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Review

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Acupuncture for Chronic Pain
Individual Patient Data Meta-analysis

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Abstract

Background Although acupuncture is widely used for chronic pain, there remains considerable controversy as to its value. We aimed to determine the effect size of acupuncture for 4 chronic pain conditions: back and neck pain, osteoarthritis, chronic headache, and shoulder pain.

Methods We conducted a systematic review to identify randomized controlled trials (RCTs) of acupuncture for chronic pain in which allocation concealment was determined unambiguously to be adequate. Individual patient data meta-analyses were conducted using data from 29 of 31 eligible RCTs, with a total of 17 922 patients analyzed.

Results In the primary analysis, including all eligible RCTs, acupuncture was superior to both sham and no

and chronic headache, respectively; the effect sizes in comparison to no-acupuncture controls were 0.55 (95% CI, 0.51-0.58), 0.57 (95% CI, 0.50-0.64), and 0.42 (95% CI, 0.37-0.46) SDs. These results were robust to a variety of sensitivity analyses, including those related to publication bias.

Conclusions Acupuncture is effective for the treatment of chronic pain and is therefore a reasonable referral option. Significant differences between true and sham acupuncture indicate that acupuncture is more than a placebo. However, these differences are relatively modest, suggesting that factors in addition to the specific effects of needling are important contributors to the therapeutic effects of acupuncture.

Acupuncture is the insertion and stimulation of needles at specific points on the body to facilitate recovery of health. Although initially developed as part of traditional Chinese medicine, some contemporary acupuncturists, particularly those with medical qualifications, understand acupuncture in physiologic terms, without reference to premodern concepts.[1]

An estimated 3 million American adults receive acupuncture treatment each year,[2] and chronic pain is the most common presentation.[3] Acupuncture is known to have physiologic effects relevant to analgesia,[4,5] but there is no accepted mechanism by which it could have persisting effects on chronic pain. This lack of biological plausibility, and its provenance in theories lying outside of biomedicine, makes acupuncture a highly controversial therapy.

A large number of randomized controlled trials (RCTs) of acupuncture for chronic pain have been conducted. Most have been of low methodologic quality, and, accordingly, meta-analyses based on these RCTs are of questionable interpretability and value.[6] Herein, we present an individual patient data meta-analysis of RCTs of acupuncture for chronic pain, in which only high-quality RCTs were eligible for inclusion. Individual patient data meta-analysis are superior to the use of summary data in meta-analysis because they enhance data quality, enable different forms of outcome to be combined, and allow use of statistical techniques of increased precision.

Methods

The full protocol of the meta-analysis has been published.[6] In brief, the study was conducted in 3 phases: identification of eligible RCTs; collection, checking, and harmonization of raw data; and individual patient data meta-analysis.

There were no language restrictions. The initial search, current to November 2008, was used to identify studies for the individual patient data meta-analysis; a second search was conducted in December 2010 for summary data to use in a sensitivity analysis.

Study selection

Two reviewers applied inclusion criteria for potentially eligible articles separately, with disagreements about study inclusion resolved by consensus. Randomized controlled trials were eligible for analysis if they included at least 1 group receiving acupuncture needling and 1 group receiving either sham (placebo) acupuncture or no-acupuncture control. The RCTs must have accrued patients with 1 of 4 indications—nonspecific back or neck pain, shoulder pain, chronic headache, or osteoarthritis—with the additional criterion that the current episode of pain must be of at least 4 weeks duration for musculoskeletal disorders. There was no restriction on the type of outcome measure, although we specified that the primary end point must be measured more than 4 weeks after the initial acupuncture treatment.

It has been demonstrated that unconcealed allocation is the most important source of bias in RCTs,[7] and, as such, we included only those RCTs in which allocation concealment was determined unambiguously to be adequate (further details are in the review protocol[6]). Where necessary, we contacted authors for further information concerning the exact logistics of the randomization process. We excluded RCTs if there was any ambiguity about allocation concealment.

Data extraction and quality assessment

The principal investigators of eligible studies were contacted and asked to provide raw data from the RCT. To ensure data accuracy, all results reported in the RCT publication, including baseline characteristics and outcome data, were then replicated.

