

Hinman RS, McCrory P, Pirotta M, and et al. Acupuncture for Chronic Knee Pain: A Randomized Clinical Trial. Journal of the American Medical Association 2014; 312(13):1313-1322.

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Design: Randomized clinical trial

Objective: To determine the efficacy of laser and needle acupuncture for chronic knee pain.

Population /sample size/setting:

- 282 community volunteers (143 males, 139 females) aged ≥ 50 years with chronic knee pain were recruited from metropolitan Melbourne and regional Victoria, Australia from February 2010 to December 2012 via advertisements in the media and at clinics.
- Zelen-design clinical trial (randomization occurred before informed consent)
- Treated by family physician acupuncturists
- Inclusion criteria included age 50 years or older, knee pain longer than 3 months' duration, had knee pain most days with average severity of 4 or more out of 10 on a numeric rating scale (NRS), and had morning stiffness lasting less than 30 minutes.
- Exclusion criteria included history of any systemic arthritic condition, knee arthroplasty, knee injection or knee surgery in past 6 months, referral to pain clinic, or use of morphine or pethidine within past 6 months. Also excluded were current use of oral or injectable anticoagulant medication, wait-listing for any knee surgery for either knee, use of acupuncture in past 12 months, any bleeding disorder, allergy to light, knee pain subject to compensation claim, inability to give written informed consent, any other condition affecting lower limb function (e.g. trauma, malignancy, neurological condition), or any other medical condition precluding participation in the trial (e.g. kidney or liver disease, deep vein thrombosis).

Interventions:

- Participants initially consented to an observational study with repeated questionnaires over 1 year. Participants who returned baseline questionnaires were consecutively randomized into one of 4 groups.
- 282 patients were randomized. The 4 groups were; no acupuncture (control) group (n=71, mean age = 62.7), needle acupuncture (n=70, mean age = 64.3), laser acupuncture (n=71, mean age = 63.4) and sham laser acupuncture (n=70, mean age = 63.8).
- Participants assigned to the control group continued in the observational study, unaware they were in an acupuncture clinical trial, and thus blinded.
- Participants allocated to one of the 2 laser groups and their acupuncturists were blinded to laser and sham laser acupuncture by using pre-programmed laser machines, but participants allocated to needle acupuncture and their acupuncturists were not blinded.
- Participants who accepted intervention provided further informed consent to participate.
- Participants who declined acupuncture continued in the observational study.
- All participants completed questionnaires before treatments at baseline, post-treatment at the end of 12 weeks, and at one year to evaluate maintenance of effects for all outcome variables.

- A combined Western and traditional Chinese medicine style of acupuncture using 6 or more points was delivered according to usual practice by 8 family physicians registered as acupuncturists.
- For laser and sham laser acupuncture, Standard Class 3B laser devices were used (measured output 10mW and energy output 0.2 J/point), with a red non-laser light at the probe tip that lit up in active and sham modes to maintain blinding. Laser and sham laser acupuncture interventions did not include any needle acupuncture.
- Twenty minute treatments were delivered once or twice weekly for 12 weeks, with 8 to 12 sessions in total permitted.

Main outcome measures:

- Primary outcome variables included self-reported average knee pain and function over the previous week at 12 weeks follow-up. Pain was measured using a 0 to 10 point numeric rating scale (NRS) with a minimal clinically important difference (MCID) of 1.8 points, similar to the visual analog scale (VAS). Physical function was measured using the Western and McMaster Universities Osteoarthritis Index (WOMAC, Likert version 3.1) function subscale, scored from zero to 68 with higher scores indicating worse function with a MCID of 6 non-normalized units.
- Secondary outcomes measured at 12 weeks and one year included average knee pain on walking and standing, average daily activity restriction over the previous week, pain on the WOMAC pain subscale, health-related quality of life, physical and mental component summary scores of the Short Form Health Survey (SF-12), and one year follow-up of primary outcomes. In addition, at follow-up, participants rated global change overall, in pain, and in physical function.
- Sample size: To achieve 80% power at a 2-sided 5% significance level, 66 patients were required in each treatment group which was rounded up to 70.
- At 12 weeks and 1 year assessments, 26 (9%) and 50 (18%) participants were lost to follow-up, respectively.
- There was no statistically significant difference between groups at baseline, except the sham laser group had slightly more participants with symptoms exceeding 10 years duration.
- Slightly fewer allocated to receive sham laser acupuncture declined treatment (9/70, 13%) compared with needle (13/70, 19%) and laser acupuncture (12/71, 17%).
- In the 2 laser groups, most participants and acupuncturists were unable to identify whether active or sham acupuncture was delivered.
- For the ITT analyses at 12 weeks, there were no significant differences in the primary outcome of overall pain between active laser and sham laser acupuncture, between needle and active laser acupuncture, between needle and sham laser acupuncture, and between control and sham laser acupuncture. Both needle (-1.1) and active laser acupuncture (-.08) resulted in statistically significant modest reductions in pain compared with control at 12 weeks, but the MCID (-1.8) was not attained.
- For the ITT analyses at 12 weeks, there were no significant differences in function between active laser and sham laser acupuncture, or any other group comparisons, except that needle acupuncture compared with control significantly improved physical function (-3.9) modestly (MCID of -6.0 was not met), but needle acupuncture was not different from sham laser acupuncture.

