A Meta-Analysis of Acupuncture for Chronic Pain

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Results of 14 randomized controlled trials of acupuncture for chronic pain were pooled in a meta-analysis and analysed in three subgroups according to site of pain; and in two subgroups each according to type to trial, type of treatment, type of control, 'blindness' of participating agents, trial size, and type of journal in which results were published. While few individual trials had statistically significant results, pooled results of many subgroups attained statistical significance in favour of acupuncture. Various potential sources of bias, including problems with blindness, precluded a conclusive finding although most results apparently favoured acupuncture.

While acupuncture is increasingly used by the general public and treatment costs are often reimbursed by health insurance companies, its clinical efficacy remains scientifically unproven.[1,2] This study was undertaken to investigate the hypothesis that the individually inconclusive trials performed to date might, when their results were pooled in a meta-analysis (MA), yield a more definitive result.

MATERIAL

This MA is based on results of all trials of acupuncture for treatment of chronic pain, published in English, listed in Index Medicus from 1970 onwards that were randomized controlled trials (RCTs) of chronic pain that measured outcome in terms of number of patients whose condition improved. The World Health Organization's collection of (English language) Chinese, traditional, and alternative medical journals and literature yielded additional trials. References were obtained from previous reviews[3,4] and from Catherine Hill's, as yet unpublished, excellent and comprehensive bibliography.

Trials were discarded if they were uncontrolled,[5-10] not randomized[11-13] or did not measure results in terms of numbers of patients improved and provide the number of patients randomized.[14-16] A complete list of excluded trials is not presented.

Published study plans of the selected RCTs are summarized in Table 1. Few published baseline data after

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randomization.[17] Additional technical,[18] methodological[19] and paradigmatic[20] problems in evaluation of alternative medicine have been reviewed elsewhere.

Formula acupuncture (FA) uses a set of fixed points repeatedly. Classical acupuncturists (CA) traditionally vary points used from patient to patient, and from treatment to treatment. Most trials achieved 'Teh Chi' or a 'needling' feeling, ie numbness in the area of the needle, proof that a point has been located correctly.

The 'control' was sometimes a continuation of medical treatment. Although these RCTs focused on chronic rather than acute pain, thus reducing the probability of remission, use of continued conventional treatment controls is still unsatisfactory. Transcutaneous neural stimulation (TNS) was often used, sometimes on acupuncture points. Treatment of chronic pain with medical placebo (sugar pills) was not performed. Placebos most frequently used included placebo acupuncture and mock TNS. Clearly, blindness of patients was possible only when placebo acupuncture was used. Relative costs were not mentioned in any trial.

METHOD

'Meta-analysis'[21,22] is a set of methodological techniques used to define accumulated knowledge by pooling results of studies.[23] Methods used differ according to homogeneity of study outcome. RCTs selected were tested for homogeneity using the 'Q' statistic.[24] The overall pooled risk difference and its 95% confidence interval (CI) between acupuncture and control groups was evaluated on the basis of a 'random effects' model, necessary as a result of the lack of underlying homog-

TABLE 1 *Acupuncture studies*

Study number	First author and year	Site of pain	Treatment group		Number in groups		Number pats. better		Test of significance	Retest on rates	Blindness
			Experimental	Control	Exper.	Control	Exper.	Control			
Low back pain											
1	Coan 1980	Low back pain	CA, EA	Delayed acupuncture	25	25	19	5	No	**	None
2	Laitinen 1976	Low back pain	FA	TNS on acupuncture pts	50	50	29	23	NS	NS	Patients
3	Edelist 1976	Low back pain	EFA	Placebo acupuncture	15	15	6	5	No	NS	Patients + evaluators
4	Fox 1976	Low back pain	FA	TNS on acupuncture pts	12	cross over	8	6	NS	NS	None
5	Mendelson 1983	Low back pain	CA	Lidocaine injection + placebo acupuncture	95	cross over	26	22	NS	NS	Patients + evaluators
Head and neck											
6	Hansen 1983	Chronic facial pain	CA	Placebo acupuncture	20	cross over	12	9	*	NS	Patients
7	Coan 1982	Neck pain	CA, ECA	Medical (continued)	15	15	12	2	No	**	None
8	Loh 1984	Headache	CA, EA	Medical (continued)	55	cross over	24	9	No	**	None
9	Dowson 1986	Headache	FA	Placebo TNS	25	23	8	6	NS	NS	Evaluators
10	Petrie 1983	Cervical pain	FA	Mock TNS	7	6	7	2	**	*	None
11	Loy 1983	Cervical spondylosis	ECA	Physiotherapy	26	27	6	3	No	NS	None
Other											
12	Berry 1980	Shoulder-cuff lesions	FA	Placebo	12	12	5	9	NS	NS	Assessor
13	Ghia 1976	Pain below the waist	EFA	Tender spots on neck	19	19	8	9	NS	NS	Patients
14	Godfrey 1978	Musculoskeletal pain	FA	Inappropriate acupuncture	88	84	53	45	NS	NS	Triple blind

