09

[a]Comparisons were made using *t*-tests for continuous variables and χ^2 tests for discrete variables.

TABLE 2. Results of longitudinal linear regression analysis comparing mean outcome scores for the acupuncture and control group at baseline, 4, 8 and 12 weeks for the intention-to-treat model[a] ($n = 73$)

	Baseline				4 weeks				8 weeks				12 weeks			
	n	Mean	S.D.	*t*-test[b]	Mean	S.D.	*t*-test[b]	Comparison with baseline[c]	Mean	S.D.	*t*-test[b]	Comparison with baseline[c]	Mean	S.D.	*t*-test[b]	Comparison with baseline[c]
WOMAC totals																
Acupuncture	36	48.69	16.23	$P = 0.52$	33.36	17.66	$P < 0.001$	$P < 0.001$	28.08	17.96	$P < 0.001$	$P < 0.001$	31.58	18.27	$P < 0.001$	$P < 0.001$
Control group	37	50.87	12.30		50.05	14.03		$P = 0.66$	50.11	14.52		$P = 0.68$	50.43	14.10		$P = 0.97$
WOMAC disability																
Acupuncture	36	34.56	12.20	$P = 0.52$	24.11	13.17	$P < 0.001$	$P < 0.001$	20.31	13.26	$P < 0.001$	$P < 0.001$	23.17	13.92	$P < 0.001$	$P < 0.001$
Control group	37	36.19	9.22		36.11	10.04		$P = 0.95$	36.14	10.55		$P = 0.70$	36.78	10.71		$P = 0.69$
WOMAC pain																
Acupuncture	36	9.58	3.26	$P = 0.78$	6.25	3.46	$P < 0.001$	$P < 0.001$	5.34	3.62	$P < 0.001$	$P < 0.001$	5.56	3.44	$P < 0.001$	$P < 0.001$
Control group	37	9.78	2.83		9.46	3.50		$P = 0.76$	9.46	3.56		$P = 0.48$	9.51	3.01		$P = 0.53$
Lequesne																
Acupuncture	36	11.81	3.47	$P = 0.79$	10.17	3.85	$P < 0.008$	$P < 0.008$	8.89	4.32	$P < 0.001$	$P < 0.001$	9.34	4.09	$P < 0.001$	$P < 0.001$
Control group	37	12.03	3.52		12.65	3.32		$P = 0.21$	12.62	3.12		$P = 0.19$	12.41	3.47		$P = 0.41$

[a]Interactions of group with time were highly significant: groups differ on patterns over time.
[b]*t*-test of group differences at time period (appropriate because of effects differing over time).
[c]Within-group analysis to test change from baseline.

TABLE 3. Mean WOMAC scores for the combined acupuncture and cross-over group at baseline, 4, 8 and 12 weeks, and change from previous time period ($n = 62$)

	Baseline Mean (± S.E.)	4 weeks Mean (± S.E.)	Comparison with baseline *P* value	8 weeks Mean (± S.E.)	Comparison with baseline *P* value	12 weeks Mean (± S.E.)	Comparison with baseline *P* value
WOMAC totals	48.5 ± 1.89	34.08 ± 2.04	0.001	31.10 ± 2.29	0.001	33.92 ± 2.39	0.001
WOMAC disability	34.55 ± 1.49	24.35 ± 1.56	0.001	21.86 ± 1.66	0.001	23.71 ± 1.82	0.002
WOMAC pain	9.03 ± 0.41	6.27 ± 0.40	0.001	5.48 ± 0.44	0.001	6.00 ± 0.49	0.004
Lequesne	12.79 ± 0.92	10.93 ± 1.07	0.001	10.09 ± 1.01	0.001	9.92 ± 0.64	0.088

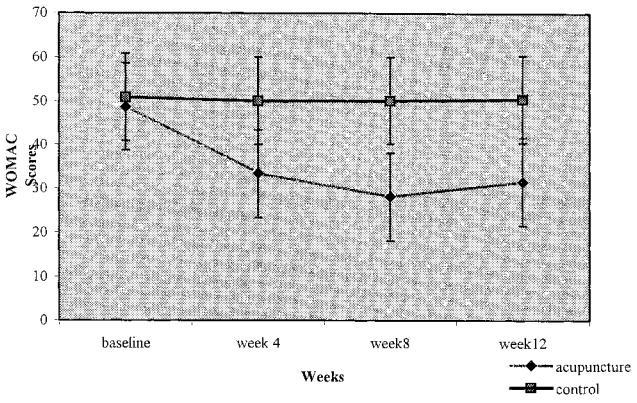

FIG. 3. WOMAC scores for intention-to-treat analysis ($n = 73$): control group vs acupuncture group.