- In all of the 12 week comparisons between the groups for pain and function for the ITT analyses, all differences were less than the MCID.
- For the ITT analyses at the one year follow-up, there were no significant differences in the primary outcomes of overall pain and function between any groups compared with the control group or between any groups compared with each of the other groups. In all of the one year comparisons between the groups for pain and function, all differences were less than the MCID.
- Most secondary outcomes showed no significant differences between any group comparisons for the ITT analyses, except that needle acupuncture compared with control improved pain on walking and standing at 12 weeks, but was not maintained at 1 year. Needle acupuncture compared with control significantly improved activity restriction at 1 year. Needle acupuncture compared with control also significantly reduced WOMAC pain at both 12 weeks and one year, but the MCID was not met.
- When analyzed as treated at 12 weeks, there were small statistically significant differences in the primary outcomes of overall pain and function for all groups compared with the control group, except for active laser versus control for function. For overall pain compared to control, the estimates were -1.5 for needle, -1.0 for active laser, and -1.2 for sham laser. For function compared to control, the estimates were -4.4 for needle, -3.0 for active laser, and -3.6 for sham laser. None of the estimates met the MCID of 1.8 points for pain or 6 units for WOMAC function. When analyzed as treated, there were no significant differences in the primary outcomes of overall pain and function between any groups compared with each of the other groups.
- When analyzed as treated at the one year follow-up, there were no significant differences in the primary outcomes of overall pain and function between any groups compared with the control group or between any groups compared with each of the other groups. In all of the one year comparisons between the groups for pain and function, all differences were less than the MCID.

Authors' conclusions:

- Needle and active laser acupuncture were no more effective than sham laser acupuncture. Even though needle and active laser acupuncture improved pain after treatment compared with control after 12 weeks, improvements were not sustained at 1 year and were of a clinically unimportant magnitude.
- Improvement in WOMAC physical function with needle acupuncture relative to control at 12 weeks was of a clinically unimportant magnitude and did not persist at 1 year. Furthermore, this improvement was not different from sham laser.
- Sample size may have contributed to the nonsignificant findings between active and sham laser acupuncture. The study was powered for between-group differences based on MCIDs in primary outcomes.
- The findings from this study advise against the use of acupuncture for patients older than 50 years of age with moderate to severe chronic knee pain.
- In this study, any benefits of acupuncture were exclusively attributed to incidental effects, given the lack of significant differences between active acupuncture and sham treatment. Subjective outcome measures, such as self-reported pain and physical function, as used in this study, are particularly subject to placebo responses. This study may have observed

significant differences between active and sham acupuncture had objective outcome measures been included.

- This study did not go beyond the 1-year time period for acupuncture outcomes, and it is possible that there are benefits of treatment beyond 1 year that this study did not capture.

Comments:

- This is a well conducted randomized clinical trial.
- Primary outcome measures were not clearly stated. The main aim of this study was to compare laser acupuncture to needle acupuncture. The comparison of needle acupuncture with sham laser acupuncture was not in the aims or hypotheses of this trial. Thus the conclusion that needle acupuncture was not better than sham acupuncture was based on a pot-hoc hypothesis.
- Major strengths of this study include its Zelen design, comparison of needle and laser acupuncture, acupuncturist blinding in laser groups, and measurement of 1-year outcomes to evaluate maintenance effects. These are important additions to the acupuncture literature.
- This Zelen-design clinical trial minimized potential for performance and response bias in the laser acupuncture group by including a blinded sham laser acupuncture treatment, thereby reducing treatment expectations that can often inflate benefits, both of which could have influenced outcomes.
- A major strength of the study was the incorporation of both of a control group that received no acupuncture treatment and a blinded sham acupuncture treatment group. Sham laser acupuncture is a credible control for needle acupuncture and provides for blinding of patients and acupuncturists which is not possible with needles.
- It appears that both the laser acupuncture and sham laser acupuncture groups were informed that they were in a randomized clinical trial (RCT), but were blinded to which laser group they were randomized to. Participants randomized to the control group continued in the observational study, and were unaware they were in an RCT and thus blinded. It appears that the needle acupuncture group was not informed that they were in an RCT, but were continuing in the observational study. The needle acupuncture group was not blinded to their treatment.
- Previous trials have not been able to blind participants who do not receive acupuncture. The Zelen design allowed blinding of the control participants, thereby minimizing the risk of discouragement in the untreated patients. For acupuncture trials in particular, knowledge of the intervention itself in the control group may influence the study outcome, so the Zelen-design completely eliminated this influence in the control group.
- Lack of acupuncturist and participant blinding to needle acupuncture may have introduced treatment bias, response bias, or both in this group and may explain why needle acupuncture improved pain and function relative to control at 12 weeks.
- Patients' distinct acupuncture preconceptions, and the positive attitudes they may have toward acupuncture are consistently associated with significantly better treatment outcomes. Knowledge of the intervention may also influence recruitment. Patients in this trial had no knowledge they were recruited for an acupuncture study. The influence of this type of recruitment bias is greatly reduced in this Zelen-design clinical trial and also ensured that not only patients with positive acupuncture attitudes were recruited. Because the recruited patients may have held less-positive expectations about acupuncture

compared with previous research, this may help explain the minimal acupuncture effects (relative to control) that were observed in this study. This is a major advantage over previous acupuncture studies.