Note: Studies numbered as in Figure 1. Crossover studies summed over treatment order.

Legend: CA   = acupuncture point selection varied according to the needs of the patient.
    FA   = formula acupuncture, a standard set or sets of points applied to all patients.
    ECA or EFA = acupuncture or formula acupuncture in conjunction with electrical stimulation of the needles.
    TNS = transcutaneous neural stimulation.
    = $p < 0.05$. ** = $p < 0.01$. NS = no significant difference.

eneity of the studies. Cochran's semi-weighted estimator for the risk difference was used.[24] The results of two additional indicators, the logarithm of the odds ratio, and the logarithm of one minus $(1-)$ the relative difference, were also examined.[25]

Complete information on crossover studies was unavailable in published trial reports, and these were treated as two independent samples summed over treatment order. If there is agreement between treatments, this procedure simply loses power.[25] In order to be certain that confusion was not generated by procedural differences between crossover and standard randomized trials, these were also analysed as two separate subgroups for each pain site.

For detailed evaluation, trials were classified (Table 2) into one of three subgroups according to the general anatomical site of pain (lower back, head and neck, and other sites) and into one of two subgroups according the nature of the control (placebo or treatment). Classical acupuncture was distinguished from formula acupuncture. Trials in which any agents (patients, therapists, or evaluators) were blind were identified. Large trials, 50 patients or more, were identified. Trials published in journals with the words 'Chinese' or 'acupuncture' in their title were distinguished from those in 'traditional western' medical journals.

Due to the large number of these classification criteria and the small total number of trials, subgroups based on combined classification criteria (eg. partially blind trials using classical acupuncture) were not exhaustively analysed. There are 192 ways in which

TABLE 2 *Composition of subgroups*

Subgroup (Homogeneity)	Study numbers[1]
Low back pain**	1, 2, 3, 4, 5
Head and neck pain**	6, 7, 8, 9, 10, 11
Other site of pain**	12, 13, 14
Crossover design**	4, 5, 6, 8
Standard design**	1, 2, 3, 7, 9, 10, 11, 12, 13, 14
Placebo control**	3, 6, 9, 10, 12, 14
Conventional treatment**	1, 2, 4, 5, 7, 8, 11, 13
Classical acupuncture**	1, 5, 6, 7, 8
Formula acupuncture*	2, 3, 4, 9, 10, 12, 13, 14
Some blindness*	2, 3, 5, 6, 9, 12, 13, 14
No blindness**	1, 4, 7, 8, 10, 11
Large trial (50 or over)**	1, 2, 5, 8, 11, 14
Small trial (less than 50)**	3, 4, 6, 7, 9, 10, 12, 13
Chinese medical journal**	1, 2, 7
Mainstream medical journal**	3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14

[1] Studies numbered as in Table 1.
* Studies not homogeneous at p<0.05.
** Studies not homogeneous at p<0.01.

two criteria could be combined. Hence residual, and potentially relevant, heterogeneity within initial groups could not be systematically avoided.

Editors may have been biased against publishing inconclusive studies. Pooling of published studies would then obtain a biased result. The influence of publication bias was evaluated by estimating the number of unpublished randomized controlled trials of acupuncture for the treatment of chronic pain with inconclusive results that would need to exist in order to negate the findings obtained[26] (the 'file drawer' problem).

