A blinded randomised trial of acupuncture (manual and electroacupuncture) compared with a non-penetrating sham for the symptoms of osteoarthritis of the knee

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Abstract

Objectives To compare the effect of acupuncture (manual and electroacupuncture) with that of a non-penetrating sham ('placebo' needle) in patients with osteoarthritic knee pain and disability who are blind to the treatment allocation.

Methods Acupuncture naïve patients with symptomatic and radiological evidence of osteoarthritis of the knee were randomly allocated to a course of either acupuncture or non-penetrating sham acupuncture using a sheathed 'placebo' needle system. Acupuncture points for pain and stiffness were selected according to acupuncture theory for treating *Bi* syndrome. Both manual and electrical stimulation were used. Response was assessed using the WOMAC index for osteoarthritis of the knee, self reported pain scale, the EuroQol score and plasma β-endorphin. The effectiveness of blinding was assessed.

Results There were 34 patients in each group. The primary end point was the change in WOMAC pain score after the course of treatment. Comparison between the two treatment groups found a significantly greater improvement with acupuncture (mean difference 60, 95% CI 5 to 116, P= 0.035) than with sham. Within the acupuncture group there was a significant improvement in pain (baseline 294, mean change 95, 95% CI 60 to 130, P<0.001) which was not seen by those who had sham acupuncture (baseline 261, mean change 35, 95% CI -10 to 80, P=0.12). Similar effects within group, but not between groups, were seen with the secondary end points of WOMAC stiffness, WOMAC function, and self reported pain. One month after treatment the between group pain difference had been lost (mean difference 46; 95% CI -9 to 100, P=0.10) although the acupuncture group was still benefiting compared to baseline (mean difference 59; 95% CI 16 to 102, P=0.009). The EuroQol score, a generic measure of health related quality of life, was not altered by the treatments. A minority of patients correctly guessed their treatment group (41% in the acupuncture group and 44% in the control group). Plasma β-endorphin levels were not affected by either treatment.

Conclusions Acupuncture gives symptomatic improvement for patients with osteoarthritis of the knee, and is significantly superior to non-penetrating sham acupuncture. The study did not confirm earlier reports of release of plasma β-endorphin during acupuncture.

Keywords

Osteoarthritis, acupuncture, knee pain, WOMAC, β-endorphin.

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Introduction

Acupuncture is an increasingly popular treatment for osteoarthritis and other painful musculo-skeletal conditions. Many patients suffering from osteoarthritis of the knee, who have not been helped by one or more Western therapy regimes, find relief from alternative medical approaches including acupuncture.[1-8] We have previously reported an open, randomised study that confirmed the value of acupuncture.[9] While open studies consistently show benefit, the mechanism remains unclear.[10]

Controlled trials on the effect of acupuncture treatment have yielded inconsistent results,[11;12] which may be due to a variety of technical reasons.[13;14] Systematic reviews have concluded that there is limited evidence that acupuncture is more effective than no treatment for chronic pain.[15-17] However, the authors of a meta-analysis of acupuncture for peripheral osteoarthritis stated that 'sham-controlled RCTs suggest effects of acupuncture for pain control in patients with peripheral joint osteoarthritis'.[18] A recent systematic review reported that acupuncture, when it meets criteria for adequate treatment, is significantly superior to sham acupuncture for chronic knee pain.[19]

Streitberger and Kleinhenz have developed a 'placebo' acupuncture needle in which the needle retracts into the handle with no skin penetration.[20] In a single-blind, randomised crossover pilot study using this system there were no significant differences for any of the sensations measured.[21] In a study of acupuncture for osteoarthritis of the hand, all 14 patients believed that their skin had been penetrated both by the placebo needle and a real acupuncture needle.[22] Using the same system, real acupuncture was found to be more effective than sham for improving the pain and disability of osteoarthritis of the knee,[23] but not when used as an adjunct to physiotherapy.[24]

