Sham interventions in randomized clinical trials of acupuncture—a review

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SUMMARY. Background and objectives: For non-drug interventions such as acupuncture, it is difficult to establish placebo or sham controls that are both inert and indistinguishable. We reviewed sham-controlled clinical trials of acupuncture to investigate (a) which types of sham interventions have been used in the past; (b) in what respects true and sham interventions differed; and (c) whether trials using different types of sham yielded different results. Methods: 47 randomized controlled trials comparing true and sham acupuncture interventions for pain and a variety of other conditions were identified from systematic reviews and through a search in PubMed. Details of patients, interventions, sham interventions and outcomes were extracted in a standardized manner. Results: In two trials the sham intervention consisted of superficial needling of the true acupuncture points, four trials used true acupuncture points which were not indicated for the condition being treated, in 27 trials needles were inserted outside true acupuncture points, five trials used placebo needles and nine trials used pseudo-interventions such as switched off-laser acupuncture devices. True and sham interventions often differed in a variety of other variables, such as manipulation of needles, depth of insertion, achievement of an irradiating needling sensation (de-chi), etc. There was no clear association between the type of sham intervention used and the results of the trials. Conclusion: Randomized trials investigating the specific effects of acupuncture have used a great variety of sham interventions as controls. Summarizing all the different sham interventions as 'placebo' controls seems misleading and scientifically unacceptable.

INTRODUCTION

Randomized, double-blind, placebo-controlled trials are generally considered as the best tool to separate the "specific" and the "unspecific" or "placebo" effects of a therapy. If the intervention is a drug, the "specific" component is the pharmacologically active agent while the placebo is an inert substance. The issue becomes more complicated if the therapy under test is a complex physical intervention as, for example, physiotherapy, chiropractic manipulation, or acupuncture. There can be little doubt that the correct localization of points is vital for the theory of acupuncture to hold some validity. A possible control intervention is, therefore, needling at incorrect sites. However, there is evidence that such a sham intervention cannot be considered as physiologically inert.[1] Furthermore, there is also some evidence that the localization of incorrect points may be of relevance, as differences between experimental and control groups have been larger in trials in which more distant sham points were used.[2] Apart from localization, acupuncturists also consider other variables as potential modifiers of needling effects: depths of needling, manipulation of the needle, triggering of a specific irradiating needling sensation (de-chi), etc. Given this complex situation, it is not surprising that a variety of sham techniques have been used in clinical trials.[3–5] We reviewed sham-controlled clinical trials of acupuncture to investigate (a) which sham interventions have been used in the past; (b) in what respects "true" and "sham" interventions differed;

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and (c) whether trials using different types of sham yielded different results.

METHODS

We included randomized controlled trials published in English or German in which patients received either true acupuncture (at least four sessions with needle insertion at acupuncture points) or sham (at least four sessions of an intervention described as "sham" or "placebo") for preventative, palliative or curative purposes. Studies in healthy volunteers investigating pain thresholds, etc. or studies measuring solely laboratory parameters were excluded, as were studies on specific subtypes of acupuncture (as ear acupuncture, laser acupuncture) or which did not provide any details on true and sham interventions (e.g. studies published as abstracts only). A minimum of four sessions was required to warrant some clinical relevance of the included studies.

We aimed at including a total of approximately 50 primary studies on the treatment of chronic pain and other conditions in which acupuncture is widely used. First we screened recent systematic reviews of acupuncture for chronic pain in general,[6] back pain,[7] headache,[8] osteoarthritis of the knee,[9] fibromyalgia,[10] stroke rehabilitation,[11] asthma,[12] tinnitus,[13] and smoking cessation.[14,15] In total, these reviews included 122 studies; but only 37 met the inclusion criteria. Therefore, an additional search was performed in April 2002 in PubMed (www.ncbi.nlm.nih.gov/PubMed/). The search terms used were "acupuncture AND (placebo OR sham)" as text words. The search was limited to the "publication type randomized controlled trial" and a publication date after January 1, 1998. A total of 57 studies were found, resulting in 11 additional trials meeting all inclusion criteria. On further scrutiny, we found that one[16] trial was a subgroup analysis of another included trial.[17] We excluded the publication reporting the subgroup analysis, leaving 47 included studies.