In order to ensure that MA methodology was comprehensively applied, the analysis was measured against a list of qualities and a scoring system proposed for medical MAs.[27]

DATA
Five trials dealing with low back pain (trials 1 to 5 in Table 1) met the selection criteria. Coan did not report statistical analysis of results.[28] Results were statistically significant though long-term follow-up showed regression of beneficial effects. Laitinen[29] and Edelist[30] did not attain significance. Fox[31] inserted only three needles, unilaterally, for one minute at each point sequentially. These third and fourth trials offered less treatment than is conventional. In Mendelson,[32] both patients and the final evaluator of pain were blind, potentially confusing effects of treatment order were noted, and no statistically significant results were obtained.

The second group treated headache, neck pain, cervical pain, cervical spondylosis and chronic facial pain and included six trials that met the selection criteria (trials 6 to 11 in Table 1). In Hansen, placebo treatment involved superficial insertion of acupuncture needles at non-acupuncture points. A pain index yielded a Wilcoxson test with $0.05>p>0.025$, and a sign test of subjective preferences of patients yielded $p = 0.035$, one-tailed, both in favour of acupuncture.[33] Coan[34] and Loh[35] both attained statistical significance. These latter results in favour of acupuncture may have been pure placebo effects, as control groups merely continued medical treatment. Dowson[36] used a true placebo (mock TNS), and did not obtain statistical significance. Cervical pain responded significantly (p<0.01) to acupuncture in one small study[37] but not in another.[38]

Three trials (trials 12 to 14 in Table 1) treated varied diagnoses. A single blind trial of multiple therapies for shoulder cuff lesion is one of two trials in which treatment did worse than control.[39] The second evaluated acupuncture for chronic pain below the waist against

'tender area needling'. Control did not explicitly exclude classical acupuncture points.[40] In Godfrey 'most appropriate' acupuncture points, were compared to 'least appropriate' points. Triple-blindness may have been achieved. Directions were given by an acupuncturist who had evaluated the patient to another who could not see the patient (whose head was hidden by a screen). No statistically significant results were obtained.[41]

RESULTS

Individual Trials

A Chi-squared test on proportions of patients improved in studies that had not published statistical tests of results,[28,34,35] yielded values of p<0.01. The risk difference is illustrated in Figure 1 for the 14 trials. Only two out of 14 trials obtained the result that patients treated with acupuncture did worse, on average, than the control group. The 95% CIs for four of these 14 trials did not include the 'zero risk difference' result. All four favoured acupuncture.

Meta-analysis of Cumulated Trials

Studies were not homogeneous according to the Q-statistic (p<0.01). The overall risk difference (indicator 'A') between acupuncture and control groups was 0.184 (SE = 0.062), in favour of acupuncture (p<0.01). Acupuncture was also superior overall according to the logarithm of the odds ratio (indicator 'B') and the logarithm of '1—the relative difference' (indicator 'C').
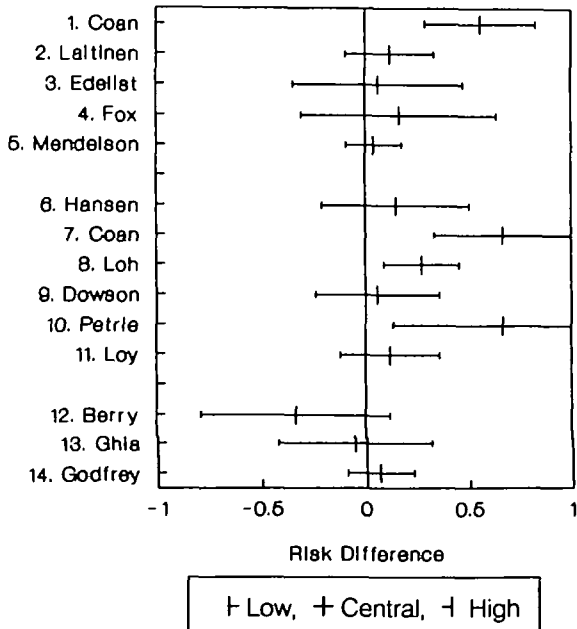
None of the subgroups (Table 2) within which results were cumulated were homogeneous according to the 'Q' test (p<0.05 for all subgroups).

