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The effect of acupuncture on patients with rheumatoid arthritis: a randomized, placebo-controlled cross-over study

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Abstract

Objective. Acupuncture is commonly used by patients with chronic painful musculoskeletal disorders. There are, however, few well-designed studies of its efficacy. This paper describes a randomized placebo-controlled cross-over design to evaluate acupuncture as a useful treatment adjunct in the management of patients with rheumatoid arthritis (RA).

Methods. Sixty-four patients were centrally randomized from a hospital-based rheumatology out-patient clinic. Fifty-six patients were suitable for study, all were on second-line therapy and aged 18–75 yr. There had been no change in therapy for the preceding 3 months. Patients who had previous acupuncture, anticoagulation, fear of needles or infection were excluded. Single-point (Liver 3) acupuncture or placebo was given with an intervening 6 week wash-out period. The acupuncturist, patient and statistician were blinded as far as possible. The outcome measures included the inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), visual analogue scale of pain, global patient assessment, 28 swollen and tender joint count, and a general health questionnaire.

Results. The results demonstrated no significant effect of treatment or period and no significant interaction between treatment and period for any outcome variable. No adverse effects were reported.

Conclusion. Acupuncture of this type cannot be considered as a useful adjunct to therapy in patients with RA. Possible reasons why this is the case are discussed.

KEY WORDS: Acupuncture, Rheumatoid arthritis, Treatment.

Patients with rheumatoid arthritis (RA) receive many medically prescribed drugs and often require extensive hospital and surgical treatment. However, patients frequently self-prescribe, and complementary therapies such as acupuncture and homeopathy are widely used [1]. These therapies may be expensive and their therapeutic efficacy is largely unproven, but they do have considerable impact upon the patient's perception of their disease. Furthermore, use of these therapies affects the patients' attitude to conventional medical therapy and compliance therewith.

In recent years, there has been increasing research which attempts to reinterpret traditional acupuncture within the framework of Western scientific medicine. Currently, it is thought that acupuncture modulates pain transmission and the pain response by activation of the endogenous nociceptive system. Endorphins, encephalins and various neuropeptides have all been shown to be released on needle insertion. Human and animal studies have demonstrated that the effect of acupuncture analgesia is reversible by naloxone [2]. Endogenous opioid peptides may, therefore, form a key role in the analgesic effects of acupuncture. Randomized controlled trials provide some evidence for the efficacy of acupuncture. Christensen *et al.* [3] and Berman *et al.* [4] have shown that acupuncture is significantly better than control for osteoarthritis of the knee. Acupuncture is as effective as intra-articular steroid in osteoarthritis of the hip [5]. The best evidence is provided by systemic reviews. One such review [6] found insufficient studies of good quality to draw conclusions, but a meta-analysis of acupuncture for head and neck pain showed a positive trend using placebo-controlled studies [7]. In other non-inflammatory pain disorders, acupuncture appears to be beneficial [8]. In contrast, the evidence for acupuncture efficacy in inflammatory disease is lacking.

Finding a suitable placebo for use in clinical acupuncture research is most difficult [9]. Placebo or sham procedures previously used include needling acupoints superficially with or without manipulation, or needling points known not to be acupoints. Such procedures may themselves be effective, acting as 'counter-irritant'. Further, blinding is difficult to achieve [10].

The present study employs a randomized, prospective,

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placebo-controlled cross-over technique to evaluate the effect of single-point acupuncture *vs* sham acupuncture as a treatment adjunct in RA. The technique of sham acupuncture that we have used is that described by Lao *et al.* [11] and Moore *et al.* [12], and later adapted by White *et al.* [13]. Liver 3 (Li3) was the acupoint used. Stimulation of this point is thought to produce generalized effects by its influence on the functioning of the nervous, endocrine and immune systems. Needling at this point is safe, reproducible and causes little discomfort. It is a convenient point to choose in order to assess whether the cross-over trial is feasible in acupuncture research methodology. Single-point acupuncture (Li3) has been used effectively in previous studies of hay fever and headache [14, 15]. It has not been used in RA before.

