

Acupuncture for Chronic Knee Pain: A Critical Appraisal of an Australian Randomized Controlled Trial

Kehua Zhou, MD, DPT, LAc,^{1,2} Arthur Yin Fan, CMD, PhD, LAc,³ and Tong Wang, PhD⁴

ABSTRACT

Background: Chronic knee pain caused by osteoarthritis (OA) is common in the general population. For knee OA with chronic moderate-to-severe pain, acupuncture treatment is recommended. Previous randomized controlled trials (RCTs) and meta-analyses have indicated that acupuncture can decrease pain and improve function in patients with knee OA. Interestingly, a recent Australian RCT by Hinman et al. reported that acupuncture was not beneficial for knee OA.

Objective: As the quality of the Hinman study is of significance to clinical decision-making, the current authors decided to perform a critical appraisal of this study.

Methods: Critical appraisals were performed on the study design, statistical methods, and conclusions. Ethical concerns and the use of control groups are discussed in this article.

Results: The RCT by Hinman et al. had multiple flaws in study design, acupuncture protocol, sample-size calculation, results analyses, and thus conclusions; in addition, there are ethical concerns regarding bias from a high likelihood of conflicts of interest for the researchers.

Conclusions: Rather than adding to the understanding and information about acupuncture's benefits in knee OA at 12 weeks, the study by Hinman et al. added more confusion to the available evidence. The results and conclusions of this RCT, thus, may not be valid or appropriate. For the interests of patients, clinicians, and health care policy makers regarding the use of acupuncture for chronic knee pain, the abovementioned flaws should be taken into consideration. In addition, ethical concerns and conflicts of interest in the study may motivate medical scientists to reconsider the value of this study.

Key Words: Acupuncture, Chronic Knee Pain, Critical Appraisal, Knee Osteoarthritis

INTRODUCTION

CHRONIC KNEE PAIN caused by osteoarthritis (OA) is common in the general population, with prevalences of: 27% in people younger than age 70; 34.1% among people ages 70–79; and 44% in people age ≥80.¹ Symptoms of knee OA include significant impairments and functional limitations in stair climbing, walking, and housekeeping; thus the condition causes considerable disability.² Current evidence-based conservative management of knee OA consists of weight loss; exercises;

orthotics; and pharmacologic agents, including nonopioid or opioid analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) or coxibes, and intra-articular glucocorticoids.³ Nonetheless, management of knee OA remains unsatisfactory because of issues related to patients' adherence to nonpharmacologic interventions and side-effects of drugs. For knee OA causing chronic moderate-to-severe pain, acupuncture treatment is recommended by the American College of Rheumatology.³

Acupuncture, an intervention with thousands of years of history, has been widely used in China and eastern Asian

¹Department of Health Care Studies and ²Daemen College Physical Therapy Wound Care Clinic, Daemen College, Amherst, NY.

³McLean Center for Complementary and Alternative Medicine, PLC, Vienna, VA.

⁴American College of Acupuncture and Oriental Medicine, Houston, TX.

countries for managing chronic knee pain.⁴ Acupuncture's use for addressing knee OA is becoming increasingly popular in Western countries because of the favorable results of acupuncture with respect to relieving pain and improving function in high-quality randomized controlled trials (RCTs).⁵⁻⁹

For example, Manheimer et al.⁵ reported that, compared to sham acupuncture or education, acupuncture produced better improvements in functional activities after 8 and after 26 weeks of treatment. Vas et al.⁶ reported that 12 weeks of acupuncture decreased pain and improved physical and psychological functioning. Similar results have also been reported by other researchers.⁷⁻⁹ Compared to minimal acupuncture or no acupuncture, acupuncture was found to improve pain and joint function after 8 weeks of treatment and these therapeutic effects decreased over time at 52 weeks' follow-up.⁷ Williamson et al.⁸ reported that 6 weeks of acupuncture, compared to physical exercises, could provide similar pain relief to patients with severe knee OA. In addition, Whitehurst et al.⁹ reported that, compared to exercise and advice alone, the addition of acupuncture to exercise and advice appeared to be a cost effective treatment for aspects of quality-adjusted life-years.