Ninety-five per cent confidence intervals for the risk difference estimator (indicator 'A') are presented as Figure 2. The results for all three indicators are presented as Table 3.

There was quite good agreement between results obtained from the three summary statistics used. In 14 of the 19 subgroups analysed, indicators 'A', 'B', and 'C', provided the same result in terms of significance (or insignificance) of the difference between treatment and control groups.

Considering pooled results by site of pain, only the subgroup of trials for head and neck pain attained significance for all three indicators. Low back pain attained significance in favour of acupuncture according to indicators 'B' and 'C' if crossover trials were included. Results for other sites of pain showed an insignificant result in favour of the control group.

Acupuncture compared to conventional treatment was more favourable to acupuncture than trials against placebo. Patients receiving classical acupuncture at sites that varied from treatment to treatment did better than patients receiving formula acupuncture at fixed sites.

Trials with at least one blind agent were less favourable to acupuncture than trials without blind agents. Trials with some blindness did not attain significance for any indicator.
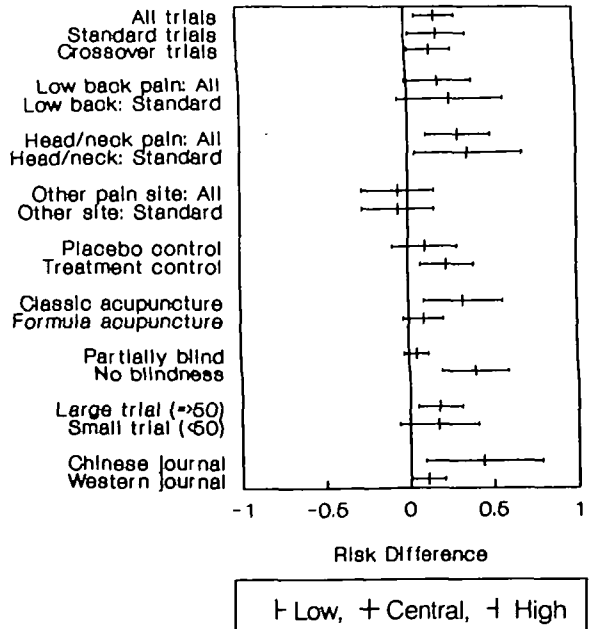

FIGURE 1. 14 RCTs of acupuncture; 95% CI for the risk difference.

FIGURE 2. Pooled trial subgroups; 95% CI for the risk difference.

TABLE 3   *Results obtained with meta-analysis of results of all trials and subgroups of trials defined, using the risk difference, the logarithm of the odds ration, and the logarithm of '1—the relative risk difference', with tests of significance at 95% presented (*)*

| | Indicator | | |
| | 'A' | 'B' | 'C' |
Trial group or subgroup	Weighted average of risk difference	Logarithm of the odds ratio	Logarithm of '1—the relative difference'
All trials	0.184*	0.645*	−0.219*
All standard trials	0.196*	0.633	−0.223
All crossover trials	0.147*	0.680*	−0.221
All trials for low back pain	0.191	0.753*	−0.299*
Standard trials for low back pain	0.258	1.069	−0.461
All trials for head and neck pain	0.303*	1.124*	−0.293*
Standard trials for head and neck	0.361*	1.328	−0.304
All trials for other pain sites	−0.056	−0.173	0.054
Standard trials for other sites	−0.056	−0.173	0.054
Placebo control group	0.105	0.202	−0.102
Treatment control group	0.235*	1.000*	−0.309*
Classical acupuncture	0.329*	1.411*	−0 513*
Formula acupuncture	0.092	0.260	−0.119
At least partial blindness	0.048	0.228	−0.081
No blindness in the trial	0.398*	1.662*	−0.555*
50 subjects of more (large trial)	0.183*	0.810*	−0.250*
Less than 50 subjects (small)	0.177	0.422	−0.163
Chinese or acupuncture journal	0.441*	1.947*	−0.886*
Mainstream medical journal	0.109*	0.383*	−0.135*

Large trials were more favourable to acupuncture than small trials. Results published in journals that had the word 'acupuncture' or 'Chinese' in their titles were significantly superior to those reported in 'traditional western' medical journals, but both these groups showed results favourable to acupuncture according to all three indicators.