Methods

Ethical approval for the study was obtained from the Berkshire Ethics Committee.

All patients had definite or classical RA [16] and were treated with analgesia, including non-steroidals, anti-inflammatory drugs and second-line agents such as gold, penicillamine, salazopyrin or methotrexate. The patients were sequentially recruited, regardless of disease activity and current level of pain, from routine rheumatology out-patient department attenders if they fulfilled the inclusion criteria. Patients had to be 18–75 yr old, receiving a second-line agent and have had no change in their therapy in the preceding 3 months, including no intra-articular injections or pulse steroid therapy. Patients were excluded if they had had previous acupuncture, were anticoagulated, had localized skin infection, were receiving other complementary therapy or had a fear of needles.

Randomization

After giving informed consent, patients were allocated a number. This number was then given to a central office and the treatment sequence, either A or B, was allocated according to standard randomization tables. This allocation was made by the department secretary, who had no other role in the study. A letter to the patient's primary care physician was sent, informing them of the study.

Assessments

Five assessments were made, as follows:

A: Week 1 (first baseline)
B: Week 6 (end of the first treatment)
C: Week 12 (second baseline)
D: Week 17 (end of the second treatment)
E: Week 22 (6 weeks after the end of the second treatment)

The assessments included the following: measurement of inflammatory markers [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)]; visual analogue scale of pain (VAS P); visual analogue scale of patient's global assessment (VAS G); 28 swollen joint count; 28 tender joint count; number of analgesic tablets taken daily; General Health Questionnaire—28 (GHQ) (GHQ A: anxiety; B: somatic symptoms; C: socialization; D: depression) [17]; Modified DAS index [this Disease Activity Score (DAS) is a combined index to assess activity in RA [18]. It is calculated using four of the above variables according to the formula below. The DAS can be used to compare groups of patients, but also to determine the response of a single patient. A change of 1.08 is significant.] $\text{Mod.DAS} = 0.555\sqrt{28}$ tender joints $+ 0.284\sqrt{28}$ swollen joints $+ 0.7$ In (ESR) + 0.0142 (patient's global assessment VAS).

Treatment sequence

After randomization, each patient received five treatments of either acupuncture (Sequence A) or placebo (Sequence B) at weekly intervals. This was followed by a wash-out period of 6 weeks, after which each patient received the other therapy. Five treatments were deemed reasonable in order to demonstrate a therapeutic effect. Experience of the authors has shown that if some effect is not present after the fifth treatment, then it is unlikely to occur—even in systemic disease such as RA.

Blinding

All assessments were performed by a single observer, who did not know which treatment sequence the patient was receiving or the randomization. All records of treatment and documentation of adverse effects were kept separately from the assessment record. The statistician was kept blinded until the analysis was complete.

Acupuncture treatment

Liver 3 was the acupuncture point used bilaterally; it is located between the first and second metatarsal bones in the first dorsal interosseous space of the foot, 4 cm proximal to the web margin.

Explanation of the acupuncture technique was given to all subjects; 0.25 × 30 sterile disposable needles were used. The patient was treated supine. The needles were left *in situ* for 4 min and manipulated manually at 2 min for 5 s. Electro-acupuncture and moxibustion were not used.

The placebo treatment took the same form as above. The needle introducer was held without pressure on Li3 and no skin puncture for 4 min. In both the placebo and real acupuncture groups, the subject's lower limbs were shielded by a screen so that the feet were out of the patient's vision. There was minimal conversation between patient and acupuncturist.

