Sham device versus inert pill: randomised controlled trial of two placebo treatments

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Abstract

Objective To investigate whether a sham device (a validated sham acupuncture needle) has a greater placebo effect than an inert pill in patients with persistent arm pain.

Design A single blind randomised controlled trial created from the two week placebo run-in periods for two nested trials that compared acupuncture and amitriptyline with their respective placebo controls. Comparison of participants who remained on placebo continued beyond the run-in period to the end of the study.

Setting Academic medical centre.

Participants 270 adults with arm pain due to repetitive use that had lasted at least three months despite treatment and who scored ≥3 on a 10 point pain scale.

Interventions Acupuncture with sham device twice a week for six weeks or placebo pill once a day for eight weeks.

Main outcome measures Arm pain measured on a 10 point pain scale. Secondary outcomes were symptoms measured by the Levine symptom severity scale, function measured by Pransky's upper extremity function scale, and grip strength.

Results Pain decreased during the two week placebo run-in period in both the sham device and placebo pill groups, but changes were not different between the groups (−0.14, 95% confidence interval −0.52 to 0.25, P = 0.49). Changes in severity scores for arm symptoms and grip strength were similar between groups, but arm function improved more in the placebo pill group (2.0, 0.06 to 3.92, P = 0.04). Longitudinal regression analyses that followed participants throughout the treatment period showed significantly greater downward slopes per week on the 10 point arm pain scale in the sham device group than in the placebo pill group (−0.33 (−0.40 to −0.26) *v* −0.15 (−0.21 to −0.09), P = 0.0001) and on the symptom severity scale (−0.07 (−0.09 to −0.05) *v* −0.05 (−0.06 to −0.03), P = 0.02). Differences were not significant, however, on the function scale or for grip strength. Reported adverse effects were different in the two groups.

Conclusions The sham device had greater effects than the placebo pill on self reported pain and severity of symptoms over the entire course of treatment but not during the two week placebo run in. Placebo effects seem to be malleable and depend on the behaviours embedded in medical rituals.

Introduction

Questions and debate surround the scientific understanding of placebo effects.[1] A National Institutes of Health conference declared that understanding how placebo effects are modulated is an urgent priority,[2,3] while, at the same time, a meta-analysis cast doubt over whether clinical placebo effects even exist.[4] Devices are thought to have enhanced placebo effects but poor methods preclude definitive conclusions,[5] and bioethicists have called for research "to test [whether] some treatments produce enhanced placebo effects."[6]

We investigated whether a validated sham acupuncture device has a greater placebo effect than an inert pill in people with persistent upper extremity pain due to repetitive use, often called repetitive strain injury.

Methods

Study design

We carried out a parallel arm, single blind, randomised controlled trial created from the placebo run-in periods for two nested randomised controlled trials, one comparing acupuncture with a validated acupuncture sham device and the other comparing amitriptyline with placebo pill. Our primary investigation was the comparison of sham device with placebo pill during run in. We followed both placebo groups beyond the run-in period to examine the time course of placebo effects.

Participants in the acupuncture group received treatments twice a week. In the amitriptyline group, participants took one pill every day and a research assistant called them every other week to monitor them. We deliberately compared placebo treatments as total entities and did not control for each component of the intervention—for example, participants allocated to the device group had more contact with the practitioner, while those in the pill group took the placebo daily at home. At the end of the run-in period, participants were randomised again within each treatment group to receive either continued placebo or active treatment of the same type. Those in the acupuncture group were given two treatments each week over an additional four weeks. The pill group received amitriptyline or placebo pill for an additional six weeks. The longer treatment period for the pill group allowed adequate time for amitriptyline to maintain a steady state blood concentration.

Study population

The study included adults with distal pain in the arms that had lasted for at least three months and resulted from repetitive use or prolonged static postures. Intensity of pain at enrolment had to be ≥3 on a 10 point numerical pain scale. See bmj.com for exclusions. Participants were allowed to continue any anti-inflammatory and non-excluded drugs but were discouraged from starting new treatments during the study.

