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Acupuncture and knee osteoarthritis: does dose matter?

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Osteoarthritis (OA) is an extraordinarily prevalent and disabling disease [1]. Current management options for pain and functional limitation are constrained by modest efficacy or a range of unwanted side effects. Our society is being impacted through underemployment and the opioid epidemic and our health care systems are overstretched, as a consequence of the trajectory of increasing joint replacement requirements [2]. In this context, development of new treatments or identification of efficacy of existing therapies to address the huge unmet need of pain are strongly desired.

Acupuncture is a component of traditional east Asian medicine and has been used as a healing practice for many centuries [3]. Acupuncture is generally thought to have arisen in China with documented clinical practice in the Huangdi Neijing "Yellow Emperor's Inner Classic" over 2000 years ago. However, ancient Chinese burial sites have uncovered acupuncture tools (Bian Stones) that predate this period. Following its development in ancient China, acupuncture spread throughout South East Asia, Europe, and is becoming increasingly popular in North and South America.

Acupuncture typically involves the insertion of thin (32-36 gauge) solid needles into specific points in the body (acupoints). Once needles are inserted, they may be stimulated mechanically, electrically, or thermally. Needles are then retained in the body for 20-30 minutes during a single session. When provided as a course of treatment, acupuncture is performed over multiple sessions spread over a number of weeks.

The efficacy of acupuncture in the context of pain, and knee osteoarthritis more specifically, is controversial. Initial literature struggled to consistently demonstrate efficacy of acupuncture over and above sham; however, the Acupuncture Trialist Collaborative showed in an individual participant meta-analysis (n=20,827 patients; 39 trials) that acupuncture was superior to sham acupuncture for multiple pain conditions: OA had an effect size of 0.20-0.30 [4]. While this was statistically significant ($p<0.001$), the clinical relevance is questionable, leaving most guidelines to conditionally recommend the use of acupuncture for OA [5, 6].

In this issue of the Journal, a multicentre randomized sham-controlled trial, recruited 480 participants with knee OA (KOA) who were randomly assigned to receive electro-acupuncture, manual acupuncture or sham acupuncture 3 times weekly for 8 weeks. Participants, outcome assessors and statisticians were masked to treatment group assignment. Compared with sham acupuncture, intensive electro-acupuncture resulted in less pain and better function at week 8 and these effects persisted through week 26. Intensive manual acupuncture had no benefit for KOA at week 8, although it showed benefits at week 26.

A key issue in the field of acupuncture research is the notion of "dose". It is unknown what the optimal dose of acupuncture is and even more importantly, how to classify dose. Does dose reflect the number of treatments, the number of needles, the depth of penetration, the amount or type of stimulation, or the duration of needle retention? In this study, the authors used 3 treatments a week, which is more frequent than typical studies done in the West and potentially may not be feasible in some health care settings. A recent systematic review suggests that treatment frequency matters and a dose of three sessions per week may be superior to less frequent treatment [7].

Another key issue in acupuncture research is when to assess efficacy. Some prior studies have assessed treatment efficacy shortly after the last acupuncture treatment. However, results from the Acupuncture Trialist Collaborative have demonstrated that treatment effects can persist up to 3 to 12 months following treatment. The clinical usefulness of this means that a patient may not need to seek acupuncture for months after the initial round of treatments has completed. Indeed in this present study, the authors find that acupuncture effects persisted up to 26 weeks post treatment and for manual acupuncture versus sham acupuncture, surprisingly the effects become significant at 26 weeks, when they were not at 8 weeks.

In the present study, the response rates at week 8 were 60.3% for electro-acupuncture, 58.6% for manual acupuncture, and 47.3% for sham acupuncture. The between-group differences were modest and favoured EA. A remarkably consistent finding in the acupuncture clinical literature in pain is the marked improvement of patients to sham acupuncture. This has been attributed to a high placebo response with this intervention. Indeed the field of placebo effects has benefited somewhat from studies of acupuncture. When acupuncture is compared to more non-invasive controls or a wait list, the effect size of acupuncture for OA increases to 0.50-0.60 which is of clinical importance [4]. Interestingly sham acupuncture is more effective than a placebo pill for pain [8].This suggests that not all placebos are equal (for example placebo pills may have less analgesic action than placebo surgery) resulting in potentially more invasive placebo maneuvers having more clinical action. Approximately 40% of participants in this trial had received acupuncture before; however, this did not appear to influence response rate.

Another aspect of acupuncture therapy to consider is safety. Acupuncture is generally considered to be safe with few adverse events seen in the literature. This is important to consider as some existing treatments for KOA come with significant side effects e.g. opioids and gastrointestinal bleeding with NSAIDS. As a consequence, the number needed to treat relative to the number needed to harm for this intervention is quite favorable. Another factor to consider with acupuncture is its cost, particularly considering the number of visits required and that many health systems don't reimburse for this treatment leading to substantial out of pocket expense. When examined in Europe, acupuncture in general, has been shown to be cost-effective [9-11].

This trial has some notable limitations. The significant size of the placebo effect seen in the sham acupuncture group means that some of the action of this intervention is simply needle insertion, irrespective of location. Other contextual effects and non-needling components have been demonstrated to be important for this intervention [12]. Also, it is difficult to double-blind an acupuncture study as the acupuncturist typically knows if they are performing real or sham acupuncture. There is a double-blind needle that has been developed wherein the acupuncturist

does not know if they are inserting a needle into the skin or not, but those sham needles were not used in this study. In future work, it would be important to clarify the contribution expectation of efficacy communicated by those administering the treatment had, as prior work demonstrated this was substantial [13]. For clinicians, recognising the potent effects of placebo, the optimisation of contextual effects, through enhanced care is worthy of further consideration [14].

So is acupuncture ready for prime time and further dissemination? Acupuncture is already widely practised and readily available in many countries and healthcare systems. In some systems, reimbursement is limited, which may be a barrier to further implementation and heterogeneity of protocols used as an additional concern. Will guidelines ultimately take on this evidence and change their conditional recommendations to be more positive? Time will tell. In the interim, there continues to be further need for research, in particular, dose response relationships, effects of blinding the acupuncturist, feasibility of 3 times weekly regimens and clarifying the mechanism of effect, particularly given the persistence of benefit. There is some suggestion that the benefit is partly mediated by changes in major inflammatory factors (TNF-α, IL-1β and IL-13) which may in part explain the persistence of effect [15].

Competing interest statement

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