Statistical analysis

As the majority of variables were not normally distributed, non-parametric methods of analysis were used and the groups have been summarized using medians and 95% confidence intervals for medians. The methods of analysis of a cross-over trial described by Hills and Armitage [19] were used to assess the effects of treatment, period and the treatment/period interaction. Patients in treatment Sequence A received acupuncture in period B and placebo in period D. Patients in

TABLE 1. Baseline characteristics of the patients

	Sequence A ($n = 29$)		Sequence B ($n = 27$)	
Variable	Median	IQR	Median	IQR
Age (yr)	61	53–66	57	46–66
Duration of RA (yr)	8	5–15	12	8–20

IQR, interquartile range.

treatment Sequence B received placebo in period B and acupuncture in period D. The effect of treatment was assessed using a Mann–Whitney *U*-test to compare half the difference between period B and period D in patients on Sequence A with half the difference between periods D and B in Sequence B. The effect of period was assessed by comparing half the difference between periods B and D on Sequence A with half the difference between periods B and D on Sequence B. The treatment/period interaction was assessed by comparing the sum of the two treatment periods in Sequence A and B. The baseline characteristics (period A) of the two sequence groups were compared using Mann–Whitney *U*-tests or Fisher's exact tests. The changes from the first to the second baseline period (A and C) in the two sequence groups were compared using Mann–Whitney *U*-tests.

Results

Sixty-four patients were randomized; eight failed to attend the first assessment. The remaining 56 subjects attended all assessments and were analysed. No patient withdrew from the study.

The baseline characteristics of the two sequence groups (median and interquartile range) are shown in Table 1. There is a significant chance difference in the duration of RA ($P = 0.04$) between the two sequence groups. There is no significant difference in their mean age or previous and current drug use (Fisher's exact test).

Thirteen outcome variables were evaluated. Table 2 summarizes the baseline assessment. The only significant difference between the two sequence groups is for the GHQB anxiety.

The two baseline periods A and C were compared. The changes in baseline characteristics (C – A) from assessment A to C in the two sequence groups are seen in Table 3, which contains the median change and 95% confidence interval from the median change in each sequence group, the estimated difference in median changes and its 95% confidence interval, and the *P* value from the Mann–Whitney *U*-test. There is no significant difference between the two sequence groups in the change from the first to the second baseline assessments. In addition, within each sequence group, all the confidence intervals for the change from the first to the second baseline assessment include zero, so there is no evidence of a time trend during the course of the study.

In comparing treatment periods B and D, the non-parametric methods of analysis of a cross-over trial [19] were used to assess the effects of treatment, period and interaction. The results are seen in Table 4, which contains the estimated median difference between the two treatments (active minus placebo) and its 95% confidence interval, the estimated median difference between the two treatment periods (B minus D) and its 95% confidence interval, and the estimated median interaction (treatment difference in period B minus treatment difference in period D) and its 95% confidence interval. Again, there is no significant effect of treatment or period, and no significant interaction between treatment and period for any outcome variable. No adverse effects were reported with either acupuncture or placebo acupuncture.

Comment

This trial shows no significant difference between acupuncture and placebo acupuncture treatment in patients with RA. Despite claims in both the Orient and the West that acupuncture may be beneficial in RA, there have been no satisfactory double-blind controlled stud-

TABLE 2. Baseline assessment

	Sequence A		Sequence B		Difference A − B		
Variable	Median	95% CI	Median	95% CI	Median	95% CI	*P*
CRP	10	5–27	7	5–26	0	−8 to 5	0.7
ESR	25	11–29	22	12–37	−3	−12 to 7	0.5
VAS pain	48	34–54	51	37–62	−4	−17 to 11	0.5
VAS GH	34	28–39	46	29–58	−9	−21 to 3	0.14
Swollen JC	2	1–6	3	2–4	0	−1 to 2	0.8
Tender JC	6	2–10	8	6–10	−2	−5 to 2	0.3
GHQ A	2	1–3	1	0–3	0	0–1	0.3
GHQ B	1	0–2	0	0–1	1	0–1	0.02
GHQ C	1	0–3	1	0–2	0	−1 to 1	0.9
GHQ D	0	0–0	0	0–0	0	0–0	0.9
GHQ Total	5	3–6	1	1–7	1	−1 to 4	0.4
DAS	5.0	3.8–6	5.3	4.7–6	−0.4	−1.3 to 0.6	0.4
Analgesics	1	0–2	2	0–4	0	−2 to 0	0.7

JC, joint count.