There are now guidelines for the assessment of therapies for osteoarthritis,[25] and proposals to standardise acupuncture trials.[16] The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the visual analogue scale (VAS) for pain are validated methods for monitoring symptom change in osteoarthritis of the knee.[26;27] Although the WOMAC has a functional component, the EuroQol score provides a generic quality of life assessment.[28;29]

Exactly how acupuncture works remains unclear but natural opioids have been implicated.[30] Elevation of plasma β-endorphin immediately after an acupuncture treatment has been reported.[31] The opportunity was taken during this clinical study to measure the plasma β-endorphin before and after the first acupuncture treatment.

In this present study we monitored the effect of acupuncture on patients with symptomatic osteoarthritis of the knee using a randomised, sham controlled, patient-blind study with blinded evaluation (by patient) and blinded statistical analysis. The success of patient blinding was assessed. The study was not designed to elicit the duration of any benefit.

This study was approved by the South Birmingham Local Research Ethics Committee and by the Research and Development Department of the University Hospital Birmingham NHS Foundation Trust.

Methods

The study followed the guidelines for osteoarthritis therapy studies,[25] and those for acupuncture trials,[16] and is reported in line with CONSORT standards.[32] Details of the study plan are given in Figure 1.

Patients, over 18 years old, who had symptomatic and radiological osteoarthritis of the knee for more than six months with an inadequate response to one or more conventional medical treatments, were recruited. They were attending a hospital rheumatology department and were not on a surgical waiting list. Exclusions included any previous acupuncture, pregnancy, other forms of arthritis and the usual contra-indications for acupuncture. Patients expressing interest at a screening visit were given verbal and written information. The volunteers continued taking their usual analgesia or non-steroidal anti-inflammatory drugs, the dose of which remained unchanged for the duration of the trial. Additional breakthrough analgesia was not used. If both knees were symptomatic then the patient chose the most painful.

The results of an earlier study using the same sham needle were used to estimate the effect size.[33] The outcome was a change in a functional score (the Constant-Murley) that showed an effect size of 0.7. Assuming the same level of effect in the change in pain scores in the two groups in the present trial, then to achieve 80% power and with a two-sided significance level of 5%, 30 patients would be required in each arm. Sixty eight were recruited to allow for possible dropouts.

