

Methodological challenges in design and conduct of randomised controlled trials in acupuncture

Yu-Tong Fei and colleagues examine the problems with designing and implementing trials of acupuncture

Acupuncture is one of the most commonly used complementary and integrative therapies worldwide. During the past five years, results of over 4000 acupuncture trials have been published. As with other non-pharmacological interventions, challenges exist when designing and conducting randomised controlled trials in acupuncture. We discuss the most important challenges specific to acupuncture, some of which may apply to other non-pharmacological therapies. Detailed solutions to these challenges are discussed in another article in this series.¹

Simplified and poorly documented protocols

Like surgery, behavioural therapy, and other non-pharmacological interventions, acupuncture treatment has a number of components. Although the selection of acupoints is usually documented in randomised controlled trials,² other vital elements that acupuncturists consider equally important are often under-reported and oversimplified.³ These include acupuncture dose, length of needles, depth of insertion, number of needles, and manipulation

after insertion; patient-doctor communication during the diagnostic and treatment process; expertise of acupuncturists; combination with other therapies; and personalisation of the intervention.^{4,5}

Complex intervention

Methods to locate acupuncture points vary. In 2008, the World Health Organization regional office for the Western Pacific published a manual of standard acupuncture point locations,⁶ which has been well adopted. However, there are other acupoint location systems which vary somewhat from the WHO standards but are esteemed by specific schools of acupuncturists, such as Yang Jiasan's acupoint system.⁷

Acupuncture theory varies, contributing to differences in treatment regimens. Practitioners using traditional Chinese medicine theory to guide acupoint selection might prefer to use meridian based or symptom based acupoint selection methods. Western medical acupuncture bases its treatment on sensory stimulation. As an acute pain stimulus, acupuncture can elicit a euphoric feeling by increasing release of opioid peptides (such as endorphins and dynorphins), thereby alleviating ongoing pain.⁸ Acupuncture stimulation serves the function of a stimulus and can achieve muscle reflex relaxation.⁹ To treat musculoskeletal pain,¹⁰ most western practitioners in primary care, rheumatology, orthopaedic, and pain clinics will likely choose Ashi or trigger points (box 1).

Current evidence for acupoint specificity varies and complicates selection of treatment regimens. Acupoint specificity refers to different treatment effects that the selection of acupoints brings. A randomised controlled trial investigated acupuncture as an adjunct to antianginal drug therapy for chronic stable angina. The study showed that stimulating acupoints on the disease affected meridians resulted in four fewer angina attacks than stimulating acupoints on non-affected meridians (95% confidence interval -2.43 to -5.71) during week 13 to 16.¹⁵ However, individual patient data meta-analysis on acupuncture

for chronic pain showed no significant association between pain relief and the acupoint prescription (fixed, flexible, and individualised prescription).¹⁶

Acupuncture treatment dosage can differ significantly and impact the treatment effect.¹⁷ Duration, intensity, repetition intervals, and number of treatments and needles are important components of acupuncture dosage. Existing randomised trials of acupuncture have, however, either under-reported this critical information or used vastly different treatment dosages. For example, the latest Cochrane review¹⁸ addressing acupuncture for the treatment of depression found that only two thirds of the included randomised controlled trials reported needling duration, while in 63 included trials, treatment frequency varied from twice daily to once a week.

Existing evidence has explored the impact of acupuncture dose on treatment effect but rarely addressed the possible interaction between dose components. An individual patient data meta-analysis of acupuncture for chronic pain found a significant association between pain relief and the number of acupuncture treatment sessions but not de qi (box 1), frequency of sessions, duration of sessions, and number of needles used.¹⁶ Other studies found a larger number of needles,¹⁹ higher intensity,²⁰ and greater frequency of treatment²¹ may increase treatment effects. For example, in a randomised controlled trial on knee arthritis, electroacupuncture (>2mA) with a strong current relieved more pain.²² When designing randomised controlled trials in acupuncture, large variability and limited research evidence make it challenging for trialists to determine the appropriate treatment dosage.

Needle manipulation technique may affect the magnitude of the treatment effect.²³ The complex manipulation techniques include lifting, thrusting, twirling range, de qi sensation, and frequency of electrostimulation. Devices might help to detect and standardise the needle manipulation features but are not yet widely known and rarely used in trials.²⁴

KEY POINTS

- Acupuncture is a complex intervention and when tested in trials is often oversimplified and poorly documented
- Acupuncture therapies are complex because of their multifaceted techniques, dependence on expertise, often combined therapies, and highly personalised treatment regimen
- Contextual effects, especially patient-practitioner interaction and participants' expectations, may impact the treatment effect of acupuncture and a trial's feasibility
- Sham acupuncture is difficult to implement and has a specific effect that might result in underestimation of the real acupuncture treatment effect

