

**Manheimer E, Cheng K, Linde K, et al. Acupuncture for peripheral joint osteoarthritis Review). Cochrane Database of Systematic Reviews 2010, Issue 1. Art # CD001977.**

**Design:** Meta-analysis of randomized clinical trials

**Date:** 11-14-14

**Study Question:** For treating people with osteoarthritis of the knee or hip, what are the differences in the effects of traditional needle acupuncture compared with a sham, another active treatment, or with a waiting list control?

**PICOs:**

- Patients: Adults diagnosed with osteoarthritis of the knee or hip
- Interventions: Traditional acupuncture; dry needling and laser acupuncture were excluded
- Comparison interventions: Non-acupuncture controls included sham intervention, waiting list controls, or another active treatment.
- Outcomes: Pain, function, or symptom severity
  - o Pain was preferably measured by validated scales such as the WOMAC scale from 0 to 20 points
  - o Function was measured using the WOMAC scale from 0 to 68 points which is a patient-reported measure of function
  - o Timing of outcomes was short term (closest to 8 weeks and  $\leq 3$  months), and long term (closest to 6 months and  $> 3$  months) following randomization
- Study types: Randomized clinical trials comparing acupuncture versus a non-acupuncture control with at least 6 weeks of treatment.

**Study selection:**

- Databases included MEDLINE and EMBASE through December 2007 and the Cochrane Central Register of Controlled Trials through 2008, Issue 1.
  - o Reference lists of retrieved articles were also scanned
- Two authors independently assessed articles on trial quality for inclusion and extracted data from the trials, resolving any disagreements through discussion
- Risk of bias was assessed using the new tool recommended by the Cochrane Reviewer's Handbook which uses the following criteria; adequate sequence generation, allocation concealment, blinding of participants, providers, and outcome assessors, incomplete outcome data and follow-up data addressed, and selective reporting. Other potential threats to validity were assessed including similarity of groups at baseline; co-interventions avoided or similar; compliance acceptable in all groups; similar timing of the outcome assessment in all groups; and intention-to-treat analysis.
- Heterogeneity in meta-analysis was graded with the  $I^2$  statistic: from 0 to 40% might not be important; from 30 to 60% may mean moderate heterogeneity; from 50 to 90%

- may mean substantial heterogeneity, and from 75 to 100% was considerable heterogeneity. Data was not pooled if  $I^2$  was between 75% and 100%. If  $I^2$  was  $\geq$  50%, the pooled results were interpreted with caution.
- Evaluated whether the meta-analyses of acupuncture met the MCID; The clinically relevant effects for knee osteoarthritis have been estimated to be standardized mean differences of 0.39 for WOMAC pain and 0.37 for WOMAC function
  - The authors planned subgroup analyses on whether or not the sham used had any physiological activity, high vs low quality trials, 7 clinical acupuncture variables, fixed effect as a sensitivity analysis, and 2 other sensitivity analyses.

## Results:

- 16 studies with 3498 people were included in the analysis of results
- 12 RCTs included only people with OA of the knee, 3 only OA of hip, and one of both
- 20 studies were excluded that did not meet the inclusion criteria
- All studies but one were published in English.
- The following comparisons were evaluated:
  - 1) Acupuncture versus a sham intervention;
  - 2) Acupuncture versus a waiting list;
  - 3) Acupuncture versus another active treatment;
  - 4) Acupuncture plus another active treatment versus that other active treatment alone.Different joints were analyzed in separate joint specific meta-analyses
- Only 2 of the 5 high quality trials had any obvious methodological flaws and these were due to higher drop-out rates in the sham or control group than in the acupuncture group which contributes to some risk of bias. The shams used in three of the sham-controlled trials may not have sufficiently blinded participants to the treatment being evaluated.
- In comparing acupuncture vs a sham control, meta-analysis pooled data from nine studies at 8 weeks (short-term), 8 involving knee OA and one involving hip OA
  - o The pooling of outcome data took the form of a standardized mean difference (SMD), in which group differences are expressed in terms of standard deviations (by convention, less than 0.2 SD is no difference, 0.2 to 0.5 SD is a small difference, 0.5 to 0.8 SD is a moderate difference, and more than 0.8 SD is a large difference)
  - o The pooled SMD from the 9 studies (1835 participants) showed small but statistically significant improvements in OA pain, with a -0.28 SD (95% confidence interval from -0.45 to -0.11), but the results had substantial heterogeneity ( $I^2$  was 64%).
    - In a subgroup analysis restricted to the knee-only trials, results were unchanged
    - In a subgroup analysis restricted to only the 5 high quality trials (all were knee RCTS) for short-term pain, results were similar