Nonetheless, conflicting results exist in the literature on RCTs on acupuncture for knee OA. For example, Foster et al.¹⁰ reported that the addition of acupuncture (six sessions of 30 minutes over 6 weeks) to exercise and advice did not provide additional benefits with respect to pain intensity, compared to exercise and advice alone. Suarez-Almazor et al.¹¹ reported that a minimal amount of 10 electroacupuncture treatments over 6 weeks was not superior to sham acupuncture for pain in knee OA, but stated that acupuncturists' styles had significant effects on pain reduction and satisfaction.

An article by Hinman et al. (the Hinman study),¹² published in 2014, seems to add more complexity to the issue regarding acupuncture effects on knee OA. Hinman et al.¹² reported minimal pain decreases with acupuncture at 12 weeks, and concluded that acupuncture conferred no benefits in pain relief or function for patients older than age 50 with moderate-to-severe knee OA.

Interestingly, the available meta-analyses favor acupuncture as a good referral option for chronic knee pain (caused by knee OA) or pain in general.¹³⁻¹⁵ For example, in a meta-analysis published in 2010, Manheimer et al.¹³ reported that, after 8 weeks and after 26 weeks, acupuncture may lead to small reductions of pain and small improvements in physical function of patients with knee OA. These results were supported by another meta-analysis in 2012 regarding acupuncture for chronic pain in which researchers analyzed results of 29 of 31 eligible RCTs, with a total of 17,922 patients, and concluded that acupuncture is effective for the treatment of chronic pain.¹⁴ A later meta-analysis performed specifically for knee OA was published in 2013; the researchers reported

that acupuncture seemed to be more effective than other physical treatments for alleviating pain in knee OA in the short-term.¹⁵

The practice of modern medicine depends on available research—most often results from RCTs and meta-analyses—thus, the quality of research studies is of great significance for clinical decision-making, especially with respect to selection of interventions and parameters/dosages of interventions. As meta-analyses continue to build on available RCTs, additional high-quality RCTs are needed to add to our understanding of acupuncture's effects on knee OA, for example what optimal dosages and treatment frequencies should be. The Hinman study¹² provides researchers and clinicians with a potential opportunity to understand the topic better.

Nonetheless, as the study was published fairly recently, a critical appraisal of the study seems to be needed to explore the quality of evidence before reaching a new understanding. Thus, the purpose of the present article is to appraise the recently published RCT by Hinman et al. critically.¹²

APPRAISAL OF THE STUDY DESIGN

Multiple concerns exist in the study design of the research by Hinman et al.¹² In a vigorous RCT, ideally, investigators should focus their RCT on a single major objective,¹⁶ such as acupuncture for chronic knee pain. With respect to the design of the control group, researchers should compare a new experimental therapy group (acupuncture in the study by Hinman et al.¹²) to a "no therapy" (e.g., sham acupuncture control) group,¹⁶ and, if possible, to a positive control condition, using a treatment that has been tested as an effective therapy.

In the Hinman study,¹² four groups were included, namely, (1) the control group, (2) a needle acupuncture group, (3) a laser acupuncture group, and (4) a sham laser acupuncture group. In this study, Hinman et al.¹² apparently tested two new interventions, namely, acupuncture and laser acupuncture. Rather than establishing a sham acupuncture group, Hinman et al.¹² compared needle acupuncture against sham laser treatment as one of the controls in the study.

In the Hinman study,¹² minimal clinically important difference (MCID) was determined by 6 rheumatology experts as being a 35% fall in baseline pain score, which is equal to an effect size (ES) of 0.6 for function measures, per calculations performed by White and Cummings.¹⁷ An ES of 0.6 is higher than the generic value of 0.5 recommended by the National Institute for Health and Care Excellence (NICE) for testing NSAIDs.¹⁸ The MCID was based on expert opinions, which can sometimes be invalid and unreliable. In addition, selection of ES as 0.6 (per calculation based on the MCID) in the study¹² created a stricter requirement to prove the efficacy of acupuncture over NSAIDs.

