

The non-specific effects of acupuncture treatment: When and how to control for them

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SPECIFIC AND NON-SPECIFIC EFFECTS OF ACUPUNCTURE

When acupuncture is performed in a clinical setting, the net result of treatment is a combination of specific and non-specific effects. Specific effects are said to arise directly from the puncture and subsequent needle manipulation of particular acupuncture points. All other factors that arise concomitantly with the treatment and contribute to its outcome are considered as non-specific effects. As detailed below, such non-specific effects emanate from a variety of sources including, but not limited to, treatment environment, patient expectations, practitioner intention, patient-practitioner rapport, natural history of the condition, and generalized effects of needle puncture.

When and how to control for non-specific effects depends in large part on the research question being asked. For example, if one is asking whether acupuncture has a better outcome than no treatment or at least as good an outcome as usual (biomedical) care, then, in either case, the totality of acupuncture treatment will be assessed with no attempt to separate specific from non-specific effects. In contrast, if one asks whether acupuncture outcome for a given condition depends on the needling of a particular set of points, then the control arm must be rigorously designed to control for the full range of non-specific effects, i.e. it should mimic the treatment in every way except for point selection. More generally, it is

necessary to control for the non-specific effects of acupuncture treatment when designing a trial to answer the following type of question: 'Is acupuncture per se (acupoint selection and/or needle manipulation), effective in the treatment of condition x?'

DEFINITIONS OF PLACEBO AND SHAM TREATMENT

The term 'placebo control', historically associated mainly with pharmaceutical trials, implies the use of a truly *inert* intervention. Since there is good evidence to suggest that needling at non-acupoint sites induces physiological responses, including effects on microcirculation,¹ homosegmental analgesic responses² and diffuse noxious inhibitory control,^{3,4} any control treatment that involves invasive needling is clearly not inert. Thus, placebo should not be used as a generalized descriptor of control treatments in clinical trials of acupuncture.

One terminology solution that has been proposed⁵ is to use the term 'sham' for any control treatment involving invasive needling and 'placebo' for non-invasive control procedures, such as an empty guide tube,^{6,7} a cocktail stick⁸ or toothpick,⁹ or a retractable needle.^{10,11} Although invasive and non-invasive is a useful distinction for control treatments, the term 'placebo' is replete with many unresolved issues.^{11a,11b} It is recommended instead

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that 'sham' be adopted when describing any needle control treatment for acupuncture trials, a terminology consistent with clinical trials of medical devices. Further, the terms 'invasive sham' and 'non-invasive sham' should henceforth be used to clarify the two broad sub-categories of procedures in clinical trials of acupuncture that seek to control for non-specific effects of acupuncture.

NATURE OF NON-SPECIFIC EFFECTS OF ACUPUNCTURE TREATMENT

A range of non-specific effects have been identified (see Table 1), each of which may need to be controlled for depending upon the precise question to be addressed in the study.¹²⁻²⁴ A variety of procedures and questionnaires can be used to address these different effects.

PARAMETERS IMPORTANT IN SELECTING AND DESIGNING SHAM INTERVENTIONS

Three basic parameters of acupuncture treatment have been identified that are modified in different forms of acupuncture and can be modified for the different *sham* interventions:

- Depth of needling
- Needle manipulation
- Location of needling.

A wide variety of different *sham* procedures have been used in clinical trials of acupuncture. The following are the most common forms that can be found.^{5,20,24,32}

Non-invasive sham techniques

Retractable blunt needles, pressing with guide tube, pressing with cocktail stick, pressing with toothpick, pressing with needle handle, taping needle onto the skin, sham-TENS, sham-laser.

Invasive sham techniques

- (1) Same depth and manipulation of needling at sites not on a channel.
- (2) Different depth and manipulation of needling at sites not on a channel.
- (3) Shallow needling with no manipulation at sites not on a channel.

- (4) Shallow needling with no manipulation at the same prescribed treatment points.
- (5) Shallow needling with no manipulation at non-relevant acupuncture points.
- (6) Same depth and manipulation of needling at non-relevant acupuncture points.