Details on patients, interventions, outcomes and results in the primary studies were extracted using a standard form by one author (F.D.) and checked by the second (K.L.). If possible, the number of patients randomized to treatment and control groups and the respective number of responders (global assessments or, in headache studies, more than 33 or 50% frequency or headache index reduction) were reported. Furthermore, the results of each trial were summarized by both reviewers using a vote count: +: "true" acupuncture statistically significantly superior to "sham" for main outcome measure(s); (+): trend in favor of "true" acupuncture (no statistically significant difference, but consistent, potentially clinically relevant trends for most important outcome measures); 0: no difference; (−): trend in favor of "sham"; −: "sham" significantly superior.

The sham interventions used were categorized independently by both reviewers according to the following classification scheme: I: superficial needling of true points; II: irrelevant acupuncture points (needling of common acupuncture points which, however, were considered ineffective for the condition treated); III: non-acupuncture points (needling "outside" of acupuncture points); IV: placebo needles (use of devices which mimic acupuncture but where skin penetration does not occur); and V: pseudo-interventions (use of interventions which clearly differ from "true acupuncture," e.g. use of switched off-laser acupuncture devices). Disagreements occurred for three studies and were resolved by discussion.

Furthermore, we checked whether "true" and "sham" interventions differed in the following respects: points chosen, penetration of the skin, depths of needling, manipulation or stimulation of the needle, achievement of de-chi (an irradiating feeling considered to be associated with effective needling), number of points, number of sessions, duration of sessions.

As we assumed that most readers would ask whether the use of different types of sham interventions had an impact on outcome we included some basic analyses on this question although their validity seemed highly questionable a priori (because the included studies were markedly heterogeneous in respect of patients, acupuncture interventions, type and timing of outcome measurements). First, we simply compared vote counts for the different "sham" categories. Then, we calculated responder rate ratios (proportion of patients responding in the treatment group/proportion of patients responding in the control group) for all individual trials that presented dichotomous data (or data which could be dichotomized) for the response to treatment, and pooled the ratios using the Cochrane Collaboration's RevMan 4.1. software (random effects model).

RESULTS

Information on conditions treated, number of patients, the sham interventions used and the overall results of the 47 included trials is listed in Table 1. A great variety of different sham interventions were used. Thirty-three trials used techniques which involved insertion of a needle (see Table 2). In two of these, needles were inserted superficially at points that were used in the true treatment group (category I). In four trials the sham points were common acupuncture points which were considered irrelevant for the condition being treated (category II). In 27 studies needles were inserted "outside" of acupuncture points (category III). How these non-points were localized differed considerably between the trials which reported on this aspect: in some they were 1–3 cm from true points, in others they were in the same neural segment but in areas where no acupunc-