Interestingly, as noted by Fleckenstein and Banzer,¹⁹ patients were treated with NSAIDs without reporting dosages and frequencies in the Hinman et al. study.¹² In addition, Hinman et al.¹² also reported use of other pain medications in the study. However, while not providing information regarding dosages and frequencies of these pain medications, more importantly, Hinman et al.¹² did not report the dropout rates for patients taking pain medications or possible significant changes in drug therapy regimens during treatment in these patients. With a sample size of 70 patients in each group with more than half of the patients taking pain medications in each group, the aforementioned effects of pain medications should be addressed appropriately before final analyses of acupuncture effects were considered by Hinman et al.¹²

In addition, Hinman et al. failed to comply with the Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) statement on acupuncture trials,²⁰ and did not report information related to acupuncture rationale, details of needling (i.e., depth of needle insertion and possible needle manipulations), and treatment regimen. The acupuncture treatment protocol in the Hinman study,¹² was stated as “once or twice weekly for 12 weeks with eight to 12 sessions in total.” As argued by He,²¹ this acupuncture protocol may not be appropriate and, thus, may be considered as suboptimal. Even with the suboptimal acupuncture protocol, Hinman et al. did not report patient compliance. As pointed out by He,²¹ all the high-quality RCTs published utilized acupuncture with a higher frequency and for a longer time; thus, the dosage of the acupuncture protocol is a concern.

Acupuncture De Qi is widely recognized as an important factor for the therapeutic effectiveness of acupuncture;²² however, Hinman et al.¹² did not report any information related to De Qi, the premise of acupuncture effectiveness. As a result, none of these items were included in the discussion section of the final report by Hinman et al.¹²

APPRAISAL OF THE STATISTICAL ANALYSIS

Concerns of statistical analysis include sample size calculation, use of a Zelen design, and intention-to-treat analysis. As stated by White and Cummings,¹⁷ with a control group of sham laser acupuncture, a sample size of 800 is likely to be needed to detect the effects of acupuncture. In addition, in a Zelen-design RCT, the sample size will be larger than a traditional RCT because of the increased chance of patient dropouts from the original group(s) and switching of patients to other groups.²³ However, only 70 patients were included in each group of the Hinman study.¹² Although details of sample-size calculation were described in a previous publication by this group of researchers,²⁴ the number of 70 subjects per group still raises concern about the accuracy of the calculation.

A Zelen design can overcome uncomfortable feelings experienced by patients in a study and lessen Hawthorn effects.^{23,25} However, dropout rates in Zelen design studies are usually high. In the Hinman study,¹² the dropout rates were 2.82% (2/71) in the control group, 22.86% (16/70) in the acupuncture group, 18.31% (13/71) in the laser acupuncture group, and 22.86% (16/70) in the sham laser acupuncture group at 12 weeks. According to acceptable standards for RCTs, dropout rates <10% are acceptable, dropout rates between 10% and 20% indicate that the resulting data quality is poor, and drop-out rates of more than 20% means that the data quality is considered very poor.²⁶ For poor quality data (a dropout rate of $\geq 20\%$), no adequate recommendation can be provided.²⁶ As stated by Unnebrink and Windeler, “no statistical methods will ever be able to replace missing information and the optimal solution is to keep the missing data to a minimum.”²⁷

Nonetheless, chained equations with predicative mean matching were used by Hinman et al.¹² for the final analyses of the study; estimated data were used for 10 patients (18.52%) in the acupuncture group, 7 patients (12.07%) in the laser acupuncture group, and 4 patients (6.90%) in sham laser group at 12 weeks. Consequently, in total, 21 patients actually did not receive any corresponding intervention, and yet, their data were included in the original group for the intention-to-treat analysis. Questions exist about whether or not this is the correct way to process the data in such circumstances (high dropout rate, possible small sample size, and flaws in study design).

APPRAISAL OF CONCLUSION DRAWING

Although flaws existed in the study design and sample-size calculation, Hinman et al.¹² did find that acupuncture produced modest reduction in pain and improvements in function, but the effect was not maintained at 1 year. Nonetheless, these authors drew a conclusion based on the previously set MCID, stating that needle acupuncture confers no benefit for patients with knee OA. Given the possible flaws in the establishment of the MCID, the data in the RCT by Hinman et al.¹² were likely to prove, at least, therapeutic effectiveness of acupuncture on knee OA at 12 weeks.