Each of these sham interventions can be used to answer different research questions. They are not equivalent to each other and thus should not be confused with each other. For example, the invasive sham techniques can be expected to provide adequate control for the generalized needling effects as well as for non-needle related treatment effects (see the first five types of effects listed in Table 1). In contrast, the non-invasive techniques control only for the non-needle effects. Additionally, questions have been raised about the appropriateness of using sham-TENS or sham-laser as the sham treatment since they are different from acupuncture and will probably produce a different psychological impact.^{18,33}

The invasive needling procedures 1 and 6 allow one to answer the question of the *specific effects of the acupuncture points*, since the same techniques of stimulation are applied in both intervention arms. *Specific effects of the treatment techniques* can be addressed by the invasive needling procedure 4, since the same acupuncture points are used in both intervention arms. Procedures 2, 3 and 5 use different techniques and locations of treatment than the test acupuncture. These models could thus be used to examine the *overall effect of treatment* (combination of technique and location effects). Each of the different sham procedures has their strengths and weaknesses and needs to be carefully considered in relation to the question being asked and the research context.

Research design features in controlling for non-specific effects of acupuncture treatment

Blinding

Double blinding is virtually impossible in clinical trials of acupuncture.³⁴ It is possible to blind patients, but practitioner blinding is very challenging. Some researchers consider it possible to blind the practitioner, but this is challenged by others and remains a point of controversy.

It is recommended instead to always use patient and assessor blinding, what has in the past been called the *modified double-blinding* approach. More recently the definition of 'double-blind' has come to incorporate this approach as well.³⁵ While the term 'double-blind' is understood by most researchers to

Table 1 Types of non-specific effects of acupuncture		
Effects	Possible method of control	Relevant Reference No.s
<i>Context effects</i> (e.g. appearance of the treatment room)	Randomization	14, 16, 22, 25
<i>Patient based effects</i> (e.g. patient expectations, credibility of treatment)	Assessments/ Questionnaires	7, 12, 13, 26–29
<i>Practitioner based effects</i> (e.g. enthusiasm of the practitioner)	Assessments/ Questionnaires	12, 13, 29–31
<i>Patient-practitioner interaction effects</i> (e.g. patient–practitioner communications?)	Assessments/ Questionnaires	12, 13, 29–31
<i>Regression to the mean, natural course of the disease, etc.</i>	Randomization	14, 16, 22, 25
<i>Generalized needling effects</i> (e.g. diffuse noxious inhibitory control analgesic effects, ³ homosegmental analgesic effects, ² relaxation effects, ^{12,21} microcirculatory effects, ¹	Assessments/ Questionnaires	12, 13

refer to the more limited definition of patient and practitioner blinding, it may be advantageous to incorporate the more recently expanded definition as it will allow a study using this approach to come up in literature searches of 'acupuncture' and 'double-blind' trials. The term 'double-blind' can be used as a MESH heading, but its precise definition needs to be clearly stated. If a study is listed as 'double-blind' when the patients and evaluator are blind, we recommend labeling the study 'double-blind (patients, evaluator)'. The methods of blinding should be described and patient blinding must be assessed.

Randomization

All studies should use an appropriate method of randomization and describe the method used.

Patient selection

Where feasible, it may be advantageous to recruit only acupuncture-naïve patients, to assist in maintaining the blind. When patients who have had acupuncture before are included, it would be useful to conduct appropriate sub-analyses to compare results with and without acupuncture experienced patients.

Validation of control procedure

When a sham intervention is used as the control treatment, it is necessary that the procedure appears the same as the acupuncture treatment to patients and that the practitioner has the same appearance and behavior in each treatment arm. The importance of validation of a control procedure in clinical trials

of acupuncture was first described by Vincent²⁷ and has been incorporated in a number of studies.^{6–9,36}

In order to better understand complex issues such as the credibility of treatment, and to assist interpretation of the credibility data, it will also be necessary to include in the published study the critical sentences from the patient consent form that describe the treatment interventions to the patients. The wording of the consent form can have a large impact on how credibility of treatment is perceived.