Reviewers assessed the quality of blinding for eligible RCTs with sham acupuncture control. The RCTs were graded as having a low likelihood of bias if either the adequacy of blinding was checked by direct questioning of patients (eg, by use of a credibility questionnaire) and no important differences were found between groups, or the blinding method (eg, the Streitberger and Kleinhenz sham device[8]) had previously been validated as able to maintain blinding. Randomized controlled trials with a high likelihood of bias from unblinding were excluded from the meta-analysis of acupuncture vs sham; a sensitivity analysis included only RCTs with a low risk of bias.

Data synthesis and analysis

puncture from each RCT was then entered into a meta-analysis using the *metan* command in Stata software (version 11; Stata Corp): the meta-analytic statistics were created by weighting each coefficient by the reciprocal of the variance, summing, and dividing by the sum of the weights. Meta-analyses were conducted separately for comparisons of acupuncture with sham and no-acupuncture control, and within each pain type. We prespecified that the hypothesis test would be based on the fixed effects analysis because this constitutes a valid test of the null hypothesis of no treatment effect.

Results

Systematic review

We identified 82 RCTs (**Figure 1**),[11-93] of which 31 were eligible (**Table 1** and **eAppendix**). Four of the studies were organized as part of the German Acupuncture Trials (GERAC) initiative,[11-14] 4 were part of the Acupuncture Randomized Trials (ART) group[15-18]; 4 were Acupuncture in Routine Care (ARC) studies[19-22]; 3 were UK National Health Service acupuncture RCTs.[23,24,98] Eleven studies were sham controlled, 10 had no-acupuncture control, and 10 were 3-armed studies, including both sham and no-acupuncture control. The second search for subsequently published studies identified an additional 4 eligible studies,[94-97] with a total of 1619 patients.

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table 1. Characteristics of Included Studiesa

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Table 1. Characteristics of Included Studies[a]

An important source of clinical heterogeneity between studies concerns the control groups. In the sham RCTs, the type of sham included acupuncture needles inserted superficially,[13] sham acupuncture devices

the no-acupuncture control groups varied among usual care, such as an RCT in which control group patients were merely advised to "avoid acupuncture"[98]; attention control, such as group education sessions[28]; and guidelined care, in which patients were given advice as to specific drugs and doses.[13]

Data extraction and quality assessment

Usable raw data were obtained from 29 of the 31 eligible RCTs, including a total of 17 922 patients from the United States, United Kingdom, Germany, Spain and Sweden. For 1 RCT, the study database had become corrupted[29]; in another case, the statisticians involved in the RCT failed to respond to repeated enquiries despite approval for data sharing being obtained from the principal investigator.[30]

The 29 RCTs comprised 18 comparisons with 14 597 patients of acupuncture with no-acupuncture group and 20 comparisons with 5230 patients of acupuncture and sham acupuncture. Patients in all RCTs had access to analgesics and other standard treatments for pain. Four sham RCTs were determined to have an intermediate likelihood of bias from unblinding[13,27,31,32]; the 16 remaining sham RCTs were graded as having a low risk of bias from unblinding. On average, dropout rates were low (weighted mean, 10%). Dropout rates were higher than 25% for only 4 RCTs: those by Molsberger et al[30,97] (27% and 33%, respectively, but raw data were not received and neither RCT included in main analysis); Carlsson et al[32] (46%, RCT excluded in a sensitivity analysis for blinding), and Berman et al[28] (31%). This RCT had a high dropout rate among no-acupuncture controls (43%); dropout rates were close to 25% in the acupuncture and sham groups. The RCT by Kerr et al[31] had a large difference in dropout rates between groups (acupuncture, 13%; control, 33%) but was excluded in the sensitivity analysis for blinding.

Meta-analysis

Forest plots for acupuncture against sham acupuncture and against no-acupuncture control are shown separately for each of the 4 pain conditions in **Figure 2** and **Figure 3**. Meta-analytic statistics are shown in **Table 2**. Acupuncture was statistically superior to control for allanalyses ($P < .001$). Effect sizes are larger for the comparison between acupuncture and no-acupuncture control than for the comparison between acupuncture and sham: 0.37, 0.26, and 0.15 in comparison with sham vs 0.55, 0.57, and 0.42 in comparison with no-acupuncture control for musculoskeletal pain, osteoarthritis, and chronic headache, respectively.

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Figure 2. Forest plots for the comparison of acupuncture with no-acupuncture control. There were fewer than 3 trials for shoulder pain, so no meta-analyses were performed. A, Osteoarthritis; B, chronic headache; C, musculoskeletal pain

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Figure 3. Forest plots for the comparison of true and sham acupuncture. A, Osteoarthritis; B, chronic headache; C, musculoskeletal pain; D, shoulder pain.