Table 1 Studies included in the analysis

First author (reference)	Indication	*n*	Sham intervention (category)	Vote
Axelsson[18]	Tinnitus	20	Low frequency electro-stimulation (V)	0
Ballegaard[19]	Angina pectoris	49	Superficial needling at non-points (III)	0
Baust[20]	Migraine	44	Three defined non-points (III)	0
Carlsson[21]	Back pain	51	Mock transcutaneous nerve stimulation (V)	+
Christensen[22]	Asthma	17	Defined non-points outside of segment (III)	(+)
David[23]	Rheumatoid arthritis	56	Needle introducer at Liv 3 (IV)	0
Deluze[24]	Fibromyalgia	70	Points 2 cm from correct points (III)	+
Dias[25]	Asthma	20	Non-indicated acupuncture points (II)	(−)
Dowson[26]	Migraine	48	Mock transcutaneous nerve stimulation (V)	0
Fink[27]	Osteoarthritis (hip)	67	Superficial needling at non-points (III)	0
Gaw[28]	Osteoarthritis	40	Outside but contiguous to true points (III)	0
Gosman-Hedström[29]	Stroke	104	Superficial needling of two true points (I)	0
Hansen[30]	Tinnitus	20	Superficial needling of close non-points (III)	0
Hansen[31]	Chronic facial pain	20	Non-points in the same region (III)	+
Hansen[32]	Tension-type headache	25	3 cm from true points (III)	+
He[33]	Smoking cessation	46	Non-indicated acupuncture points (II)	+
Henry[34]	Migraine	30	1 cm from true points (III)	0
Irnich[35]	Chronic neck pain	177	Inactivated laser acupuncture device (V)	(+)
Jobst[36]	COPD	26	Non-points close to the patella (III)	+
Joos[37]	Asthma	38	Non-indicated acupuncture points (II)	+
Karst[17]	Tension-type headache	69	Placebo needle at correct points (IV)	0
Kleinhenz[38]	Rotator cuff tendinitis	52	Placebo needle at correct points (IV)	+
Korpan[39]	Chronic pain	14	Non-acupuncture points (III)	0
Kubiena[40]	Migraine	30	1.5–2 cm from true points (III)	(+)
Lautenschläger[41]	Fibromyalgia	50	Inactivated laser acupuncture device (V)	+
Lehmann[42]	Chronic pain	53	Sham transcutaneous nerve stimulation (V)	+
Leibing[43]	Back pain	131	Superficial needling 1–2 cm from true points (III)	0
Mencke[44,45]	Shoulder-arm syndrome	75	Non-points in the same segment (III)	+
Mencke[44,45]	Low back pain	65	Non-points in the same segment (III)	+
Mendelsson[46]	Chronic back pain	95	Lidocain injection at non-points (III)	0
Mitchell[47]	Asthma	31	Non-indicated acupuncture points (II)	0
Molsberger[48]	Osteoarthrosis (knee)	103	Superficial needling of non-points (III)	+
Naeser[49]	Stroke	16	Individually chosen non-acupuncture points (III)	+
Petrie[50]	Chronic neck pain	13	Mock transcutaneous nerve stimulation (V)	+
Petrie[51]	Chronic neck pain	26	Mock transcutaneous nerve stimulation (V)	0
Pintov[52]	Migraine	22	Probably superficial needling true points (I)	+
Shi[53]	Headache	34	Inactivated laser acupuncture device (V)	+
Steiner[54]	Smoking cessation	32	Non-acupuncture points (III)	0
Takeda[55]	Osteoarthritis (knee)	40	Superficial needling 1 inch from true points (III)	(+)
Tashkin[56]	Asthma	25	In vicinity to real acupuncture points (III)	0
Tavola[57]	Tension-type headache	30	Superficial needling of non-points (III)	(+)
Vilholm[58]	Tinnitus	54	Superficial needling at random points (III)	0
Vincent[59]	Migraine	32	Superficial needling 2–3 cm from true points (III)	(+)
Weinschütz (I)[60]	Migraine	40	Superficial needling 1–2 cm from true points (III)	(+)
Weinschütz (II)[60]	Migraine	41	Superficial needling 1–2 cm from true points (III)	+
White[61]	Tension-type headache	10	Blunt cocktail stick in a plastic tube (IV)	n.a.
White[62]	Tension-type headache	50	Blunt cocktail stick in a plastic tube (IV)	0

n.a.: not assessable; vote count: +: true acupuncture significantly superior to sham; (+): trend in favor of true acupuncture; 0: no difference; (−): trend in favor of sham; −: sham significantly superior.

Table 2 Overview of sham interventions used in the 47 trials

Category		Trials
I	Superficial needling of "true" acupuncture points	2
II	Irrelevant acupuncture points	4
III	Non-acupuncture points	27
	Sum of trials with a "penetrating" sham	**33**
IV	Placebo needles	5
V	Pseudo-interventions	9
	Sum of trials without skin penetration	**14**

Table 3 Overview of differences between true and sham interventions in the 27 trials using needling of non-acupuncture points for sham control (category III)

Aspect	Identical	Not identical	Unclear
Depth of needling	4	13	10
Manipulation	5	10	12
Number of points	14	1	12
Achievement of de-chi	1	15	11
Number of sessions	24	1	2
Duration of sessions	22	–	5

ture points are known, others avoided needling in the same neural segment and choose non-points in distant areas. In 14 trials there was no insertion of needles into the skin. Five used devices which mimic acupuncture but where skin penetration does not occur (category IV—placebo needles): three trials used telescope needles with a blunt tip fixed with a plastic ring covered by a plaster, two trials used a blunted cocktail stick in a plastic tube. Finally, nine trials applied pseudo-interventions which were quite different from needle acupuncture such as inactivated laser acupuncture devices or mock transcutaneous nerve stimulation (category V).