There was no change in Lequesne scores for the control group at any time period.

Within-group analyses

Those study participants who received acupuncture as part of their original group assignment and those who crossed over from the control condition to the therapeutic acupuncture condition were not significantly different ($P > 0.05$) at baseline on race, gender, age and disease duration ($n = 62$). They were also not significantly different at baseline on the WOMAC total score ($P = 0.92$), WOMAC disability ($P = 0.99$), WOMAC pain ($P = 0.11$) and Lequesne ($P = 0.19$).

The functional sample of all participants, both acupuncture group and partial cross-overs, who completed at least 4 weeks of acupuncture ($n = 60$) included 45% males and 55% females; 86% were White with a group age range of 50–86. The mean number of years that the sample members had experienced moderate to severe OA symptoms was 7.13 with a range of 6 months–36 yr.

A repeated measures analysis found significant changes in WOMAC total scores over time ($P < 0.001$). Table 3 shows that the time effect was seen at 4 weeks ($P < 0.001$), at 8 weeks ($P < 0.001$) and at 12 weeks ($P < 0.001$). There were no significant differences between the original acupuncture group and the partial cross-over group at any of the time periods.

Data comparing patient scores between baseline and week 4, 8 and 12 assessments on the WOMAC total, WOMAC disability subscale and WOMAC pain subscale along with the Lequesne are also presented in Table 3. On all three points of measurement and for all outcome measures, there were significant differences reported from initial baseline scores. There were no differences between the amount of change at any time period. These findings address question 2: 'whether the therapy effects last for 4 weeks following termination of treatment'. Table 3 data indicate that although the 12 week mean scores (no acupuncture therapy for 4 weeks) were significantly improved from the baseline scores, there was some decay in improvement from the 8 week scores.

Side-effects

No patients reported side-effects from the 16 acupuncture therapy sessions, including those initially randomized to the control group who received acupuncture later, although the patients were elderly and therefore may have been more vulnerable to adverse effects.

Discussion

The results of this study indicate that a group of elderly patients with moderate/severe OA of the knee showed significant improvement at the 4, 8 and 12 week measurement points over their baseline pain and function scores. As OA is the most prevalent form of arthritis and a leading cause of disability in the elderly, the identification of adjunctive acupuncture therapy as one which demonstrates effectiveness in decreasing pain and improving function is a potentially useful clinical finding. This improvement was produced by an 8 week course of acupuncture delivered biweekly along with the current conventional therapy regime. These findings were consistent when all enrollees were analysed in an intention-to-treat analysis with last score carried forward, or when only completers were analysed.

The last score carried forward technique replaces missing values with the last recorded score. This technique is a conservative method to account for missing values while keeping patients in the analysis, particularly when characteristics of drop-outs are different in the two treatment groups. It assumes that patients who drop out of the study neither continue to improve or decline, based on their previous scores. In the situation of a continuation of improvement or the rebounding of point estimates towards baseline in treatment group patients who dropped out, one would expect the effect of treatment to be either slightly enhanced or ameliorated in the remaining treatment group. The changes would appear to have little, if any, effect on the analysis.

Christensen *et al.* [32], similar to the findings in this study, reported significant pain relief in patients treated with acupuncture compared to a waiting list control group. Junnila [43] treated one group of patients with acupuncture and one group of patients pharmacologically, with results indicating significantly more pain relief in the group treated with acupuncture. Dickens and Lewith [28] used mock transcutaneous electrical nerve stimulation (TENS) as a control and found that the patients treated with acupuncture experienced significantly more pain relief from baseline to end of treatment, but there were no significant differences between the two groups. Takeda and Wessel [29] and Gaw *et al.* [30] reported no significant difference in pain reduction between patients treated with acupuncture and patients treated with sham acupuncture. The findings of the Takeda and Wessel and Gaw *et al.* studies may be a result of sham acupuncture not being an inert control and in fact producing changes in the control groups due to the generalized analgesic effect possible through the nervous system [27].

