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Using the right design controls for acupuncture trials: Methodological rigor and validity in research

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ABSTRACT

Acupuncture treatment can be defined as a medical procedure with an acupuncture needle at acupoints. Establishing suitable control settings is essential, based on the target elements of the acupuncture therapy. In order to properly design a clinical trial or an experiment, a control group must be established. Here, we overview the significance of the control group and its limitations in acupuncture research. Clinical trials have employed a variety of study designs and controls for acupuncture treatment in order to compare the effects of actual treatments with control groups that include no treatment or treatment as usual, sham acupuncture at true acupoints, real acupuncture at non-acupoints, and sham acupuncture at non-acupoints. In order to determine the point-specificity of acupuncture, real acupuncture at non-acupoints should be taken into consideration, whereas sham acupuncture at the same true acupoints should be used to determine the needling-specific effect of acupuncture. It is crucial to choose the optimum control for acupuncture treatments depending on the study's main goal and to interpret the results in accordance with the research design.

1. Introduction

Although still relatively new, research on the effects and mechanisms of acupuncture is increasing.[1] In the last 20 years, more than 3000 clinical trials have examined acupuncture treatments.[2] Acupuncture is a medical treatment that involves the insertion of needles into the body at specific acupoints.[3] The treatment consists of two essential elements: stimulation, which may involve the insertion of needles, and targeted acupoints, as opposed to randomly chosen body locations.[4,5] The establishment of a control group is an essential part of experimental design.[6] Using control groups in scientific research is a way to prove causation by separating the impact of an independent variable from that of confounding variables. In a well-designed experiment, all variables in the two groups should remain consistent, except for the treatment.[7,8] Based on the target elements of the acupuncture therapy, it is crucial to establish appropriate control conditions.

Acupuncture has been defined in a few ways that are unclear: (1) as a procedure that uses acupuncture needles at tender points, anatomical structures, or acupoints; (2) as a procedure that is performed at acupoints using injections, transcutaneous electrical stimulation, acupuncture needles, or lasers.[9] We described acupuncture in the current study as a medical practice that uses a needle at acupoints. The two elements of acupuncture—the acupoints and the needling—can be distinguished when looking at the control group. Real acupuncture at non-acupoints can be used to disclose the point-specificity, whereas sham acupuncture at true acupoints can be used to control the needling effects.

Research on the needling and point specificity in acupuncture has followed two distinct routes.[4,10] First, much clinical research on the stimulating effects of acupuncture has used sham needle devices that exclude a specific component of acupuncture treatment, i.e., needle penetration.[11,12] Treatment procedures using sham needle devices are otherwise identical to those of real acupuncture. Second, studies have examined the point specificity of the acupuncture effect, stimulating non-acupoints distant from true acupoints with real acupuncture needles. The Acupuncture Controls Guideline for Reporting Human Trials and Experiments (ACURATE) was recently released to report sham acupuncture procedures and related components.[13] However, adequate control of acupuncture treatment in clinical trials remains controversial.[14]

Numerous study designs and controls for acupuncture treatment have been used in clinical trials,[15,16] which have compared the effects of real acupuncture treatments with various control groups, including sham acupuncture at true acupoints, real acupuncture at non-acupoints, sham acupuncture at non-acupoints, and no treatment or treatment as

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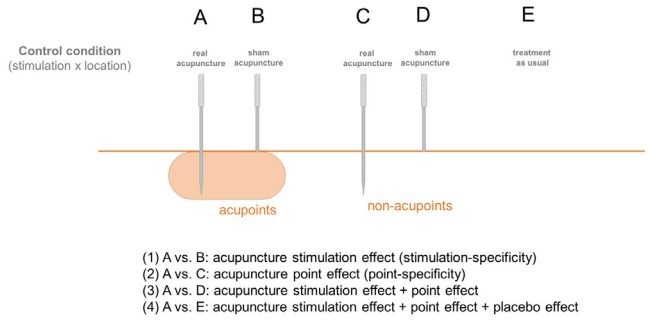

Fig. 1. Research designs and controls for acupuncture treatment in clinical trials. A, Real acupuncture at true acupoints; B, sham acupuncture at the same true acupoints; C, real acupuncture at non-acupoints; D, sham acupuncture at non-acupoints; and E, treatment as usual. We can respond to the various research questions based on the kind of control conditions that were employed in a clinical trial or experiment in acupuncture research. Here, four distinct scenarios are displayed: (1) The effect of acupuncture stimulation (condition A versus condition B), (2) The effect of acupuncture points (condition A versus condition C), (3) The effect of acupuncture stimulation combined with the effect of acupuncture points (condition A versus condition D), and (4) The combination of the acupuncture stimulation, acupuncture point, and placebo effect (condition A versus condition E).

usual (Fig. 1). Here, we discuss the significance of the control group in acupuncture research and its limits.