True and sham interventions differed in a number of aspects. For example, three of the category IV trials used the "placebo needles" at the same sites as in the "true" acupuncture groups,[17,23,38] whereas the remaining two trials at non-acupuncture points.[61,62] The duration of sessions was the same in two category II trials but was different in two other trials.[33,49] Variations among the 27 category III trials are listed in Table 3. For example, in some trials needle insertion was superficial (versus deep in the true acupuncture group), de-chi was avoided (versus achievement of de-chi) and needles were not manipulated (versus manipulation), while other trials kept these variables as similar as possible to the true acupuncture group.

A significant superiority over sham or a clear trend in this direction was reported in one out of two trials with superficial needling of correct points in the sham group, two out of four trials using irrelevant acupuncture points, 15 out of 27 trials needling non-acupuncture points, one out of four interpretable trials using a placebo needle and six out of nine trials with a pseudo-intervention. Thirty trials presented data on how many patients were responders, which allowed the calculation of reponder proportions. These were: neither of the two trials with superficial needling of correct points in the sham group, three out of four trials using irrelevant acupuncture points, 17 out of 27 trials needling non-acupuncture points, three out of five trials using placebo needles and seven out of nine trials with a pseudo-intervention. Pooled responder rate ratios were similar for the four categories of sham interventions but the results of single trials varied strongly and confidence intervals were wide (see Table 4). Trials using non-penetrating sham interventions (categories IV and V) yielded slightly (but non-significantly) larger effect sizes compared to trials using sham interventions with needle insertion.

DISCUSSION

The analysis shows that (1) a great variety of sham interventions have been used in randomized controlled trials of acupuncture and that (2) "true" and sham interventions often vary considerably in regard to several aspects that could affect the outcome. Due to the extreme heterogeneity of trials, it is impossible to draw a reliable conclusion whether different sham techniques are associated with different results.

The randomized trials included in our analysis are not a random sample of all sham-controlled studies of acupuncture. The trials were primarily identified from published systematic reviews on conditions known to be treated frequently with acupuncture. To ensure that included studies are clinically relevant and represent common acupuncture practice we excluded trials with less than four treatment sessions. Therefore, this review does not include studies on conditions like postoperative nausea or dental pain where a large number of randomized trials are available.[63–65] These conditions have probably been chosen for randomized trials because they are comparably easy to study. For example, trials on acupuncture for postoperative nausea typically involve a single treatment at a single point and a very short follow-up period. While these studies provide important evidence on the specific effects of a defined treatment and are of interest for anesthesiologists, they have little relevance for routine acupuncture practice. Implementing a valid sham control in a chronic pain trial with multiple sessions and long-term follow-up is much more difficult. When interpreting our findings, it must be kept in mind that they apply mainly to the treatment of chronic diseases.

We were surprised how many reviews and trials had to be screened to identify the preplanned number of trials. A considerable number of studies investigated specific subtypes of acupuncture (electro-acupuncture, laser acupuncture, etc.), had less than four treatment sessions despite the chronicity of the conditions or did not include a sham control condition. Both authors of this review have

Table 4 Results of 30 trials presenting dichotomous data on treatment response ordered according to type of sham control