The methodology of MA was comprehensively applied. Issues were covered in all six major areas of quality control of medical MAs. Twelve out of 23 relevant items were addressed. The analysis would be placed in the top decile of the 86 MAs reviewed by Sacks. That review obtained a mean of 7.7 items addressed with standard deviation of 2.7.

While some weaknesses of MA may not yet be fully appreciated,[42] known problems certainly include 'publication bias' and 'author self-selection bias'. The necessary number of unpublished acupuncture RCTs for chronic pain that had, on average, inconclusive results (zero risk difference) to negate the statistical significance of the pooled result in favour of acupuncture was 26 trials at p = 0.01, and 67 trials at p = 0.05.

DISCUSSION

Blindness is the only means of avoiding bias due to preconceived notions of the superiority (or inferiority) of a treatment. The 95% CI for the subgroup of 'trials with some blindness' includes the zero risk difference possibility for all indicators. If the four trials with statistically significant results are considered, only one common characteristic emerges. None had any degree of blindness. According to Godfrey,[41] full triple blindness is technically feasible. If feasible, it should be regarded as essential.

There are two potential explanations for the apparent superiority of CA over FA. Either efficacy of CA is superior, or the protocols of CA trials were inferior. Two out of six CA trials, and six out of eight FA trials, displayed some degree of blindness.

The result that trials against conventional treatment are more favourable to acupuncture than are trials against placebo may similarly be explained. Five out of eight of the former had no blindness, and only one out of six of the latter.

The superior results obtained by trials published in journals oriented towards Chinese medicine or acupuncture may indicate selective publication bias. It is possible that acupuncture treatment described in specialist journals was superior, or that study methods differed between publication subgroups. All RCTs published in journals with the words China or acupuncture in their titles were trials against conventional treatment.

It should be noted that, in MA, publication bias is made explicit. Individual studies that obtain positive results do not conventionally state that there may be large numbers of unpublished studies that obtained the opposite conclusion. The requirement that 67 inconclusive RCTs of acupuncture treatment for chronic pain exist to negate statistical significance of the pooled results is quite severe. No unpublished randomized controlled trials of acupuncture were discovered despite numerous contacts with the limited numbers of researchers in this area.

CONCLUSIONS

In pronouncing upon the efficacy, or otherwise, of a mode of treatment as contentious as acupuncture[43-45] one is advisedly cautious in distinguishing between a statistically significant, and a conclusive, result. Results favourable to acupuncture were obtained significantly more often than chance alone would allow.

Publication bias may have influenced all the pooled risk difference estimates. As a result the true probabilities of type I and type II errors cannot be assessed. It is nevertheless considered 'very unlikely' that the 67 inconclusive RCTs required to negate the statistical significance of the pooled result exist.

Conclusive findings in favour of any new therapy can only be obtained from adequate triple blind randomized clinical trials. The published study plans of some trials depict a variety of deficiencies and stricter plans tended to yield less favourable results. The fact that results for acupuncture vary greatly according to the degree of blindness underlines this point.

Analysis of cumulated results of subgroups provides useful guidelines for future research. It is also possible that the choice between formula and classical acupuncture may influence results. Preliminary indications are that future trials should consider these as distinct types of treatment.

If acupuncture has a pain relieving effect, the mechanisms by which this effect could come about are, of course, unknown. However, while much more is known about the mode of function of effective analgesic drugs such as aspirin, the precise mechanism of this commonly used drug has not yet been completely understood. Acupuncture has probably been used more often than aspirin, worldwide. For all this experience, very little is known. Participation of academic medical departments and research institutions in systematic evaluation of acupuncture should therefore be encouraged to resolve these scientific issues.

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