The elderly patients reported here who received acupuncture ($n = 62$) did not report side-effects secondary

to their acupuncture therapy. This is an important factor since these participants' therapies represented hundreds of acupuncture events that could have produced side-effects. Moreover, many of the standard care medications produce gastrointestinal problems that are quite serious, particularly in the elderly [8–12]. If, indeed, acupuncture can increase function and decrease pain as an adjunctive therapy with no reported side-effects, it is important to look at the potential for decreased use of NSAIDs as a secondary benefit to the addition of acupuncture to the treatment plan for OA of the knee.

The between-groups analysis showed differences at 4, 8 and 12 week measurement points on two standardized self-report measures for OA. The differences between those receiving acupuncture in addition to standard care and those receiving only standard care were still significant 4 weeks following the termination of the acupuncture treatment.

It should be noted that although the patients were still substantially improved over baseline at 12 weeks, some decay in effectiveness of the therapy is apparent in the mean scores for the 12 week assessment. As this decay in effectiveness is evident within 4 weeks of the last treatment, it will be important for a maintenance protocol to be developed which will allow patients to continue at the highest functional level possible following the end of their therapy period.

The absence of an objective measurement, such as a 50 ft walk time or joint range of motion, may be an issue. However, according to recommendations from OMERACT III and the Osteoarthritis Research Society task force [42], objective physiological measures are not considered part of the core assessments required for appropriate OA clinical trial data.

A major limitation to making definitive inferences from this study is the lack of a placebo control group to explore further non-specific effects (often used synonymously with placebo effects) of treatment that can include physician attention, interest and concern, and patient and physician expectations of treatment [37, 44, 45]. Placebo effects may be due to factors which extend beyond the physical characteristics of the treatment. Patients arrive at the trial with an array of a priori beliefs and expectations about acupuncture and their own pain [46, 47]. Efforts to identify personality, demographic and other characteristics that predict placebo responses have met with little success [48]. There is controversy in the literature about the use of placebo groups in studies of acupuncture [49]; some types of controls used include pharmacological treatment, sham acupuncture, TENS and mock TENS [29, 30, 50]. Adequate research designs for the testing of acupuncture therapy using sham/placebo models are still being designed and tested. A standardized reliable model has not been developed to date. This study, therefore, addressed an intermediate question of safety and efficacy of acupuncture as an adjunctive therapy.

Generalization of findings from this Phase II study should be made conservatively within the demographic and disease characteristics described, and for the therapy as delivered. No generalization to other cohort groups or disease ranges is made. A study which would assess whether an acupuncture therapy protocol is effective for groups other than the elderly should also be considered.

A refinement of the acupuncture protocol, in terms of the number of sessions required for improvement and the appropriate maintenance treatment schedule required to prevent substantial decay of effectiveness, would assist health professionals in their decision making concerning the appropriate therapy for a particular patient. This information could establish for both the patient and provider the time commitment needed for compliance with therapy and the costs associated with therapy, in addition to the evaluation of therapy effectiveness and safety. The proposed Phase III study of acupuncture treatment for knee OA would be a large multicentre RCT with three arms: real acupuncture, sham acupuncture and attention/control. Questions regarding the recommended number of treatments, the value of maintenance dosing and measurement of differences between the effects of true acupuncture and the possible non-specific effects of the treatment experience would be investigated.

Acknowledgements

This work was supported by the Maurice Laing Foundation and National Institutes of Health—National Center of Complementary and Alternative Medicine and the National Institutes of Arthritis/Musculoskeletal/Skin Diseases (Grant no. 1 R21-RR09327-01).