First author (reference)	Outcome	Acupuncture (*n*/*N*)	Sham (*n*/*N*)	Rate ratio (95% CI)
Sham control: irrelevant acupuncture points (category II)				
Dias[25]	Patient global assessment	6/10	8/10	0.75 (0.41–1.36)
He[33]	Smoking cessation	9/27	1/21	7.00 (0.96–51.0)
Joos[37]	Patient global assessment	15/20	8/18	1.69 (0.95–3.00)
Subtotal		30/57	17/49	1.52 (0.57–4.04)
Sham control: non-acupuncture points (category III)				
Ballegard[19]	Global assessment	18/24	21/25	0.89 (0.67–1.19)
Baust[20]	≥50% headache index reduction	14/23	14/21	0.91 (0.58–1.43)
Fink[27]	≥50% improvement	10/32	7/30	1.34 (0.59–3.06)
Hansen[31]	≥50% headache index reduction	3/7	0/9	8.75 (0.52–145)
Hansen[32]	≥50% headache index reduction	2/9	0/9	5.00 (0.27–91.5)
Henry[34]	Overall patient assessment	11/20	3/10	1.83 (0.66–5.12)
Kubiena[40]	≥33% headache index reduction	6/15	5/15	1.20 (0.47–3.09)
Mencke (I)[45,46]	Global improvement	33/35	15/30	1.89 (1.31–2.72)
Mencke (II)[45,46]	Global improvement	37/40	15/35	2.16 (1.46–3.20)
Mendelsson[46]	≥33% pain reduction	19/36	21/41	1.03 (0.67–1.58)
Molsberger[48]	≥50% pain reduction	36/77	8/26	1.52 (0.81–2.84)
Naeser[49]	Global assessment	4/10	0/6	5.73 (0.36–90.8)
Steiner[54]	Smoking cessation	1/16	1/16	1.00 (0.07–14.6)
Tavola[57]	≥50% headache index reduction	8/15	7/15	1.14 (0.56–2.35)
Vincent[59]	≥50% attack reduction	7/15	6/15	1.17 (0.51–2.66)
Weinschütz (I)[60]	Single-case statistics	13/20	8/20	1.62 (0.87–3.04)
Weinschütz (II)[60]	Single-case statistics	15/20	8/21	1.97 (1.08–3.59)
Subtotal		237/414	139/344	1.39 (1.12–1.73)
All categories II and III trials		267/471	156/393	1.38 (1.12–1.71)
Sham control: placebo needles (category IV)				
Karst[17]	≥50% reduction headache days	18/34	10/35	1.85 (1.00–3.42)
Kleinhenz[38]	Global assessment	17/25	14/27	1.31 (0.83–2.06)
White[62]	≥50% reduction headache days	18/25	10/25	1.50 (0.84–2.67)
Subtotal		50/84	34/87	1.49 (1.09–2.02)
Sham control: pseudo-interventions (category V)				
Axelsson[18]	Global assessment	4/11	4/9	0.82 (0.28–2.39)
Carlsson[21]	Pain improvement	16/34	2/16	3.76 (0.98–14.4)
Dowson[26]	≥50% frequency reduction	8/25	6/23	1.23 (0.50–3.00)
Irnich[35]	≥50% improvement pain mov.	29/56	16/61	1.75 (1.10–2.79)
Lautenschläger[41]	Global assessment	10/25	7/25	1.43 (0.65–3.15)
Petrie[50]	Good/very good pain relief	6/7	0/7	11.4 (0.77–167)
Petrie[51]	Moderately/greatly better	6/13	4/12	1.38 (0.51–3.74)
Subtotal		79/171	41/152	1.59 (1.15–2.18)
All categories IV and V trials		129/255	75/239	1.54 (1.23–1.91)

n/*N*: number of responders/number randomized to the respective group.

only basic knowledge of acupuncture but the "true" interventions in a number of trials did not appear representative of routine acupuncture. For example, treating patients with rheumatoid arthritis five times at a single site[23] would hardly be considered as adequate by most acupuncturists. However, the issue of level of training of the acupuncturist was beyond the scope of this study.

Classifying the included trials into categories of sham interventions and assessing the differences between true and sham treatment is partly subjective. Other reviewers might code some trials differently but it seems unlikely that they would consider the overall pattern less confusing. Are trials which use such different control interventions comparable?