Acupuncture procedure

The two groups received treatment twice weekly, on Monday and Wednesday, from baseline visit to week five. Both groups received treatment at the same acupuncture points selected for the treatment of osteoarthritis of the knee as previously published.[6;9] The sham needle was secured to the skin with a plastic ring covered by a sticking plaster. The ring
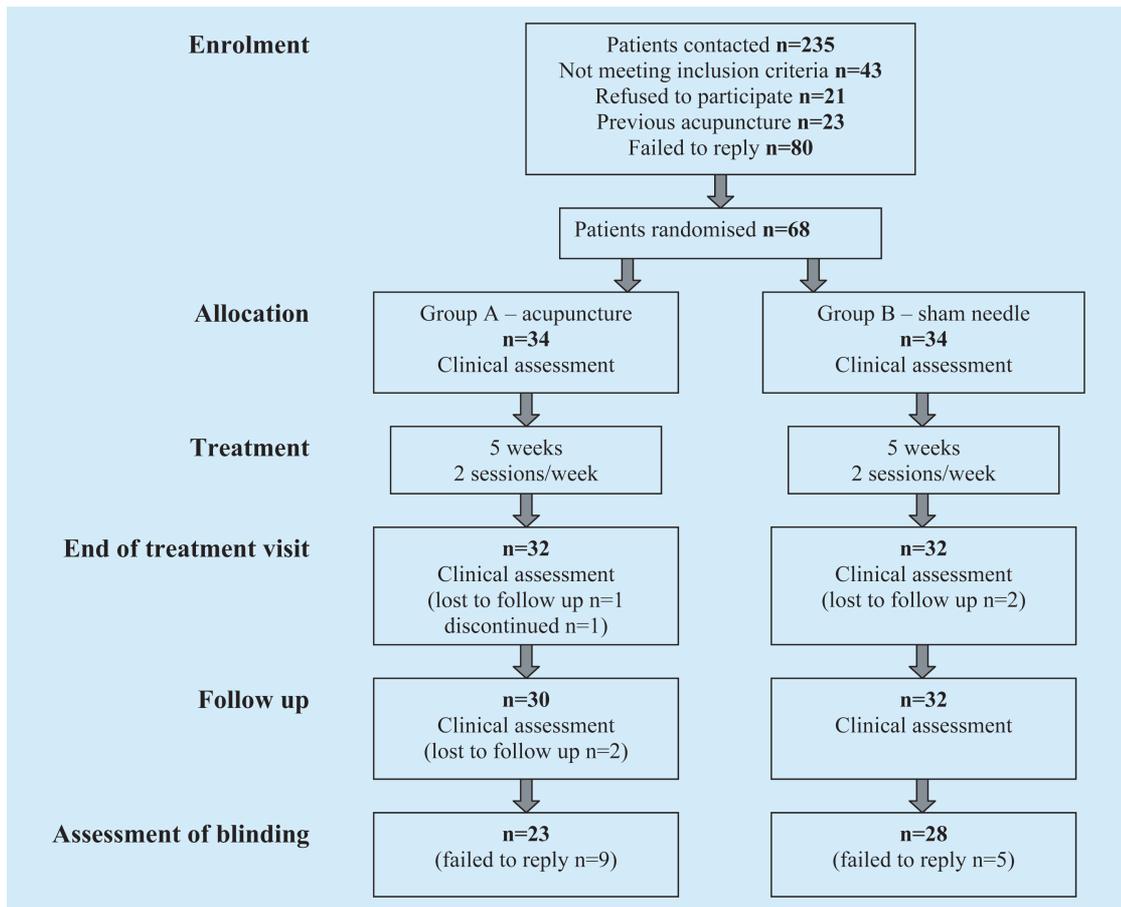
Figure 1 The flow diagram shows the number of patients at different stages of the acupuncture study.

and plaster system was also used for those having genuine acupuncture.

The patient first lay supine with a pillow under both knees for treatment of the anterior part of the knee, and then turned face down for treatment of the posterior aspect. Based on the theory for treating *Bi* syndrome, a combination of local and distal acupuncture points were used: LI 4, SP 10, *Xiyan* ('Eyes of the knee'), SP9, GB 34, ST 36, LIV 3, BL 40, and BL 57. The acupuncture needles used for treatment were 3cm, 30 gauge solid disposable filiform stainless steel. The depth of needle insertion varied with thickness of the skin and subcutaneous fatty tissues at the site of the acupuncture points; it was usually 1 to 1.5cm. Manual acupuncture treatment was given for 10 minutes with the elicitation of *de qi*.

Electrical stimulation was given to the anterior part of the knee for 10 minutes and then 10 minutes for the posterior part using a battery-operated, four-channel, 'AS Super 4' Electrostimulator (RDG Medical, Surrey UK) which generated low frequency, square-wave (2-10Hz) pulses of 1 millisecond

duration for 10 minutes.[34] In both groups, the apparatus was attached to needles at the two *Xiyan* points, SP9 and GB34, and BL40 and BL57. Electrical stimulation was delivered at 6Hz at a constant current. Voltage was set at a level just above the pain threshold. In the control group, the dummy mode of the apparatus was used, in which it produced sound signals but no electrical current. A treatment session was for a total of 30 minutes.

Assessment
Validated self assessment questionnaires were used: the WOMAC;[26] a visual analogue scale (VAS) for pain;[37] and the EuroQol.[28] The WOMAC results presented here have not been normalised and represent the total scores in each category. The questionnaires were completed at baseline, after the 10 sessions of treatment (week five) and one month after treatment (week nine).