References

1. Scott W, Hochberg MC. Arthritic and other musculoskeletal diseases. In: Brownson RC, Remington PL, Davis JR, eds. Chronic disease epidemiology and control. Washington, DC: American Public Health Association, 1993.
2. Creamer P, Hochberg MC. Osteoarthritis. Lancet 1997; 350:503–9.
3. McAlindon T, Dieppe P. The medical management of osteoarthritis of the knee: an inflammatory issue? Br J Rheumatol 1990;29:471–3.
4. Davis MA, Ettinger W, Neuhaus J, Mallon KP. Knee osteoarthritis and physical functioning: evidence from the NHANES I epidemiological follow-up study. J Rheumatol 1991;18:591–8.
5. McAlindon T, Cooper C, Kirwan J, Dieppe PA. Determinants of disability in osteoarthritis of the knee. Ann Rheum Dis 1993;52:258–62.
6. Hopman-Rock M, Odding E, Hoffman A, Kraaimaat F, Bijlsma J. Physical and psychosocial disability in elderly subjects in relation to pain in the hip and/or knee. J Rheumatol 1996;23:1037–44.
7. Hochberg MC, Altman RD, Brandt KD. Guidelines for the medical management of osteoarthritis. Part 2. Osteoarthritis of the knee. Arthritis Rheum 1995;38: 1541–6.
8. Hochberg MC. Association of nonsteroidal antiinflammatory drugs with upper gastrointestinal disease: epidemiologic and economic considerations. J Rheumatol 1992;19(suppl. 36):63–7.
9. Somerville K, Faulkner G, Langman MJS. Non-steroidal anti-inflammatory drugs and bleeding gastric ulcer. Lancet 1986;i:462–4.