- Analyses were conducted by blinded statisticians. An intention-to-treat approach was the primary analysis used, but that included all patients randomized to a particular treatment which included those that were treated and those who declined invitation to treatment. Secondary analyses addressed potential dilution effects due to the Zelen design, so “as treated” analyses were also performed which compared participants by treatment received regardless of randomization. “As treated” analyses can be biased if participants who accept their assigned treatment differ from those who decline treatment, and so these analyses should be viewed with caution. The participants in the “as treated” analyses are generally those who have positive views of acupuncture and who think they will benefit from it.
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- Sample sizes of the 4 groups ranged from 58 to 69 at 12 weeks and 51 to 62 at one year in the ITT analyses, and 54 to 69 at 12 weeks and 48 to 62 at one year in the as-treated analyses, both of which are somewhat below the required 66 needed to detect statistical significance. The smaller number of patients in each group may have resulted in a slightly underpowered study which was not sensitive enough to detect a difference in pain or function scores between intervention groups. Although a larger sample may have detected statistically significant effects of active acupuncture relative to sham, the clinical relevance of such differences would be questionable. The observed between group differences were smaller than the MCIDs, and 95% confidence intervals indicated that the ranges of plausible between-group differences were unlikely to have included differences of any clinical importance.
- Regarding acupuncture recommendations, clinical guidelines for knee osteoarthritis vary from “conditionally recommend” to “advise against”.
- The authors diligently reported the attendance at acupuncture sessions in all 3 groups. Over 90% of participants in the needle and active laser groups attended at least 8 acupuncture sessions, however, only 75% of sham laser group participants attended at least 8 acupuncture sessions. Perhaps the sham laser group would have improved even more if their treatment attendance rate was higher.
- The percentage of allocated participants that declined treatment in the 3 groups (13%, 19% and 17%) was slightly above the mean of 13.8% for other Zelen-design trials. Since all patients allocated to a treatment group, regardless of whether they declined their allocated treatment or not, must be included in the analyses, this may have diluted the measureable effects of each acupuncture treatment. However, when analyzed as treated, primary outcomes did not differ between active and sham acupuncture.
- At 12 weeks, 26 (9%) of participants were lost to follow-up, and at the one year assessment 50 (18%) were lost to follow-up. A separate analysis also corrected for any bias this may have introduced and did not alter outcomes. Even though the sham laser group had a slightly greater proportion of the drop-outs, most drop-outs in all groups were due to non-interest, and it is unlikely this would bias the study’s outcomes.
- Limiting the study protocol to a total of 8 to 12 sessions of treatment, using a low dose of 0.2 J per point, and a low power setting of 10mW, together may have impacted the ability of the study to achieve the maximal therapeutic benefit of active laser for many patients

and thereby reduced the ability of the study to show an effect for this intervention. The clinical effectiveness of laser acupuncture requires dosages of at least 0.5 J per point. This would underestimate the effect of the intervention.

- The maximal therapeutic benefit of needle acupuncture may also not have been achieved due to inconsistent treatment frequencies used among participants, usage of non-standardized acupuncture points, common treatment regimens not followed, and no documentation on whether deqi sensation was experienced by the participant. Instead of a one year follow-up, a shorter term reassessment may have been better at capturing an effect.
- To summarize the results, for both “as treated” and ITT analyses at 12 weeks and one year, there were no significant differences in the primary outcomes of overall pain and function between any groups compared with each of the other groups. This means that all treatments were essentially equal in effectiveness. When comparing the 3 treatments to the control group for the ITT analyses, there were some modest reductions in pain for needle and laser, and in function for needle acupuncture. When comparing the 3 treatments to the control group for the “as treated” analyses, there were some modest reductions in pain and improvements in function for all three treatments. None of the reductions in pain or improvements in function for any of the analyses met the predetermined MCID’s, and thus are not clinically important effects.
- I agree with the authors that these statistically significant effects are non-specific, placebo effects arising from patient –provider interactions and are not true physiological effects. This explains why there were some significant results attained for each of the treatments when compared to the controls who did not have patient –provider interactions, and why no significant results were attained when treatments were compared to other treatments that provided patient –provider interactions, including the valid control of sham laser acupuncture.

Assessment:

- There is good evidence that the small therapeutic effects of needle acupuncture, active laser acupuncture, and sham laser acupuncture for reducing pain or improving function among patients older than 50 years with moderate to severe chronic knee pain from symptoms of osteoarthritis are due to non-specific effects similar to placebo, and that acupuncture should only be offered as an option to patients who express interest in receiving it, and who expect to benefit from it.

Reference:

- Zelen M. A New Design for Randomized Clinical Trials. *The New England Journal of Medicine* 1979; 300(22):1242-1245.