The primary end point for the study was the change in pain after a course of 10 treatments as measured by the WOMAC pain subscale.

The acupuncturist was not blinded to the treatment. However, the treatment sessions were monitored by a research nurse to reduce the risk of unblinding the patients. Some weeks after the final assessment, the patients were contacted by letter and asked to state their treatment group by selecting one option on a pre-paid reply slip: 'acupuncture', 'placebo' or 'do not know'.

Three samples were taken for analysis of plasma β-endorphin concentration: at the screening visit, before the first treatment, and immediately after the first treatment. Blood was taken into chilled EDTA tubes, centrifuged within one hour and then immediately frozen. Samples were batched and couriered frozen to the laboratory. Plasma β-endorphin assays were performed by Covance Laboratories, Harrogate, UK using the Nichols Institute Diagnostic Radioisotopic Assay. The laboratory was blinded to the treatment group.

Statistical procedures
Patients were randomised using random permuted blocks with a block size of four.[35] *T* tests were used to compare the two treatment groups and paired *t* tests were applied to the change of score within groups. Significance was assessed at the 5% level

and no correction for multiple testing was carried out. Results are reported as mean and 95% confidence intervals (CI). The chi squared test was used for the patient's perception of treatment and the Mann-Whitney test for the EuroQol and the β-endorphin results.

Results
Sixty eight patients were enrolled during 2002 and 2003 from a single hospital rheumatology department: 284 case notes were reviewed and 235 patients contacted; 80 failed to reply, 23 had had acupuncture, 43 failed the inclusion/exclusion criteria and 21 declined to participate. The numbers available with complete data for analysis at each stage are shown in the flow chart (Figure 1).

The two groups were well matched for age, gender, BMI, and disease duration (Table 1). There was no statistical difference between the two groups at baseline apart from more weight bearing pain in the acupuncture group (borderline statistical significance, P=0.05)

Primary end point – WOMAC pain
The primary end point was the change in pain as measured by the WOMAC between baseline and the

Table 1 **Baseline data of participants in RCT of acupuncture for osteoarthritis of the knee**

	Acupuncture group	Sham acupuncture group
Number recruited (n)	34	34
Mean age, years	64.1 (1.6)	66.1 (1.9)
Gender – female (n)	29	26
Disease duration, years	10 (1.5)	9.56 (1.2)
BMI	33.2 (6.4)	30.2 (8.1)
Kellgren and Lawrence 2 (n)	16	20
Kellgren and Lawrence 3 (n)	18	12
Ethnicity (n) white	25	29
black	4	1
Asian	5	3
other	0	1
WOMAC pain	294 (78)	261 (100)
WOMAC stiffness	123 (41)	112 (46)
WOMAC function	1028 (277)	979 (313)
EuroQol - VAS	63 (22)	54 (20)
Total body pain - VAS	49 (24)	49 (26)
Night pain in knee - VAS	61 (26)	52 (28)
Overall pain in knee - VAS	63 (19)	53 (25)
Weight pain in knee - VAS	71 (19)	60 (23)

Values are mean (SD) unless otherwise stated

Table 2 **Primary end point: changes in WOMAC pain between baseline and end of treatment (week five)**

	n	Mean	SD	95% CI	Significance
Acupuncture v sham	31	60	110	5 to 116	P=0.035
Acupuncture	31	95	96	60 to 130	P=0.001
Sham	31	35	121	-10 to 80	P=0.12