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Study procedures

We recruited participants from the community through advertisements and referrals. Eligibility and willingness to participate was determined by telephone. Candidates had enrolment visits during which they completed questionnaires, and underwent testing of grip strength. A study physician examined the candidates to assign a clinical diagnosis according to preset criteria.

Potential participants were told they had a 50% chance of receiving inactive treatment for the entire study and a 50% chance of receiving active treatment at some time during the study. They were told the most common side effects: temporary aggravation of pain with acupuncture and sleepiness, dry mouth, dizziness, and restlessness with amitriptyline. As a recruitment incentive, they were told they could receive either acupuncture or amitriptyline free of charge after participation if they received only placebo treatment during the study.

Placebo treatments

The sham acupuncture device looks exactly like a real acupuncture needle. When the needle is "inserted into the skin" participants think they see and feel needle penetration, but the needle has a blunt tip and retracts into a hollow shaft handle. This sham device has been validated in several studies. After the run-in period, the acupuncturists followed identical protocols for administering real or continued sham acupuncture.

Participants in the pill group were instructed to take one capsule each evening to minimise daytime drowsiness. The placebo capsule contained cornstarch, and the identical-looking amitriptyline capsule contained cornstarch plus 25 mg of amitriptyline.

Blinding

Participants and research assistants were blinded to treatment assignment. Participants received a written description of treatment that was neutral on whether the treatments were effective. Acupuncturists were trained to maintain "neutral" communications with participants and a research assistant routinely monitored acupuncture sessions to ensure adherence to the protocol.

Table 1 Changes in mean (SD) outcome measures at end of two week placebo run-in period

	Sham device (n=133)	Placebo pill (n=133)	Difference (95% CI)	P value
Pain (10 point scale):				
Baseline	5.66 (1.51)	5.22 (1.71)		
2 weeks	4.95 (1.98)	4.65 (1.91)		
Change	−0.71 (1.58)	−0.57 (1.60)	−0.14 (−0.52 to 0.25)	0.49
Symptoms (Levine):				
Baseline	2.2 (0.45)	2.27 (0.52)		
2 weeks	2.1 (0.47)	2.11 (0.54)		
Change	−0.12 (0.38)	−0.16 (0.38)	0.04 (−0.05 to 0.13)	0.36
Function (Pransky UEFS):				
Baseline	24.36 (12.30)	24.47 (11.88)		
2 weeks	23.79 (12.63)	21.91 (11.78)		
Change	−0.56 (8.57)	−2.56 (7.41)	2.00 (0.06 to 3.92)	0.04
Grip strength (kg):				
Baseline	30.13 (11.31)	28.44 (12.58)		
2 weeks	30.10 (11.42)	28.97 (10.90)		
Change	−0.03 (5.94)	0.52 (5.53)	−0.55 (−1.94 to 0.84)	0.44

UEFS=upper extremity function scale.

Outcome assessments

The primary outcome was self reported intensity of pain in the most severely affected arm during the preceding week measured on a 10 point numerical rating scale ranging from no pain (1) to the most severe pain imaginable (10). Secondary outcome measures were the Levine symptom severity scale for upper extremity,[7] the Pransky upper extremity function scale,[8] and grip strength measured by a Jamar hand dynamometer.

Statistical analysis

This trial was prospectively designed to assess and compare placebo effects of a sham device and placebo pill. Evaluation of the effects of real acupuncture and amitriptyline were secondary objectives. Our power calculation showed that we needed 135 participants in each placebo group. We estimated changes in pain scores and to adjust for drop outs, we used a last value carried forward approach.

We used regression models to assess longitudinal trends in outcomes using baseline and two week data for all patients and mid-treatment and end of treatment data for participants who were randomised to continue on sham or placebo during the remainder of the study (see bmj.com).