In addition, as stated by Lao and Yeung,²⁸ Hinman et al. failed to provide rationales for a 1-year follow up after only 8–12 acupuncture sessions over a 12-week period. Patients with moderate-to-severe knee OA are likely to get worse with time without treatment; again Hinman et al.¹² did not provide sufficient information regarding NSAID use in the final report. Lack of a rationale in the follow-up protocol resulted in a conclusion of a lack of association between the follow-up results and acupuncture treatments. Thus, the conclusion should be rewritten.

ETHICAL CONCERNS AND CONTROL GROUPS

As stated by Li,²⁹ based on the information provided in the original trial registration in 2009³⁰ and the investigators' publication of the protocol in 2012,²⁴ needle acupuncture was most likely to be a positive control for testing the effects of laser acupuncture in the original design of the trial. Without clear evidence to support the original plan to test the efficacy of needle acupuncture in the study design and without a logical explanation in the discussion section of the published final report for the discrepancy between the study objectives of the original study protocol²⁴ and those in the final report,¹² readers have the right to believe that the analyses for the comparison "needle acupuncture vs. sham laser" were based on *post hoc* hypotheses.

The inference of *post-hoc* analyses in the Hinman et al. study¹² is supported by the flawed establishment of control groups and blinding in the study. The sham laser acupuncture actually could not be treated as a valid negative control for needle acupuncture, because these two interventions—needle acupuncture and sham laser acupuncture—are not comparable in either intervention characteristics or physical appearance. In addition, no blinding efforts were made for the needle acupuncture and laser acupuncture groups. In contrast, blinding was only considered between laser acupuncture and sham laser acupuncture. Thus, even if needle acupuncture were included in the primary hypotheses, as reported by Hinman et al. in the final report,¹² this would be a major flaw in the trial design, because the trial did not follow the scientific principles regarding blinding and establishment of control groups for an RCT of acupuncture. Consequently, the current authors believe that the comparisons between needle acupuncture and laser acupuncture were based on *post-hoc* analyses.

Per clinical research guidelines,³¹ analyses—and thus conclusions—based on *post-hoc* hypotheses and analyses must be clearly stated in final reports. *Post-hoc* analyses provide retrospective rather than actual prospective results. As the original sample-size calculation and other preparatory measures were aimed for a prospective RCT, the results of *post-hoc* analyses have to be interpreted with caution. Nonetheless, Hinman et al. did not provide necessary information regarding the differences between objectives in the original protocol²⁴ and those in their final report.¹² Without appropriate justification, the results from retrospective data analyses should not be used for the conclusions of prospective trials.

There are additional concerns with respect to the Zelen design, which may be highly unethical without careful consent procedures,²³ especially given the fact that acupuncture has been proven to be effective for treating knee OA in multiple RCTs,⁵⁻⁹ whereas little information is available regarding the efficacy of sham and laser ac-

puncture. Consequently, allocation of patients receiving corresponding treatments thus poses ethical concerns.

DISCUSSION

The value of the Hinman study is questionable, given the flaws in study design, result analyses, and conclusions, and ethical concerns; conflicts of interest of the investigators in the study add further concerns about the reliability and validity of the study.¹² As stated at the end of the published report,¹² the authors have multiple potential or actual conflicts of interests.¹² Declaration of potential conflicts of interest is routine for publication; the general public, and even academic professionals, usually do not pay much attention to this often purposely de-emphasized section at the end of a report. Nonetheless, alarming concerns should be raised and the professionals and the general public should be reminded about these concerns regarding the published study by Hinman et al.¹²

For example, Hinman and Bennell received royalties from the sales of a shoe (Gel Melbourne OA) by Asics. As indicated by the name of the shoe company, this shoe is claimed to be effective for treating OA, and the authors of that article have been designing and performing a study for the company to test the shoe's efficacy on knee OA.³²

As various high-quality RCTs reported efficacy of acupuncture in knee OA,⁵⁻⁹ a negative report on acupuncture for knee OA is likely to push consumers/patients and the general public to seek other options for the treatment of knee OA, including the shoe from Gel Melbourne. Additionally, after the study publication,¹² Reuters reported: "As alternatives to acupuncture, Hinman said physical therapy, knee braces and exercise can all help alleviate chronic knee pain."³³