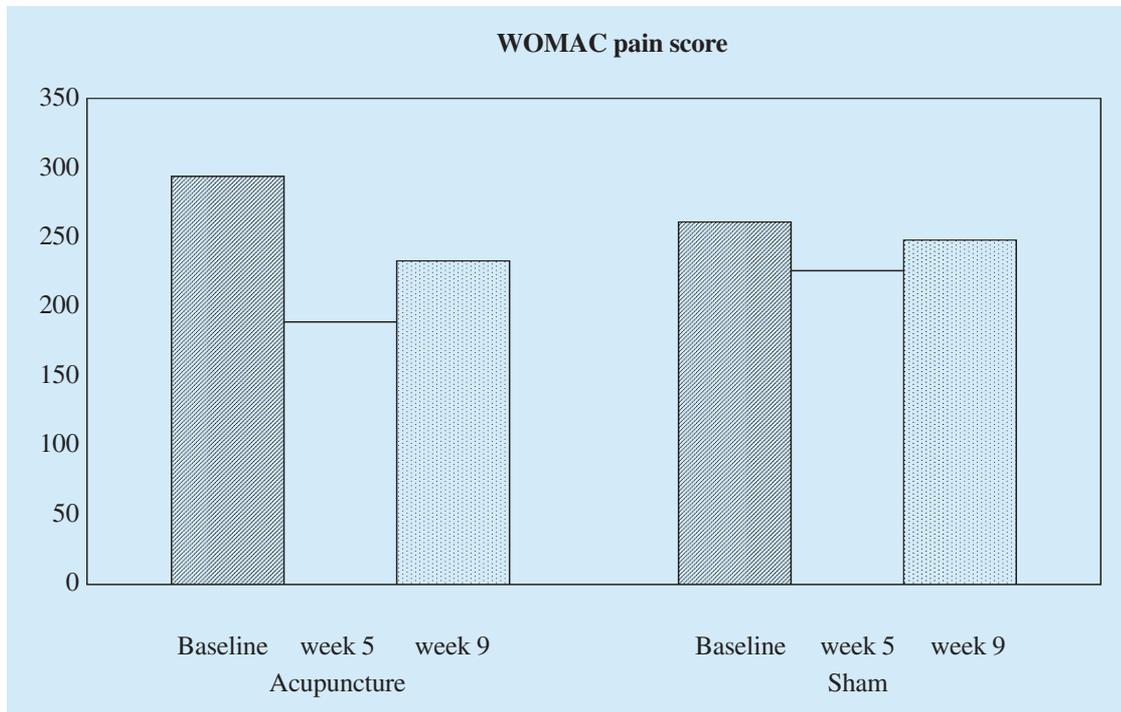Between group differences are shown in the first row, and within group changes in the subsequent rows.

Figure 2 This chart of the main outcome measure, WOMAC pain score, shows that the reduction in pain at week five was significantly greater (P=0.035) in the acupuncture group than in the sham group.

end of the course of acupuncture at week five (Table 2, Fig 2). The comparison between the acupuncture and the sham group showed a statistically significant (P=0.035) improvement in favour of the acupuncture group. Within the acupuncture group there was a highly significant improvement in the pain score (P=0.001) that was not seen with the sham group (P=0.12) (Table 2).

Secondary end points
    WOMAC pain – end of study
    Nine weeks after the treatment started there was no longer a significant difference between the groups (P=0.10) (Table 3). However the acupuncture group, on a within group analysis, still had a significant change from baseline (P=0.009). The sham group remained unchanged (P=0.44).

WOMAC stiffness and function
    There was no significant difference between the groups for WOMAC stiffness or function either at the end of treatment at week five or at the final visit at week nine (Table 3).
    However, the acupuncture group showed significant improvement from baseline in WOMAC stiffness and function at both week five and week nine (Table 3). In the sham group, there was a borderline significant change for WOMAC function at week nine (P=0.04) that was not seen at week five, and there was no change in stiffness (Table 3).