TABLE 3. Change in baseline characteristics from assessment A to C

	Sequence A		Sequence B		Difference A − B		
Variable	Median	95% CI	Median	95% CI	Median	95% CI	*P*
CRP	0	−2.5 to 0	0	−0.5 to 3.7	−1.5	−8 to 0.2	0.2
ESR	−1.5	−6 to 2.3	−3	−8 to 1.2	1	−6 to 6	0.8
VAS pain	−4	−15 to 11	0	−11 to 5	2	13 to 17	0.8
VAS GH	0	−9 to 14	−2	−16 to 6	10	−4 to 22	0.16
Swollen JC	0	1 to 1	0	−1.3 to 1	0	−1 to 2	0.7
Tender JC	−0.5	−3 to 1.5	−1	−3 to 0.3	0	−3 to 3	0.8
GHQ A	0	−1.5 to 0.5	0	−1 to 0	0	−1 to 1	0.9
GHQ B	0	−1 to 0	0	0–0	0	−1 to 0	0.09
GHQ C	0	−1 to 0	0	−1 to 0	0	−1 to 1	0.9
GHQ D	0	0–0	0	0–0	0	0–0	0.3
GHQ Total	−1	−5 to 0	0	−1.3 to 0	−1	−4 to 1	0.4
DAS	−0.2	−0.5 to 0.4	−0.4	−1 to 0.2	0.2	−0.5 to 0.9	0.6
Analgesics	0	−0.5 to 0	0	0–0	0	−1 to 0	0.2

JC, joint count.

TABLE 4. Comparison of treatment periods B and D to assess treatment, period and interaction

	Interaction			Treatment			Period		
Variable	Effect	95% CI	*P*	Effect	95% CI	*P*	Effect	95% CI	*P*
CRP	0	−21 to 5	0.9	0.5	−1 to 3	0.6	−0.3	−2.2 to 1	0.8
ESR	−1	−14 to 15	0.8	1	−1 to 4.5	0.2	−2	−4.5 to 1	0.08
VAS pain	13	−6 to 35	0.14	−3.5	−9.5 to 2	0.3	−1.5	−7 to 4	0.4
VAS GH	−6	−26 to 15	0.4	1	−6 to 9	0.7	1.5	−6 to 8.5	0.7
Swollen JC	1	−2 to 3	0.7	−0.5	−1 to 0	0.3	0.5	−0.5 to 1	0.2
Tender JC	0	−7 to 6	0.9	0.5	−1 to 1.5	0.6	−0.5	−2 to 0.5	0.3
GHQ A	0	−1 to 2	0.5	0	−0.5 to 0.5	0.7	0	−1 to 0	0.3
GHQ B	0	0–1	0.2	0	0–0.5	0.3	0	0–0	0.9
GHQ B	0	0–0	0.9	0	0–0	0.3	0	0–0	0.6
GHQ D	0	0–0	0.4	0	0–0	0.4	0	0–0	0.5
GHQ Total	0	−1 to 4	0.7	0	−0.5 to 1.5	0.8	0	−1 to 0.5	0.9
DAS	0.3	−1.6 to 1.9	0.8	0	−0.4 to 0.4	0.9	−0.1	−0.4 to 0.3	0.7
Analgesics	0	0–2	0.4	0	−0.5 to 0	0.7	0	0–0	0.9

JC, joint count.

ies. Analysis of the published studies demonstrates methodological flaws which largely invalidate the claims of success. Major problems related to the formulation of trials of acupuncture in RA include the definition of real and placebo acupuncture, selection of sample population, elimination of bias, randomization, assessment requirements and study design.