10. Buchanan WW. Implications of NSAID therapy in elderly patients. J Rheumatol 1990;4:29–32.
11. Brooks PM, Potter SR, Buchanan WW. Non-steroidal antiinflammatory drugs and OA: help or hindrance? J Rheumatol 1982;9:3–5.
12. Caradoc-Davies TH. Non-steroidal anti-inflammatory drugs, arthritis and gastrointestinal bleeding in elderly inpatients. Age Ageing 1984;13:295–8.
13. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. N Engl J Med 1994;331:1675–9.
14. Towheed TE, Hochberg MC. Health related quality of life following total hip replacement. Semin Arthritis Rheum 1996;26:483–91.
15. Lytle CD. An overview of acupuncture. Rockville, MD: US Department of Health and Human Services, 1993.
16. Sims J. The mechanism of acupuncture analgesia: a review. Complem Ther Med 1997;5:102–11.
17. Thomas M, Lundeberg T. Does acupuncture work? International Association for the Study of Pain, IV(3), 1996.
18. Melzack R, Wall PD. Pain mechanism, a new theory. Science 1965;150:91.
19. Lewith GT, Kenyon JN. Physiological and psychological explanations for the mechanisms of acupuncture as a treatment for chronic pain. Soc Sci Med 1984;19:1367–78.
20. Cheng RS, Pomeranz B. Electroacupuncture analgesia could be mediated by at least two pain-relieving mechanisms: endorphin and non-endorphin systems. Life Sci 1979;25:1957–62.
21. Clement-Jones V, MacLoughlin L, Tomlin S, Besser GM, Rees LH, Wen HL. Increased beta-endorphin but not met-enkephalin levels in human cerebrospinal fluid after acupuncture for recurrent pain. Lancet 1980;ii:946–8.
22. Han JS (ed.) The neurochemical basis of pain relief by acupuncture. Beijing: Chinese, Medical, Scientific and Technologic Publisher, 1987.
23. Pomeranz B, Chiu D. Naloxone blockade of acupuncture analgesia: endorphin implicated. Life Sci 1976;19:1757–62.
24. Ghia JN, Mao W, Toomey TC, Gregg JM. Acupunctures and chronic pain mechanisms. Pain 1976;2:285–99.
25. Nappi G, Facchinetti F, Legnante G, Parrini D, Petralgia F, Savoldi F *et al.* Different releasing effects of traditional manual acupuncture and electroacupuncture on pro-opiocortin-related peptides. Acupunct Electrother Res Int J 1982;7:93–103.
26. Stux G, Pomeranz B. Basics of acupuncture. Berlin: Springer-Verlag, 1995:1–250.
27. Berman B. Overview of clinical trials on acupuncture for pain. Presentation at NIH Consensus Development Conference on Acupuncture. Program and Abstracts National Institutes of Health, Bethesda, Maryland, November 3–5, 1997, pp. 61–2.
28. Dickens W, Lewith GT. A single-blind controlled and randomized clinical trial to evaluate the effect of acupuncture in the treatment of trapezio-metacarpal osteoarthritis. Complem Med Res 1989;3:5–8.
29. Takeda W, Wessel J. Acupuncture for the treatment of pain of osteoarthritic knees. Arthritis Care Res 1994;7:118–22.
30. Gaw AC, Chang LW, Shaw L. Efficacy of acupuncture on osteoarthritic pain. N Engl J Med 1975;293:375–8.
31. Lundeberg T, Eriksson SV, Lundeberg S, Thomas M. Effect of acupuncture and naloxone in patients with osteoarthritis pain. A sham acupuncture controlled study. Pain Clinic 1991;4:155–61.
32. Christensen BV, Iuhl IU, Vilibek H, Bulow HH, Dreijer NC. Acupuncture treatment of severe knee osteoarthrosis: a long-term study. Acta Anaesthesiol Scand 1992;36: 519–25.
33. Birch S, Hammerschlag R. Acupuncture efficacy: A compendium of controlled trials. New York: National Academy of Acupuncture and Oriental Medicine, 1996.
34. Berman B, Lao L, Greene M, *et al.* Efficacy of traditional Chinese acupuncture in the treatment of symptomatic knee osteoarthritis: a pilot study. Osteoarthritis Cartil 1995;3:139–42.
35. Hammerschlag R. Methodological and ethical issues in clinical trials of acupuncture. J Altern Complem Med 1998;4:159–71.
36. Lao L, Zhang G, Wei F, Berman BM, Meszler RM, Ren K. Electroacupuncture attenuates hyperalgesia and modulates fos protein expression in rats with unilateral persistent inflammation. Abstract to be presented at Society for Neuroscience, 28th Annual Meeting, November 7–12, 1998, Los Angeles, California.
37. Turner JA, Deyo RA, Loeser JD, Von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. J Am Med Assoc 1994;27:1609–14.
38. 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.
39. Bellamy N. Pain assessment in osteoarthritis: experience with the WOMAC osteoarthritis index. Semin Arthritis Rheum 1989;18:14–7.
40. Lequesne M. Indices of severity and disease activity for osteoarthritis. Semin Arthritis Rheum 1991;20:48–54.
41. Altman D. Better reporting of randomised controlled trials: the CONSORT statement. Br Med J 1996;313: 570–1.
42. 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. Osteoarthritis Cartil 1996;4:217–43.
43. Junnila SYT. Acupuncture therapy for chronic pain. Am J Acupunc 1982;10:259–62.
44. Guo-Wei LU. Neurobiologic research on acupuncture in China as exemplified by acupuncture analgesia. Anesthes Analges 1983;62:335–40.
45. Wall PD. The placebo effect: an unpopular topic. Pain 1992;51:1–3.
46. Taub HA, Mitchell JN, Stuber FE, Eisenberg L, Beard MC, McCormack RK. Analgesia for operative dentistry: a comparison of acupuncture and placebo. Oral Surg Oral Med Oral Pathol 1979;48:205–10.
47. Lewith G, Vincent C. Evaluation of the clinical effects of acupuncture: a problem reassessed and a framework for future research. Pain Forum 1995;5:137–42.
48. Shapiro AK, Shapiro E. Patient-provider relationships and the placebo effect. In: Matarazzo JD, Weiss SM, Herd JA, Miller NE, Weiss SM, eds. Behavioral health: a handbook of health enhancement and disease prevention. New York: Wiley-Interscience, 1984:371–83.
49. Vincent C, Lewith G. Placebo controls for acupuncture studies. J R Soc Med 1995;88:199–202.
50. Fargas-Babjak A, Pomeranz B, Rooney PJ. Acupuncture-like stimulation with codetron for rehabilitation of patients with chronic pain syndrome and osteoarthritis. In: 2nd and 3rd International Symposium on Acupuncture and Electrotherapy. School of International Affairs. New York: Columbia University, 1987.