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Table 2. Primary Analysesa

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For 5 of the 7 analyses, the test for heterogeneity was statistically significant. In the case of comparisons with sham acupuncture, the RCTs by Vas et al[37,38,41] are clear outliers. For example, the effect size of the RCTs by Vas et al for neck pain is about 5 times greater than meta-analytic estimate. One effect of excluding these RCTs in a sensitivity analysis (Table 3 and Table 4) is that there is no significant heterogeneity in the comparisons between acupuncture and sham. Moreover, the effect size for acupuncture becomes relatively similar for the different pain conditions: 0.23, 0.16, and 0.15 against sham, and 0.55, 0.57, and 0.42 against no-acupuncture control for back and neck pain, osteoarthritis, and chronic headache, respectively (fixed effects; results similar for the random effects analysis).

Table 3. Sensitivity Analyses: Acupuncture vs Sham Acupuncturea

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Table 4. Sensitivity Analyses: Acupuncture vs No-Acupuncture Control[a]

To give an example of what these effect sizes mean in real terms, a baseline pain score on a 0 to 100 scale for a typical RCT might be 60. Given a standard deviation of 25, follow-up scores might be 43 in a no-acupuncture group, 35 in a sham acupuncture group, and 30 in patients receiving true acupuncture. If response were defined in terms of a pain reduction of 50% or more, response rates would be approximately 30%, 42.5%, and 50%, respectively.

The comparisons with no-acupuncture control show evidence of heterogeneity. This seems largely explicable in terms of differences between the control groups used. In the case of osteoarthritis, the largest effect was in the study by Witt et al,[17] in which patients in the waiting list control received only rescue pain medication, and the smallest was in the study by Foster et al,[24] which involved a program of exercise and advice led by physical therapists. For the musculoskeletal analyses, heterogeneity is driven by 2 very large RCTs[19,20] (n = 2565 patients and n = 3118 patients, respectively) for back and neck pain. If only back pain is considered (**Table 3** and **Table 4**), heterogeneity is dramatically reduced and is again driven by one RCT, by Brinkhaus et al,[15] with waiting list control. In the headache meta-analysis, Diener et al[13] had much smaller differences between groups. This RCT involved providing drug therapy according to national guidelines in the no-acupuncture group, including initiation of β-blockers as migraine prophylaxis. There was disagreement within the collaboration about whether this constituted active control. Excluding this RCT reduced evidence of heterogeneity (P = .04) but had little effect on the effect size (0.42-0.45).

Table 3 and **Table 4** show several prespecified sensitivity analyses. Neither restricting the sham RCTs to those with low likelihood of unblinding nor adjustment for missing data had any substantive effect on our main estimates. Inclusion of summary data from RCTs for which raw data were not obtained (2 RCTs) or which were published recently (4 RCTs) also had little impact on either the primary analysis (**Table 3** and **Table 4**) or the analysis with the outlying RCTs by Vas et al[37,38,41] excluded (data not shown).

To estimate the potential impact of publication bias, we entered all RCTs into a single analysis and compared the effect sizes from small and large studies.[99] We saw some evidence that small studies had larger effect sizes for the comparison with sham (P = .02) but not no-acupuncture control (P = .72). However,

Nonetheless, we repeated our meta-analyses excluding RCTs with a sample size of less than 100. This had essentially no effect on our results. As a further test of publication bias, we considered the possible effect on our analysis if we had failed to include high-quality, unpublished studies. Only if there were 47 unpublished RCTs with n = 100 patients showing an advantage to sham of 0.25 SD would the difference between acupuncture and sham lose significance.

A final sensitivity analysis examined the effect of pooling different end points measured at different periods of follow-up. We repeated our analyses including only pain end points measured at 2 to 3 months after randomization. There was no material effect on results: effect sizes increased by 0.05 to 0.09 SD for musculoskeletal and osteoarthritis RCTs and were stable otherwise.

As an exploratory analysis, we compared sham control with no-acupuncture control. In a meta-analysis of 9 RCTs,[11-13,15-18,24,28] the effect size for sham was 0.33 (95% CI, 0.27-0.40) and 0.38 (95% CI, 0.20-0.56) for fixed and random effects models, respectively ($P < .001$ for tests of both effect and heterogeneity).