2. Types of study design and controls for acupuncture treatment

2.1. Real vs. sham acupuncture at the same true acupoints

To investigate the stimulating effects of acupuncture, including needle penetration, true acupoints can be 'simulated' using a sham acupuncture needle device, comparing the effects of acupuncture stimulation using real and sham needle treatments at the same true acupoints. For example, in one study, individuals with anxiety related to Parkinson's disease were assigned to receive real or sham acupuncture treatment.[17] Compared to sham acupuncture, real acupuncture treatment resulted in significantly lower Hamilton Anxiety Scale scores at the end of follow-up. In that study, the same durations of acupuncture and acupoints were used for the two groups. Therefore, the clinical improvement in the patients' anxiety seems to be associated with the effects of acupuncture stimulation (Fig. 1: condition A vs. condition B).

2.2. Real acupuncture vs. real acupuncture at non-acupoints

By comparing real acupuncture at true acupoints with real acupuncture at non-acupoints, it is possible to investigate point-specificity effects. For instance, in one study, patients with migraine prophylaxis were randomized to receive electroacupuncture or sham electroacupuncture.[18] Real acupuncture treatment was found to reduce migraine attacks more than sham acupuncture. The number of needles, electrical stimulation, and length of treatment were all the same as in the real acupuncture, except using only non-acupoints. Consequently, the long-term reduction in migraine recurrence in that study appears to have been linked to the point-specificity of acupuncture (Fig. 1: condition A vs. condition C).

2.3. Real acupuncture at true acupoints vs. sham acupuncture at non-acupoints

We can examine the mixed effect (stimulation and location) of acupuncture treatment by comparing real acupuncture at true acupoints and sham acupuncture at non-acupoints. For example, in one study, acupuncture treatments were randomized between real and sham for patients who had cesarean deliveries.[19] Real acupuncture treatment significantly reduced pain and accelerated patient mobilization after delivery compared to sham acupuncture or usual care only. In that study, sham needles that produced the feeling of needle insertion were applied near specific acupoints. Hence, both the stimulation and point-specificity of acupuncture treatment may have contributed to the management of pain in those patients (Fig. 1: condition A vs. condition D).

2.4. Real acupuncture vs. no treatment or treatment as usual

We can examine the acupuncture effects and placebo effects by comparing real acupuncture treatment with standard care. In one study, patients with head and neck cancer who experienced radiation-induced xerostomia were randomized to receive real acupuncture, sham acupuncture, or standard care as a control.[20] Real acupuncture treatment resulted in significantly less and less severe radiation-induced xerostomia than in the usual care group, and marginally less, albeit not significantly, in the sham acupuncture group. Therefore, acupuncture and placebo effects may have both contributed to the decrease in radiation-induced xerostomia (Fig. 1: condition A vs. condition E).

3. Considerations of proper controls for acupuncture treatment

3.1. Suggestions on selecting a suitable control for studies involving acupuncture

The two primary components of acupuncture are targeted acupoints and stimulation. In order to determine the point-specificity, researchers should make a comparison between real acupuncture administered at true acupoints and real acupuncture administered at non-acupoints. Conversely, when studying the stimulating effect of acupuncture, researchers ought to contrast real acupuncture at the true acupoints with sham acupuncture at the same true acupoints. Nonetheless, the following issues need to be taken into account while selecting an appropriate acupuncture control method.

3.2. Using sham acupuncture at either true or non-acupoints as a control

Early studies used non-penetrating needles as sham acupuncture to account for nonspecific effects such as therapeutic expectations and the medical environment to ascertain the therapeutic effects of acupuncture.[14] Clinical studies should have a sham control that is both physiologically inactive and identical to the active therapy (i.e., blinding success). In the case of acupuncture, it is challenging to satisfy both requirements.[14] Sham acupuncture with a sham needle device can induce a tactile sensation at the stimulated sites, regardless of whether they are acupoints or not, and produce physiological reactions.[21]

3.3. Using either real or sham acupuncture at non-acupoints as a control

It is controversial whether acupuncture has point specificity.[22,23] Experiments have indicated that varying physiological and clinical responses result from the activation of fundamental neural circuits that connect differently to distinct brain areas.[24] The point-specificity of acupuncture treatment can be determined by comparing real acupuncture at true acupoints with real acupuncture at non-acupoints (Fig. 1: condition A vs. condition B). However, we are unable to identify whether these benefits are due to either the point- or needling-specificity of acupuncture treatment when we compare real acupuncture at true acupoints with sham acupuncture at non-acupoints (Fig. 1: condition A vs. condition D). Consequently, using appropriate controls for acupuncture treatment is crucial, considering the primary aims of a study.