Our analyses of response rates suggest that overall results were similar regardless of the sham technique. However, we believe that these analyses do not allow a reliable conclusion on whether trials with different sham interventions yield different results. We have shown that even within a single category, sham and true interventions tend to differ in a variety of aspects that are potentially relevant. Furthermore, the number of trials in each category is low, and there is strong heterogeneity of patients, true acupuncture interventions and outcome measures. Response was not the primary outcome measure in the majority of trials and given the small sample size of the studies, this simple dichotomous finding did not always reflect the results reported for continuous outcomes.

The various types of sham techniques used have different advantages and drawbacks. For example, needling the "true" points superficially is a good test for the influence of the depth of needling, however, many Japanese acupuncturists consider superficial needling as highly effective.[66] When needling

Box 1 Examples of questions answered depending on the sham intervention used

Sham or control intervention	Question answered
Use of "placebo" needles at the same sites as in the true acupuncture group	Does skin penetration make a difference in comparison to pressure without skin penetration at acupuncture points?
Use of "placebo" needles at non-acupuncture points	Do point localization and skin penetration make a difference?
Superficial needling at non-acupuncture points without an attempt to achieve de-chi and without stimulation	Is a "normal" acupuncture intervention superior to a needling intervention deficient in various aspects considered relevant to good quality acupuncture?
Mock transcutaneous electrical nerve stimulation	Is acupuncture superior to a physiologically inert pseudo-intervention?
Acupuncture performed by trained and experienced acupuncturists vs. untrained health care providers	Is it necessary to study acupuncture?

non-acupuncture points there are valid reasons to choose close or distant points, to vary depth or not, etc. but no one can be sure whether this affects the results of the trial. Recently the development of placebo needles, for example,[67] has been considered a major advance. These are a welcome and useful innovation but they do not resolve the problem. Placebo needles typically have blunted tips and are put into foam or plasters fixed on the skin, to mimic the insertion of a needle. The technique is time-consuming (and so increases patient-provider contacts), as well as being problematic in hairy areas, fingers and feet. When used at true points it might be an effective form of acupressure (which has been shown effective for postoperative nausea[65]). When used at wrong points the placebo differs from the true intervention in two ways: localization and skin penetration. In conclusion, most of the sham techniques are useful but they all answer slightly different questions.[5] Some examples of sham interventions and the relevant questions are listed in Box 1.

The discussion on which sham technique is best often focuses on whether it is indistinguishable, that is, whether patients are unable to tell true from sham acupuncture. In this respect pseudo-interventions (e.g. switched off-laser acupuncture devices) must be considered inadequate, although the manner in which informed consent is achieved plays a fundamental and decisive role.[3] Ten trials[18,21,24,28,30,31,36,50,51,55] included in our analysis described how patients were informed: none seemed to have used the word placebo, some vaguely spoke of an experimental and a control condition but most seem to have suggested that two types of acupuncture were being compared. If patients do not know that they might receive a sham intervention, even distinguishable pseudo-interventions can be highly credible and accredited as adequate sham interventions. Whether incomplete informed consent to maintain blinding is ethically acceptable should be discussed in an open manner.

The choice of the sham intervention for a specific trial will depend to a great extent on the broader aim and the logistical framework of a study. If, for example, a large multi-center trial is performed to help with the decision on whether acupuncture should be reimbursed or not, it seems logical to compare an adequate acupuncture intervention with a clearly inadequate sham-control which is easily performed in a standardized manner. If the aim of a study is to provide a "clean" scientific proof that two key aspects of acupuncture—point localization and skin penetration—play a vital role, the best choice might be a factorial design with "placebo" and "normal" needles at true and non-acupuncture points.

In conclusion, we believe that our analysis shows that there is no single adequate sham intervention for acupuncture trials. Problems are likely to be similar for other non-drug-interventions. Sham interventions are useful to answer specific questions on the composite influence of the various manipulated variables (location, depth, manipulation, de-chi, etc.). However, comparing and interpreting the results of trials with totally heterogeneous interventions by regarding them simply as 'placebo-controlled' is highly misleading and scientifically unacceptable.

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