Comment

Overview of findings

In an analysis of patient-level data from 29 high-quality RCTs, including 17 922 patients, we found statistically significant differences between both acupuncture vs sham and acupuncture vs no-acupuncture control for all pain types studied. After excluding an outlying set of studies, meta-analytic effect sizes were similar across pain conditions.

The effect size for individual RCTs comparing acupuncture with no-acupuncture control did vary, an effect that seems at least partly explicable in terms of the type of control used. As might be expected, acupuncture had a smaller benefit in patients who received a program of ancillary care—such as physical therapist-led exercise[24]—than in patients who continued to be treated with usual care. Nonetheless, the average effect, as expressed in the meta-analytic estimate of approximately 0.5 SD, is of clear clinical relevance whether considered either as a standardized difference[100] or when converted back to a pain scale. The difference between acupuncture and sham is of lesser magnitude, 0.15 to 0.23 SD.

Study limitations

Neither study quality nor sample size seems to be a problem for this meta-analysis, on the grounds that only high-quality studies were eligible and the total sample size is large. Moreover, we saw no evidence that publication bias, or failure to identify published eligible studies, could affect our conclusions.

studies comparing acupuncture and sham acupuncture, health care providers obviously were aware of the treatment provided, and, as such, a certain degree of bias of our effect estimate for specific effects cannot be entirely ruled out. However, it should be kept in mind that this problem applies to almost all studies on nondrug interventions. We would argue that the risk of bias in the comparison between acupuncture and sham acupuncture is low compared with other nondrug treatments for chronic pain, such as cognitive therapies, exercise, or manipulation, which are rarely subject to placebo control.

Another possible critique is that the meta-analyses combined different end points, such as pain and function, measured at different times. However, results did not change when we restricted the analysis to pain end points measured at a specific follow-up time, 2 to 3 months after randomization.

Comparison with other studies

Many prior systematic reviews of acupuncture for chronic pain have had liberal eligibility criteria, accordingly included RCTs of low methodologic quality, and then came to the circular conclusion that weaknesses in the data did not allow conclusions to be drawn.[101,102] Other reviews have not included meta-analyses, apparently owing to variation in study end points.[103,104] We have avoided both problems by including only high-quality RCTs and obtaining raw data for individual patient data meta-analysis. Some more recent systematic reviews have published meta-analyses[105-108] and reported findings that are broadly comparable with ours, with clear differences between acupuncture and no-acupuncture control and smaller differences between true and sham acupuncture. Our findings have greater precision: all prior reviews have analyzed summary data, an approach of reduced statistical precision when compared with individual patient data meta-analysis.[6,109] In particular, we have demonstrated a robust difference between acupuncture and sham control that can be distinguished from bias. This is a novel finding that moves beyond the prior literature.

Interpretation

We believe that our findings are both clinically and scientifically important. They suggest that the total effects of acupuncture, as experienced by the patient in routine clinical practice, are clinically relevant, but that an important part of these total effects is not due to issues considered to be crucial by most acupuncturists, such as the correct location of points and depth of needling. Several lines of argument suggest that acupuncture (whether real or sham) is associated with more potent placebo or context effects than other interventions.[110-113] Yet, many clinicians would feel uncomfortable in providing or referring patients to acupuncture if it were merely a potent placebo. Similarly, it is questionable whether national or private health insurance should reimburse therapies that do not have specific effects. Our finding that acupuncture

the specific effects associated with correct needle insertion according to acupuncture theory, nonspecific physiologic effects of needling, and nonspecific psychological (placebo) effects related to the patient's belief that treatment will be effective.

In conclusion, we found acupuncture to be superior to both no-acupuncture control and sham acupuncture for the treatment of chronic pain. Although the data indicate that acupuncture is more than a placebo, the differences between true and sham acupuncture are relatively modest, suggesting that factors in addition to the specific effects of needling are important contributors to therapeutic effects. Our results from individual patient data meta-analyses of nearly 18 000 randomized patients in high-quality RCTs provide the most robust evidence to date that acupuncture is a reasonable referral option for patients with chronic pain.

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October 31, 2012

Does Acupuncture Have a Point?

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The first sentence of the excellent report by Vickers et al. states unequivocally, "Acupuncture is the insertion and stimulation of needles at specific points on the body to facilitate recovery of health." However, they seem to contradict their own premise when they conclude that "an important part of these total effects is not due to issues considered to be crucial by most acupuncturists, such as the correct location of points and depth of needling." If correct location of points is not important, then perhaps neither is the prescription of specific points to be needled; additionally, there is no ...

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