Visual analogue scale for pain
    In addition to the WOMAC, four aspects of pain were assessed by VAS. These covered 'night pain in the study knee', 'weight bearing pain in the study

Table 3 **Secondary endpoints: changes in WOMAC scores from baseline to week five and to week nine**

	Acupuncture v sham			Acupuncture			Sham		
	mean	95% CI	sig	mean	95% CI	sig	mean	95% CI	sig
WOMAC stiffness week 5	15	-8 to 39	NS	32	15 to 50	P=0.001	17	-0.2 to 35	NS
WOMAC function week 5	140	-30 to 311	NS	250	140 to 362	P=0.001	110	-29 to 249	NS
WOMAC pain week 9	46	-9 to 100	NS	59	16 to 102	P=0.009	13	-22 to 50	NS
WOMAC stiffness week 9	10	-13 to 34	NS	23	6 to 42	P=0.01	13	-2 to 29	NS
WOMAC function week 9	4	-163 to 171	NS	137	20 to 255	P=0.02	134	9 to 258	P=0.04

Between group differences are shown in the first columns, and within group changes in the subsequent columns.
sig – significance; NS – not significant.

Table 4 **Changes in VAS pain scores between baseline and weeks 5 and 9**

	Acupuncture v sham			Acupuncture			Sham		
	mean	95%	sig	mean	95%	sig	mean	95%	sig
Weight bearing pain in study knee week 5	20	7 to 33	P=0.003	32	23 to 41	P=0.001	11	1 to 21	P=0.025
Overall pain in study knee week 5	21	8 to 34	P=0.001	29	21 to 38	P=0.001	8	-2 to 18	NS
Night pain in study knee week 5	13	-1 to 27	NS	22	12 to 32	P=0.001	9	-1 to 19	NS
General body pain week 5	7	-7 to 22	NS	6	-3 to 15	NS	-1	-10 to 12	NS
Weight bearing pain in study knee week 9	11	-2 to 25	NS	19	9 to 30	P=0.001	8	-1 to 16	NS
Overall pain in study knee week 9	12	-1 to 24	NS	14	5 to 24	P=0.005	2	-6 to 10	NS
Night pain in study knee week 9	5	-9 to 19	NS	10	-1 to 22	NS	5	-3 to 14	NS
General body pain week 9	13	0 to 27	P=0.048	5	-5 to 15	NS	-8	-1 to 18	NS

Between group differences are shown in the first columns, and within group changes in the subsequent columns.
sig – significance; NS – not significant

knee', 'overall pain in the study knee' and 'general body pain'.

Between group analysis gave a highly significant difference for both weight bearing pain (P=0.003) and overall pain in the study knee at week five (P=0.001) (Table 4, Fig 3). This benefit was lost by week nine. There was a borderline difference in general body pain at week nine (P=0.048) that was not seen at week five. This may be due to deterioration in the sham group rather than change in the acupuncture group.

Apart from the general body pain, the acupuncture group showed a significant improvement over baseline at week five for weight bearing pain

(P=0.001), overall pain (P=0.001) and night pain in the study knee (P=0.001). This was maintained to week nine for weight bearing pain (P=0.001) and overall pain (P=0.005), but not for night pain (Table 4). At week five, the sham group only had a significant change from baseline in weight bearing pain (P=0.025) and no changes from baseline at week nine (Table 4).