The definition of non-acupoints is crucial. The criteria used to select non-acupoints are locations 1–2 cm from targeted acupoints.[18] 3 mm from non-treated true acupoints,[25] or a specific arm location far from

the targeted acupoint.[26] Determining non-acupoints requires consensus.[9] Acupuncture at the acupoints on disease-affected meridians is more effective at relieving angina than that at the acupoints on non-affected meridians.[26] To address point-specificity concerns, a more suitable control should be considered.

3.4. Using no treatment or treatment as usual as a control

It is possible to distinguish between placebo responses and spontaneous variation using a "no treatment" control group to ascertain the extent to which the placebo responses are due to random fluctuations. Placing patients in a group that does not receive any treatment raises ethical problems, so instead of a "no treatment" group, a "treatment as usual" group can be applied as a control group for acupuncture treatment.

In one study, when three-arm randomized controlled groups were compared between acupuncture and sham acupuncture groups and treatment as usual, it was possible to determine the acupuncture effect by comparing real and sham acupuncture, while determining the placebo effect by comparing sham acupuncture with treatment as usual. Notably, when patients expect acupuncture treatment and they are randomized to treatment as usual, this might cause disappointment and nocebo effects.[27]

4. Limitations and further considerations for future research

4.1. Reconsiderations of the definitions of real and sham acupuncture

The thinnest needle, which is one of the "nine zhen" in the Huangdi Neijing (Yellow Emperor's Classic of Internal Medicine), has become the most popular and widely used type worldwide. The other types of "nine zhen", which include two kinds that are not inserted into the body, are less popular but are still in use in Asia.[28] As a result, there may still be disagreements over the ideal definition of acupuncture and the appropriateness of sham needle device as a control measure for acupuncture treatments.[29] The arguments over what constitutes acupuncture and whether or not sham acupuncture is appropriate was not discussed in detail in this article. Instead, we illustrated real acupuncture with fine needle and sham acupuncture with sham needle devices which applied the experimental design in contemporary acupuncture research.

4.2. Reconsideration of the definitions of true and non-acupoints

Acupoints are defined as points that are stimulated by the application of an acupuncture needle. In accordance with this definition, an acupuncture needle may be inserted at (a) conventional sites, such as acupoints, as detailed in acupuncture textbooks; (b) sites chosen based on anatomical structures, such as sensory nerves, without taking traditional acupoints into consideration; or (c) sites that exhibit palpable tenderness.[9] Conventional acupoints either coincide with the target peripheral nervous system, which is directly affected by nonpharmacological neuromodulation,[30] or they are hyperirritable sites in the taut bands of skeletal muscles known as myofascial trigger points.[31] Numerous studies have been carried out to investigate the potential physiological differences between "true acupoints" and "non-acupoints".[32,33] The "true acupoints" and "non-acupoints" close to the same anatomical region should be compared.[9] On the definition of the non-acupoints, there was, nevertheless, no agreement. As such, agreement on the definitions of "true acupoints" and "non-acupoints" is required for further investigations.

5. Conclusion

Acupuncture studies have employed a variety of control conditions, including sham acupuncture at true acupoints, real acupuncture at non-acupoints, sham acupuncture at non-acupoints, and no treatment or treatment as usual. In order to determine the point-specificity of acupuncture, real acupuncture at non-acupoints should be taken into consideration, whereas sham acupuncture at the same true acupoints should be used to determine the needling-specific effect of acupuncture. It is crucial to choose the most appropriate control for acupuncture treatments based on the main goal of the research and to interpret the results in accordance with the research design.

CRediT authorship contribution statement

Younbyoung Chae: Conceptualization, Writing – original draft, Writing – review & editing. **Jun-Hwan Lee:** Conceptualization, Writing – review & editing. **Myeong Soo Lee:** Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no competing interests.

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Ethical statement

Not applicable.

Data availability

The authors can provide the data used upon reasonable request.

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