Results

Study population

We enrolled participants from June 2001 to April 2003. A total of 1110 people completed telephone screening and, after exclusions, 270 people were randomised into the placebo run-in phase (see bmj.com). At phase 2 of the study, 60 were randomised to continue on the sham device and 59 to continue on the placebo pill. Despite appropriately conducted randomisation, participants in the sham device group had more pain at baseline than those in the placebo pill group (difference on the 10 point scale 0.44, 95% confidence interval 0.05 to 0.83). As a sensitivity analysis, we used linear regression models to adjust for baseline pain scores. Otherwise the groups were well balanced. Results were similar for the second randomisation.

Outcomes

Mean changes in outcomes at the end of the run-in period show that the only significant difference between the sham device and pill groups was on the arm function scale and favoured the placebo pill group (table 1). Most of the difference in improvement was due to improved ability to sleep, open jars, and write. (The ability to sleep improved by 0.52 units in the pill group v 0.17 units in the sham device group.) These results went from marginally significant ($P=0.04$) to marginally non-significant ($P=0.08$) when we adjusted for differences in baseline pain scores.

In the longitudinal regression analyses, pain scores per week and the symptom severity scale decreased significantly more in the sham device group than in the pill group: the differences were -0.33 v -0.15, $P<0.001$, for pain scores and -0.07 v -0.05, $P=0.02$, for the symptom severity scale (table 2). Differences were not significant for arm function or grip strength. These findings persisted in significance, direction, and magnitude after we adjusted for baseline pain scores. Figures 1 and 2 plot time trends for these significant outcome measures from baseline until the end of

treatment period. At a subsequent one month follow-up visit, pain scores remained significantly lower than at baseline in both groups (−1.58, SD 2.06, P<0.001, and −1.20, SD 1.64, P<0.002), but the difference between groups was not significant (−0.38, −1.06 to 0.30, P=0.27). By descriptive analysis, changes in pain scores at the end of the placebo run in and at the end of treatment did not differ among participants in the three main diagnostic subgroups (tendonitis/epicondylitis, neuropathic/neuralgia, or other diagnoses) at any time point.

Nocebo effects of placebo treatments

The types of side effects were totally different in the two study groups and clearly mimicked the information given at informed consent (see bmj.com). At two weeks, a quarter of the participants receiving the sham device reported one or more side effects compared with nearly a third in the pill group (P=0.30). There was no overlap in reported adverse effects in study groups. No reported effect was serious even though three participants withdrew from the placebo pill group because of fatigue or dry mouth.

Discussion

In this large prospective randomised controlled trial we found no evidence for an enhanced effect with placebo devices compared with placebo pills during the two week placebo run-in period, though an effect did become evident in participants who remained on placebo for the duration of the subsequent nested trials. This result applied to the primary pain outcome and to severity of symptoms but not to other outcomes.

Recent mechanism studies of placebo treatments have shown placebo effects beyond spontaneous fluctuations (for example, the natural evolution of disease, spontaneous remission, measurement artefacts, and regression to the mean). These studies have all been short term and usually accompanied with deceptive expectations—for example, when participants are told that placebo is a "potent pain medication."[9 10] The results of our study provide evidence that a placebo effect exists over time, even when instructions are neutral. If spontaneous remission alone accounted for our findings, the type of placebo should have made no difference, and we should not have been able to detect a difference between the device and pill. That the differential placebo effect was confined to self reported measures (and not to grip strength) suggests an effect that may be confined to subjective outcomes. The magnitude of this enhanced device effect was small.

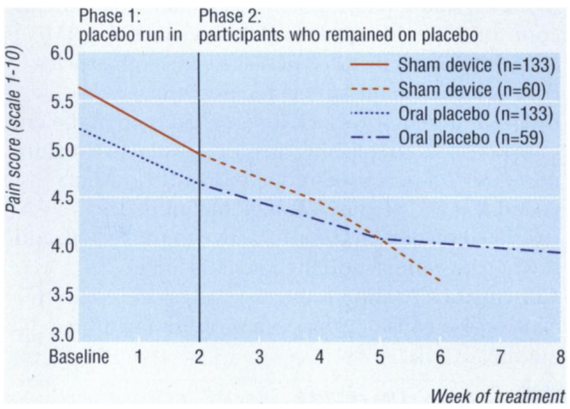

Fig 1 Time trends of outcomes for all participants during the placebo run-in period and for participants who remained on placebo treatments: pain scale