EuroQol

The EuroQol is a generic measure of health related quality of life. When the differences between treatments were compared using the Mann-Whitney test, there was no significant difference at any of the
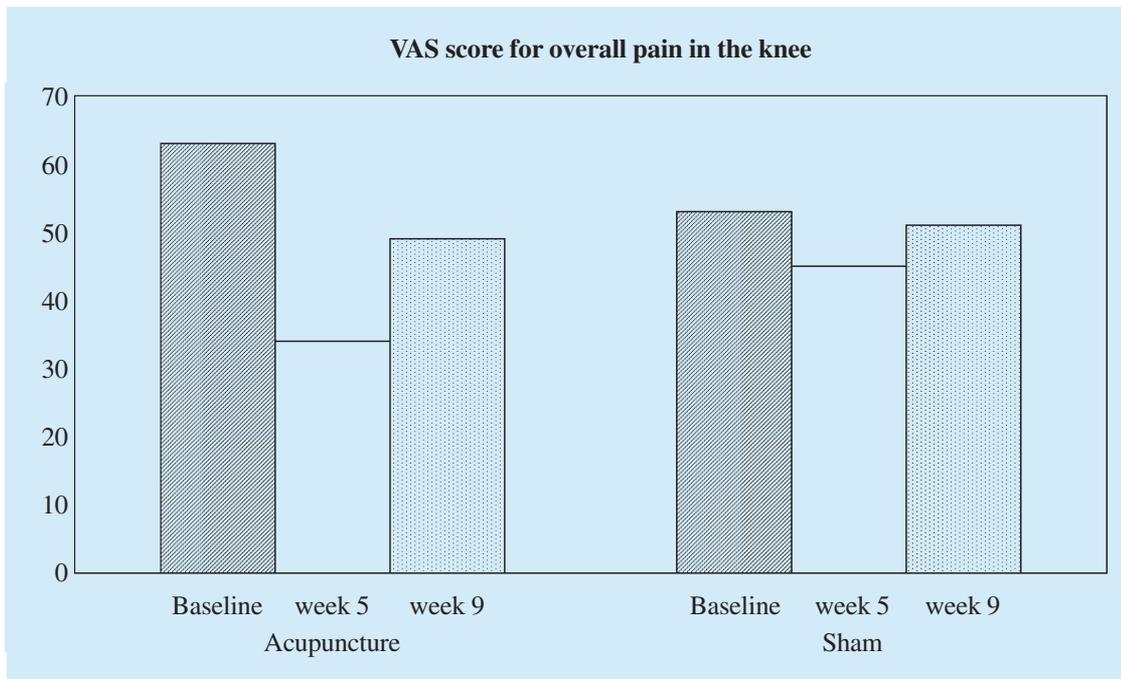
VAS score for overall pain in the knee

Figure 3 This chart of VAS score for overall pain in knee shows that the reduction in pain at week five was significantly greater (P=0.001) in the acupuncture group than in the sham group.

three time points. Baseline scores were: acupuncture mean 63, SD 21, sham mean 54, SD 20, P=0.72; end of treatment scores were acupuncture mean 68, SD 23, sham mean 59, SD 22, P=0.80; and final visit scores were: acupuncture mean 63, SD 24, sham mean 52, SD 26, P=0.98.

Patient's perception of treatment group
As the primary end point of the study was a self assessment questionnaire by the patients, it was essential that they remain blinded to their treatment. The patients gave an opinion of their treatment group, by post, after the study had been completed. Seventy one percent of the acupuncture group and 82% of the sham group replied. Of the replies, only nine of the acupuncture group (41%) and 12 of the sham group (44%) correctly chose their treatment allocation. These were not significantly different (chi squared test, P=0.39). Twenty three percent of those having acupuncture and 15% of the sham group wrongly chose their treatment allocation. Thirty six percent of the acupuncture group and 41% of the sham group were unable to decide.

β-endorphin concentrations
Three patients in the sham group had consistently high levels of β-endorphin (52, 54, and 120pg/ml).

All the rest of the patients in both groups had levels less than 50pg/ml with most below 30pg/ml. Plasma β-endorphin levels did not vary significantly during the study. Between group analysis at the three time points gave no significant difference using the Mann-Whitney test (at baseline, P=0.31; week five, P=0.06; and at week nine, P=0.31).

Adverse events and withdrawals
Four patients withdrew during the study but only one was related to treatment. Ten adverse events were reported during the study; four in the acupuncture group and six in the sham group. One patient had a flare of synovitis of the study knee and withdrew; the synovitis was not septic.