Box 1: Acupuncture terminology

- *Acupuncture*—Any type of intervention involving penetration of the skin with needles or stimulation of certain points with other methods regardless of its theoretical basis, excluding forms combined with moxibustion or medication such as warm needling, acupoint injection, or hydro-acupuncture¹¹
- *Ashi point*—An acupuncture point with no specific name or definite location, the site of which is determined by tenderness or other pathological responses¹²
- *De qi sensation*—A sensation patients describe as pulling, numbness, heaviness, dullness, or aching that they experience during needling and which the acupuncturists might feel through sensations conveyed via the needles¹³
- *Trigger point*—A sensitive area of the body that produces a reaction elsewhere when stimulated¹²
- *Manual acupuncture*—The most commonly used type of acupuncture uses skin penetration with thin, solid, metallic needles manipulated by the hands¹²
- *Electro-acupuncture*—Additional electric stimulation following needle insertion¹²
- *Syndrome pattern differentiation and its treatment*—In Chinese medicine, it refers to the diagnosis based on a comprehensive analysis of symptoms to determine the cause, nature, and location of the illness. Even within the same disease, different syndrome patterns may dictate different treatments. When selecting an acupuncture treatment regimen, syndrome pattern differentiation can guide the meridian and acupoints selection. For instance, in two patients with upper respiratory infections caused by the same virus, the patient whose primary symptom is nasal congestion may have an important different syndrome pattern from that of a patient whose primary symptom is high fever. Acupoint selection can therefore be different for these patients¹²
- *Meridians*—Primary and collateral channels, regarded as a network of passages through which Qi (the vital life force in the body that acupuncture is designed to regulate) circulates and along which acupoints are distributed. Over 400 acupoints lie on 14 meridians over the human body
- *Constitution*—The characteristics of an individual, including structural and functional characteristics, temperament, adaptability to environmental changes, and disease susceptibility¹²
- *Tube needle*—A type of acupuncture delivery method that consists of two parts: a needle and a plastic tube. Practitioners will insert the needle into the skin through the plastic tube¹⁴

Importance of expertise

As a non-pharmacological intervention, the expertise of the practitioner who delivers acupuncture might influence its effectiveness. As recommended in the Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA),²⁵ trialists should report acupuncturists' expertise.

The evidence regarding the impact of expertise is, however, conflicting. An individual patient data meta-analysis based on acupuncture trials for pain conditions included 39 trials enrolling 20 827 patients. Almost all participants (97.3%) lived in western countries. Of the 39 trials, 14 (36%) had no requirement for acupuncturists to have clinical experience, 20 trials (51%) required between six months and four years' experience, and five trials (12.8%) at least five years' clinical experience. Results revealed no apparent association between experience and the magnitude of the treatment effect.¹⁶ Between trials comparisons are, however, less robust than within trial comparisons, and a single trial not included in the meta-analysis reported that senior acupuncturists achieved a larger treatment effect than their juniors.²⁶

Used as combination therapy and highly personalised

Acupuncture regimens often include conventional treatments and multiple acupoint

stimulation therapies, such as manual or electro-acupuncture or body acupuncture plus auricular therapy. With regard to personalisation in determining treatment, the acupuncturist in traditional Chinese medicine considers the patient's syndrome pattern differentiation or meridian or body constitution (box 1). Patients with the same disease diagnosed by western medicine may show different syndrome patterns; acupuncture treatments vary accordingly.²⁷

In clinical trials, many researchers prefer fixed acupuncture treatment protocols that neglect syndrome patterns or semi-fixed treatment protocols based on simplified pattern differentiation, rather than complex real world treatment packages of multiple acupuncture interventions, to reduce the difficulty of treatment quality control. This simplification of the intervention in clinical trials may provide only indirect evidence for treatments actually used in practice, possibly resulting in an underestimation of acupuncture's treatment effect as administered in (at least eastern) clinical practice.

Trials often overlook contextual effects

The context in which clinicians deliver healthcare interventions can improve or reduce the overall effect of an intervention. Like other non-pharmacological interventions, factors such as the patient-practitioner relationship and patients'

expectations could impact acupuncture's effectiveness.²⁸

Importance of patient-practitioner interaction

The process of establishing a confident and trusting relationship can be critical to an intervention's impact.^{4,29} Patients have identified a contrast in their relationship between western biomedicine practitioners and acupuncturists.⁴ Traditional Chinese medicine diagnostic and management procedures include listening to patients speaking about their health condition and attention to patients' feeling, mood, diet, rest, physical exercise, touching of the skin, and peaceful time spent together; each communicates that the clinician's knowledge of their particular experience is essential. The process tends to build a close relationship between acupuncturists and patients.³⁰