- The pooled SMD from 9 studies (1829 participants) showed small but statistically significant improvements in OA function, with a -0.28 SD (95% confidence interval from -0.46 to -0.09), but the results had substantial heterogeneity ( $I^2$  was 69%)
- Three of the nine trials showed effect estimates that met the pre-defined clinical relevance thresholds of 0.37 and 0.39 for pain and function respectively, but the pooled estimates of -0.28 for pain and function did not meet the MCID threshold.
- In comparing acupuncture vs a sham control, meta-analysis pooled data from 4 studies (1399 participants) at 6 months (long-term), all involving knee OA
  - The pooled SMD from the 4 studies showed borderline statistically significant, clinically irrelevant improvements in knee OA pain, with a -0.10 SD (95% confidence interval from -0.21 to -0.01), but the results were homogeneous ( $I^2$  was 0%)
  - The pooled SMD from the 4 studies showed statistically non-significant, clinically irrelevant improvements in knee OA function, with a -0.11 SD (95% confidence interval from -0.22 to 0.00), but the results were homogeneous ( $I^2$  was 2%)
- In comparing acupuncture with a waiting list control, acupuncture was associated with large clinically relevant, short-term improvements in OA pain (-0.96 SD, -1.19 to -0.72; 4 trials; 884 participants;  $I^2 = 41\%$ ), and function (-0.89 SD, -1.18 to -0.60; 3 trials; 864 participants;  $I^2 = 64\%$ ). There was moderate heterogeneity, but the benefits of acupuncture in each individual trial, as well as the pooled effect, were much larger than the predefined thresholds for clinical relevance.
- Only one trial (Foster 2007) with 218 patients evaluated acupuncture as an adjuvant to an exercise based physiotherapy program (including supervised plus home exercises) which did not result in any greater improvements than the exercise based physiotherapy program alone.
- Acupuncture plus another active treatment versus that other active treatment alone trials could not be pooled and included only individual study results.
- Some minor side effects of acupuncture were minor bruising and bleeding at needle insertion sites. No serious adverse events were reported to be associated with acupuncture. The frequency of adverse events was similar between the acupuncture and control groups.

### **Authors' conclusions:**

- The effects of true acupuncture relative to sham did not meet the pre-specified thresholds for clinical relevance. The effects of acupuncture relative to sham acupuncture may be too small to be perceived by participants as beneficial and thus may not actually result in a significant functional improvement or a significant pain reduction. However, few if any other commonly used treatments for osteoarthritis meet these thresholds for minimal clinically important differences including NSAIDS.

- The effects of true acupuncture relative to a waiting list control and some of the other active treatment control groups did exceed the thresholds for clinical relevance. The only other non-pharmacological treatment for osteoarthritis with benefits close to or exceeding the thresholds for clinical relevance is exercise, with standardized mean differences of .39 for pain and .31 for function, relative to a non-exercise control group.
- Since sham acupuncture may not be an inert placebo, the studies suggest that people with osteoarthritis find meaningful benefits through acupuncture, although these benefits may be largely mediated through placebo effects.
- Since few if any OA treatments have specific effects that meet the threshold for clinically relevant benefits, this does not necessarily mean that there are no effective treatments for osteoarthritis. It might mean instead that the threshold for clinical relevance is too high for any individual treatment alone, and that a multidisciplinary approach to OA patient management, with a focus on combining several non-pharmacological therapies is necessary.
- The relative benefits of acupuncture compared with other treatments cannot be reliably assessed, because for most OA treatments there are small effect sizes with wide confidence intervals. It is unreliable to estimate the relative effects of acupuncture compared to other active treatments using indirect comparisons.
- There were no adverse events associated with acupuncture in this review.