Discussion
The present study found that patients receiving acupuncture observed a significantly greater relief of pain at the end of treatment than those who received sham acupuncture. These results support earlier research demonstrating that acupuncture can alleviate the pain and disability of osteoarthritis of the knee.[4;5;9;12;23;36–39]

The trial was designed to study the short term effect of skin penetration in acupuncture therapy and not the duration of any effect. Although other research

has indicated that benefit may last up to six months,[38] in this study, only a within group analysis showed statistically significant benefit a month after the acupuncture treatment; the statistically significant difference between the groups had been lost. A larger sample size might have given a difference but the sample size was calculated to minimise the number of volunteers required to assess the primary end point. In clinical practice patients are often given 'top up' acupuncture sessions to maintain the clinical benefit. Our study did not examine this strategy.

Statistically significant improvement within the acupuncture group was seen in almost all the parameters measured and mostly the benefit was still present after four weeks. The non-penetrating needle group showed benefit in only two of the outcome measures: weight bearing pain at the end of treatment and WOMAC function at the final visit.

It has been suggested that acupuncture does not produce a clinically relevant benefit.[40] A minimal clinically important improvement (MCII) has been established for the change in 100mm VAS score in osteoarthritis of the knee:[41] Either a 19.9mm absolute change or a 40.8% relative improvement in pain are said to be clinically relevant. In our study the VAS change for pain in the study knee after acupuncture was 29mm, a 46% relative improvement, while in the sham group it was only 8mm, or a 15% relative improvement. Hence, those having acupuncture did derive a clinically meaningful improvement at the end of their course of treatment.

As the primary end point was a self assessment questionnaire, the success of patient blinding was critical. There remains the possibility that the acupuncturist unwittingly unblinded the patients. The acupuncture sessions were monitored by a research nurse for evidence of possible unblinding during the treatment sessions; no violations were seen. The postal survey after the study demonstrates that patients were unsure of their treatment as only a minority of patients correctly identified their group. This supports earlier work confirming that the 'placebo' needle system is credible, and achieves patient blinding.[20;21] The higher success rate in the sham group may reflect their lack of clinical improvement,[42] although there was no significant difference between the two groups.

As well as the lack of skin penetration of the sham needle, the control group also did not receive active electroacupuncture. It is possible that the observed response in the acupuncture group reflects the electrical stimulus rather than the penetration of the needle. Addressing this question would require further research.

In our study, any acupressure over the acupuncture points in the sham group was not sufficient to produce an analgesic effect. This suggests that skin penetration is required to elicit the effect. Recent studies by Witt *et al* and Vas *et al* support this concept.[23;37] A study by Scharf *et al* found that needling at defined non-acupuncture points produced a similar success rate to traditional Chinese acupuncture.[38]

Release of natural opioids has long been a popular explanation for the analgesic effect of acupuncture, with reports of significant elevation of plasma β-endorphin after treatment.[30;31] An independent laboratory was used to measure the β-endorphin in this study, and no changes were seen between the concentrations measured at the screening visit, baseline and immediately after the first treatment. However, the study does not exclude a role for humeral endorphins as elevated levels have been reported in cerebrospinal fluid after electroacupuncture.[43]

A positron emission tomography (PET) study has shown activation of the insula, ipsilateral to the site of needling, during acupuncture that was not seen with the sheathed sham needle.[22] The mechanism of this physiological effect remains unclear.

Only a small number of patients was required for this study, and there were no adverse events directly attributable to acupuncture. One patient in the acupuncture group withdrew after a flare of synovitis in the affected knee. There was no evidence of sepsis.

The present study confirms the beneficial effect of acupuncture for treating the symptoms of osteoarthritis of the knee and suggests that skin penetration of the needle is required. We were unable to confirm the earlier reports of a release of endorphin into the plasma during acupuncture treatment.

their support during the study and the opportunity for some of their patients to enrol.

Conflict of interest

No conflict of interest has been declared by the authors.

Summary box

Acupuncture (manual and electroacupuncture) and non-penetrating sham acupuncture were compared as treatments for the pain of osteoarthritis of the knee in this RCT

Acupuncture caused a significantly superior reduction of pain at the end of treatment

No changes in plasma β-endorphin concentrations were seen after EA

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