Participants' expectations can modify treatment effect

Eight hundred and sixty four patients participating in four different trials investigating migraine, tension-type headache, chronic low back pain, and knee osteoarthritis were randomised to eight weeks of acupuncture treatment or sham acupuncture (superficial needling of non-acupoints).³¹ After adjustment for confounders including intervention group, age, sex, and duration of complaints, in comparison with baseline patients in both standard and sham acu-

puncture groups with a high expectation of benefit proved more likely to achieve a reduction in pain of more than 50% than those with a low expectation (odds ratio of high to low expectation 1.67, 95% confidence interval 1.20-2.32).³¹ Results are consistent with neuroscience research suggesting that anti-analgesic expectancy could block analgesia procedures and reduce pain relief.³² Trialists are increasingly making use of participants' expectations measures, such as the acupuncture expectancy scale, a validated instrument that measures the benefits patients perceive they would gain from acupuncture.³³

Prior expectations towards acupuncture may also influence patient enrolment and retention in clinical trials. Patients who hold a strong belief in or against acupuncture treatment may decline participation, either afraid of being allocated to the sham group or unwilling to accept acupuncture treatment. If they do enter a trial, their prior beliefs may influence compliance and trial retention.³⁴

Sham acupuncture is problematic

Aside from specific effects, an intervention may also have non-specific effects. Observation, assessment, and therapeutic rituals may elicit non-specific effects.³⁵ Trialists often employ a placebo control with blinding of patients to differentiate the non-specific effect of the target intervention. There are, however, challenges in using placebo control in acupuncture trials.

To achieve blinding, trialists have used many types of sham acupuncture. Sham acupuncture without skin penetration, such as the retractable blunt needle, is one of the earliest sham acupuncture inventions.³⁶ Tube needles can hide the entire treatment process from view, but the procedure neither allows the angled insertion or manipulation technique after insertion nor applies to all acupoints (for instance, points on fingers and scalp).³⁷ More importantly, it might not adequately blind the participants, particularly those who have experienced previous acupuncture treatment.³⁸ Sham acupuncture may therefore aim to simulate the experience of optimal acupuncture more closely by more shallow insertion of needles in suitable acupoints; not undertaking subsequent manipulation; selecting acupoints in the relevant meridians but not specific to the health condition; selecting acupoints in irrelevant meridians; selecting skin areas close to but differing from the optimal acupoints; or some combination.^{39 40} Though the

acupuncturist will remain unblinded, this can blind patients more successfully.

However, a serious problem exists with sham acupuncture. Evidence suggests needle insertion or even skin touching creates specific effects.⁴¹ Thus, the effects of sham acupuncture may be similar to—though presumably lesser—optimally performed acupuncture. Additional evidence comes from the work of Harris et al, who found that acupuncture increases central μ -opioid receptor binding potential, while sham acupuncture reduces or does not change it,⁴² and from the work of Zucker et al, who reported a larger pain reduction when using sham over real acupuncture in fibromyalgia patients with lower pain thresholds.⁴³ Furthermore, specific effects of different types of sham stimulation may differ: penetrating needle sham, in comparison with other shams, showed the largest chronic pain relief.¹⁶ The crucial message from this work is that trials using sham acupuncture may underestimate acupuncture's treatment effect.

Implications for future trials

Acupuncture originated from a historical system of physiology, pathology, and treatment philosophy. However, the modern context requires alignment with current scientific methods, techniques, and findings. Modern basic science is now tackling the mechanisms of acupuncture effects. For example, the 2021 Nobel Prize research findings addressing piezo receptors for touch sensations⁴¹ may shed light on how penetrating or non-penetrating needling initiates human physical reaction. Current research priorities include investigating contextual effects, acupoint specificity, and the specific effect of sham acupuncture. When designing randomised controlled trials in acupuncture, trialists should consider the relevant components (as mentioned above) to determine the appropriate treatment dosage to achieve the optimal treatment effect. Organisations, in particular WHO, could involve prestigious academic societies and leading international acupuncture trialists to develop international guidance that facilitates development of acupuncture treatment protocol.

Conclusions

Randomised controlled trials of acupuncture face specific challenges. Firstly, acupuncture treatment protocols are often simplified and poorly documented with considerations that include acupuncture techniques varying in the underlying theory and thus methods to locate acupoints,

treatment dosage and needle manipulation techniques, expertise of those delivering the acupuncture treatment, combination therapies, and, particularly in the eastern Asian countries, individualised treatment regimens. Secondly, contextual effects of treatment, including therapeutic patient-practitioner interaction and participants' expectations, are often overlooked. Thirdly, in view of the complex nature of the acupuncture intervention, sham acupuncture is both difficult to implement and might have specific effects, therefore underestimating the optimal treatment effect of acupuncture.

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