"Conflicts of interest represent the potential for biased judgment, but are *not* an indicator of the likelihood or certainty that such judgments or compromises will occur," according to De Angelis et al.³⁴ However, as indicated by Hirsch,³⁵ a *conflict of interest* exists with an unstated presumption of guilt until proven innocent. For the serious concerns of bias resulting from conflicts of interest, an editorial by De Angelis et al. in the *Journal of the American Medical Association (JAMA)* stated that "all journals *must* seriously consider funding sources and authors' disclosed financial conflicts of interest and financial relationships when deciding whether to publish a study or review."³⁶ Although *JAMA* had published the acupuncture article in October 2014,¹² the significant likelihood of bias caused by conflicts of interest of the authors should be alarming to patients, clinicians, and researchers upon understanding and analyzing the results of the study, given that the shoe article³² was published in the same year in another journal.

As some of these concerns were published, Hinman et al. did provide replies to some of the concerns. Regarding the concern of De Qi reporting, Hinman et al. answered: “Consistent with clinical practice and acupuncture training in Australia, acupuncturists aimed for deqi with needle acupuncture.”³⁷

With respect to requirements in the STRICTA guidelines,²⁰ Hinman et al.³⁷ cited an article (a meta-analysis) stating that no evidence indicates that needle numbers or placements; use of electric stimulation; or numbers, frequencies, or durations of treatments influence acupuncture outcomes.³⁸ Nonetheless, in that same meta-analysis, MacPherson et al.³⁸ did report that, upon comparing acupuncture patients to nonacupuncture controls, better pain outcomes were observed when more needles were used ($P=0.010$) and, this effect was also seen according to a patient level-analysis involving a subset of five trials when a higher number of acupuncture treatment sessions were provided ($P<0.001$).

Regarding the 1-year follow-up concern raised by Lao,²⁸ Hinman et al.³⁷ answered that “our no-treatment control group did not support this assertion because participants tended to improve slightly over 1 year.”

Regarding the concern related to the use of MCIDs, Hinman et al.³⁹ stated that White and Cummings¹⁷ focused solely on MCIDs as a dimensionless quantity. Hinman et al. also stated that they believed the approach for using MCIDs by White and Cummings¹⁷ confounds the absolute size of the effect.

With respect to ethical concerns that were raised by Li,²⁹ regarding discrepancies of the objectives between the original study protocol²⁴ and the final report¹² Hinman et al.³⁷ admitted the discrepancies existed but provided their understanding of the issue based on their description of statistical analyses in their published protocols. Additional information regarding the use of sham laser acupuncture as a control, the presentation of secondary results in the report, and the parameters of laser acupuncture in the study was also provided by the investigators to answer these concerns.^{37,39}

CONCLUSIONS

Apparently, the article entitled, “Acupuncture for Chronic Knee Pain: A Randomized Clinical Trial,” by Hinman et al., that appeared in *JAMA*, 2014,¹² has multiple flaws in study design, acupuncture protocol, sample-size calculation, result analyses, and conclusions. Instead of adding to the understanding of and information about acupuncture benefits for patients with knee OA at 12 weeks, the study added more confusion to the available evidence. Although the Hinman study¹² may provide clinicians and medical scientists with new information regarding a suboptimal dosage of acupuncture therapy for knee OA in a very restricted clinical setting, this information may be inaccurate, as multiple flaws exist throughout the study. Unfairly, these concerns about this

study are usually not reported by news agencies. Thus, the widespread influence by the probably biased results and conclusions of the Hinman study¹² will likely continue. For the interests of patients, clinicians, and health care policy makers regarding acupuncture for chronic knee pain, the abovementioned flaws should be taken into consideration. In addition, ethical concerns and conflicts of interest in the Hinman study¹² may urge our medical scientists to reconsider the value of the Hinman study.¹²

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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Address correspondence to:
 Kehua Zhou, MD, DPT, LAc
 Department of Health Care Studies
 Daemen College
 4380 Main Street
 Amherst, NY 14226
 E-mail: kzhou@daemen.edu