Many different definitions for placebo acupuncture have been used in previous trials of RA. Shen *et al.* [20] defined placebo acupuncture as the insertion of needles adjacent to traditional points without manipulation. Man and Baragar [21] selected points with no known effects and stimulated them. Man and Chen [22] inserted needles far away from the painful area without stimulation. Lee *et al.* [23] described placebo as electrostimulation of distant arbitrary points, Camberlain *et al.* [24] used the superficial insertion of needles into non-classical points not coinciding with nerve trunks using either manual or electrical stimulation and without the elicitation of the Tei-Chi.

Elimination of bias on the part of the subject and investigator is important in the evaluation. The term 'double blind' means that both the patient and the physician—evaluator—are unaware of the treatment given. Because the acupuncturist administering the real or sham treatment cannot be blind, the potential for bias can be minimized, as it was in our study, if the acupuncturist has the least possible communication with the patient and the evaluation is performed by an independent party. The patients had no history of acupuncture treatment and were unfamiliar with the procedure. The patients were asked in the final assessment if they were able to differentiate between the real and sham treatments; 48% claimed to be able to, which would be expected by chance.

Bhatt-Sanders reviewed the literature on acupuncture in RA [25]. Two of the seven studies assessed found that there was no statistical difference between real and placebo acupuncture in rheumatoid patients. Of the others, Lee *et al.* [23] found that >50% of patients reported at least a 75% reduction in pain after four treatments. Only 20% continued to have this degree of pain reduction 4 weeks post-treatment. Camberlain *et al.* [24] found that there was no significant difference between real and placebo acupuncture when evaluated in terms of a number of parameters, which included walking time, swelling, range of motion, tenderness, pain, ESR, rheumatoid factor and X-rays. Neither treat-

ment was helpful. A further review [26] examined 17 studies with regard to efficacy and scientific quality of acupuncture in rheumatic inflammatory diseases including RA, spondyloarthropathy, lupus erythematosus and scleroderma. Acupuncture was not recommended for the treatment of these diseases.

The important point of our study is that it is a study in the methodology of acupuncture research and thus confined by a clear-cut regimen. There are no other randomized, placebo-controlled and cross-over studies of acupuncture. Our study did not show any significant clinical benefit to either the sham or the acupuncture treatment and there may be a number of reasons for this.

Our patients had established erosive rheumatoid disease and may be less responsive to the acupuncture effect than those with early pre-erosive, more inflammatory disease. The acupoint Li3 may be an incorrect or inadequate point on its own to use in order to show an effect in RA. This point, however, is considered capable of inducing a significant endogenous, endorphin and encephalin response [27]. There is a precedent for its usefulness with headache, albeit that headache is 'non-inflammatory' [14]. The outcome measures used may not be sensitive enough or appropriate to reflect outcome in complementary therapy studies. Quality of life and subjective positive response are often difficult to quantify. A traditional Chinese acupuncture approach may have involved an increased frequency of treatment, e.g. twice a week, left the needles *in situ* for a longer period or used more than a single point (Li3) for treatment. However, an observation that does need to be addressed is the lack of response to acupuncture; indeed, in RA, acupuncture has little or no effect. This contrasts with the effect of acupuncture (as well as sham acupuncture) seen in osteoarthrosis. Ernst [28], in a systemic review of acupuncture as a symptomatic treatment of osteoarthrosis, found that both acupuncture and sham needling were effective at alleviating pain in axial and peripheral joint osteoarthrosis. Both alleviate symptoms to roughly the same degree. The mechanism of pain production in RA is different from that of mechanical and degenerative disease. It is driven by pro-inflammatory cytokines and these, together with the other complex factors of immune dysfunction in RA, may not be susceptible to acupuncture-stimulated endorphin/encephalin manipulation.

When new data delineating further mechanisms of acupuncture become known, it may be better understood why acupuncture seems to have a more beneficial effect in degenerative joint disease and pain than in inflammatory joint disease. One must conclude that acupuncture, of the sort described in this paper, cannot be considered a useful adjunct to therapy in RA.

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