ADDITIONAL CONCERNS IN CONTROLLING FOR NON-SPECIFIC EFFECTS OF ACUPUNCTURE

Interactions of non-specific and specific treatment effects

It has been demonstrated that placebo-related non-specific effects can involve endorphin pathways.^{37–39} It has also been documented that the heterosegmental analgesic effects of needling can involve endorphin pathways.⁴⁰ Since there is strong evidence that one of the major pathways through which the specific analgesic effects of acupuncture occur is the endorphin pathway,^{41–44} it is likely that the various specific and non-specific effects of acupuncture analgesia will interact with each other.

When the various components of a therapy interact, it becomes difficult, if not impossible, to assess the relative size of each component and thus to control for the non-specific treatment effects.¹⁵ There is clear evidence from biomedical research for

the interaction of therapies with each other and the interaction of placebo-related and intervention-specific treatment effects.^{17,45} These findings raise concerns about the general assumption in clinical trials that specific and non-specific effects can be readily separable. They also raise questions about the feasibility of controlling for non-specific treatment effects when acupuncture is used as an adjunctive therapy rather than as a stand-alone therapy, such as in stroke rehabilitation, the treatment of asthma, addiction and angina pectoris.⁴⁶ The probability of interaction between therapies and components of therapies may make non-specific controls unrealistic when acupuncture is given as an adjunctive therapy in a trial of acupuncture.

Treatment target

In some forms of acupuncture, notably traditionally based systems, the goal of acupuncture treatment is not only the relief of a specific symptom(s), but an improvement in the general health and functioning of the patient. In Chinese traditional medicine this is known as the *zhibenfa* (Japanese *honchiho*) or *root treatment* as distinct from the *zhibiaofa* (Japanese *hyochiho*) or *branch treatment* which attempts to relieve the symptom or symptoms of the patient.⁴⁷

While there are many historical and modern descriptions of how to select and apply the *zhibenfa*, the goal is the same, to attempt to create a change in the ability of the body to heal itself or recover from some abnormal process that resulted in the symptoms. It may well be that the mechanisms, which have yet to be investigated and understood, may be similar to those activated or utilized in the *placebo* response. Essentially a placebo response involves an activation of various pathways triggered by belief or other psychosocial factors that help the body to self-regulate and heal itself. This raises fundamental questions about the desirability of trying to control for placebo effects (and thus its pathways of action) when the activation of these self-healing pathways may be the target of treatment. Since this concern is probably relevant for other complementary and alternative medicine therapies that target an improvement of the ability of the body to heal itself, it seems clear that this issue needs considerably more discussion.

GENERAL RECOMMENDATIONS

- (1) Researchers should first decide whether they are interested in testing the overall effectiveness of acupuncture – combined effects of acupuncture point(s) selection and needling technique(s) or the effectiveness of

either of these parameters alone. Such studies, which call for use of an invasive sham control, also control for a range of non-needle-related treatment effects. If a study wishes to examine the specific effects of treating a particular point or set of points, the same treatment techniques should be applied to both the treatment points and at a set of control treatment points. If a study wishes to examine the specific effects of a particular technique or set of techniques, the same acupuncture points should be used in the different intervention arms, varying the treatment techniques in each. Alternatively, researchers may choose only to control for non-needle treatment effects. Such a choice might be made on ethical grounds (not wanting to use control invasive needling in patients) or for practical reasons (since generalized needling effects may result in invasive sham having a greater effect than non-invasive sham, a larger sample size may be required). In this case, a non-invasive sham control must be employed.

- (2) We cannot be satisfied that a truly *inert* intervention is possible as the control treatment in acupuncture studies. Therefore the *sham* intervention cannot be considered equivalent to placebo in the same way that a placebo pill is considered to be an inert intervention in a placebo controlled pharmaceutical trial. We thus suggest that all trials attempting a *sham* control to examine the specific effects of acupuncture do so in the following way:
 - (a) Describe the trial as *placebo controlled* as one of the key terms in the paper to ensure that it will show up in the MESH headings;
 - (b) Clearly state in the Abstract and Methods that the *sham* intervention is **not** equivalent to placebo. Use the term *invasive sham* or *non-invasive sham* to more precisely describe the control procedure.
- (3) When acupuncture is used as one modality within a complex treatment intervention, e.g. in combination with herbal medicine and massage as might occur in a trial of traditional Chinese medicine, it is usually not feasible to design a multi-modality control treatment. We recommend using pragmatic research models in such cases.

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