### Comments:

- The pooled **short-term** results for pain and function comparing acupuncture vs a sham control show;
  - o Overall low quality evidence
  - o Small, statistically significant effect sizes for OA pain and function (SMD = -0.28)
  - o Clinically significant thresholds established were not met (SMD = 0.39 for WOMAC pain and 0.37 for WOMAC function)
  - o Substantial heterogeneity ( $I^2 = 64\%$  and  $69\%$ )
  - o Improvement in pain on a scale of 0 to 20 was only 0.9 points greater in the acupuncture group than in the sham group (MCID = 1.3 points).
  - o Improvement in function on a scale of 0 to 68 was only 2.7 points better in the acupuncture group than in the sham group (MCID = 3.6 points).
- The pooled **long-term** results for pain and function comparing acupuncture vs a sham control show;
  - o Overall high quality evidence
  - o Very small, borderline or statistically non-significant effect sizes for OA pain (SMD = -0.10) and function (SMD = -0.11)
  - o Clinically significant thresholds established were not met (SMD = 0.39 for WOMAC pain and 0.37 for WOMAC function)
  - o Homogeneous results ( $I^2 = 0\%$  and  $2\%$ )
  - o Improvement in pain on a scale of 0 to 20 was only 0.4 points greater in the acupuncture group than in the sham group (MCID = 1.3 points).

- Improvement in function on a scale of 0 to 68 was only 1.2 points better in the acupuncture group than in the sham group (MCID = 3.6 points).
- Since acupuncture benefits may diminish over time, it may be important to continue monthly acupuncture treatments in the months prior to the long-term assessment. Only one of four RCTs that evaluated long-term outcomes in this systematic review conducted acupuncture treatments up until the final 6 month measurement point. It is possible that acupuncture's long-term benefits may have been missed in this review.
- One study appears to be an outlier in showing a significant advantage of acupuncture treatment over sham acupuncture (Vas 2004) and accounts for about half of the heterogeneity.
  - When Vas 2004 is removed from the analysis of only the 5 high quality studies, the heterogeneity is significantly reduced from  $I^2$  of 79% to 35%, and the pooled SMD is decreased from -0.27 (95% CI from -0.51 to -0.03) to -0.14 (95% CI from -0.28 to -0.01).
- The observed very small pooled benefits of acupuncture relative to sham may possibly be due to expectation or placebo effects rather than specific effects of the needle placement, particularly among participants who have a preference for acupuncture.
- The authors noted that few if any other commonly used treatments for osteoarthritis meet these thresholds for minimal clinically important differences for pain and function. However, other studies of acupuncture commonly use even larger established clinically significant thresholds for pain and function. The MCIDs for pain on the Numeric Rating Scale (NRS) is 3.6 points and on the VAS is 3.4 points on a 20 point scale compared to this study's pre-planned threshold of only 1.3 points. The MCIDs for function on the WOMAC is 6 points on a 68 point scale compared to this study's pre-planned threshold of 3.57 points. Unfortunately, this study was not able to meet the commonly established MCIDs for pain and function or even meet the lower than usual MCIDs that it established for this study.
- It appears that acupuncture or any intervention in isolation will not be sufficient to adequately reduce OA pain and improve function. Perhaps a combination of interventions which includes acupuncture and exercise or NSAIDS etc. will work best to provide an acceptable beneficial effect on OA pain and function.

### **Assessment:**

High quality Cochrane meta-analysis which supports good evidence that in people with osteoarthritis of the knee or hip, the effects of true needle acupuncture treatment relative to sham acupuncture may be too small to be perceived by participants as beneficial, and thus may not actually result in significant, clinically relevant functional improvement or significant pain reduction.