Table 2 Average weekly changes in outcome measures*

	Average weekly change (95% CI)		
	Sham device	Placebo pill	P value
Pain (10 point scale)	−0.33 (−0.40 to −0.26)	−0.15 (−0.21 to −0.09)	<0.001
Symptoms (Levine)	−0.07 (−0.09 to −0.05)	−0.05 (−0.06 to −0.03)	0.02
UEFS (Pransky)	−0.73 (−1.10 to −0.37)	−0.59 (−0.88 to −0.30)	0.54
Grip strength (kg)	0.04 (−0.21 to 0.28)	0.05 (−0.15 to 0.24)	0.92

UEFS=upper extremity function scale.
*Based on longitudinal regression analysis and generalised estimating equations, last value carried forward for missing data. Reported values are estimated coefficients for study week in model (that is, slope over time).

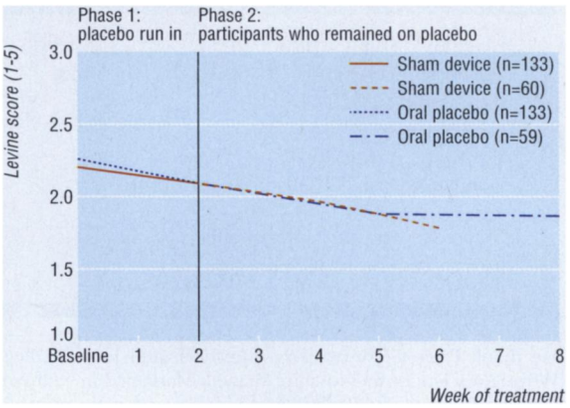

Fig 2 Time trends of outcomes for all participants during the placebo run-in period and for participants who remained on placebo treatments: Levine symptom severity scale

The placebo pill had a greater effect during the first two weeks on the function outcome. This may be due to improvement in sleep, which may have been due to the emphasis of sleepiness as a possible side effect of amitriptyline. This finding disappeared by the end of the treatment phase.

Our findings contribute to the debate on the influence of information provided at informed consent and subsequent reported adverse effects; results of previous smaller prospective randomised controlled trials have been contradictory. We found that reported side effects perfectly mirrored the information provided to participants.

Limitations of our study are that, firstly, we did not have a group of participants who had no treatment, which would have helped to clarify the role of spontaneous remission. None the less, our comparison of two different placebos has the advantage of being less susceptible to bias compared with an unblinded waiting list control. A second limitation was the relatively short placebo run-in period we used. Thirdly, we chose a longer treatment period during the second phase for the amitriptyline arm than the acupuncture arm. While this was reasonable for evaluating real treatment, the net effect was to create complexity for the analysis of placebo effects. Finally, we chose to compare the placebos as unified entities and not to examine how components of the interventions such as daily treatment versus twice weekly treatment, may have influenced results.

What is already known on this topic

Placebo devices are thought to have enhanced placebo effects compared with oral pills, but rigorous evidence is lacking

Controversy exists over the existence of placebo effects over and beyond the natural course of disease and whether information provided by informed consent influences reports of adverse events

What this study adds

A validated sham acupuncture device has a greater placebo effect on subjective outcomes than oral placebo pills

A placebo analgesia effect beyond the natural course of disease is detectable over time

Adverse events and nocebo effects are linked to the information provided to patients

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Competing interests: TJK works as a consultant for Kan Herbal Co, Scotts Valley, CA.

Ethical approval: The institutional review boards of Cambridge Health Alliance, Beth Israel Deaconess Medical Center, Harvard Medical School, and Harvard School of Public Health approved the study.

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Importance of free access to research articles on decision to submit to the *BMJ*: survey of authors

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Abstract

Objectives To determine whether free access to research articles on bmj.com is an important factor in authors' decisions on whether to submit to the *BMJ*, whether the introduction of access controls to part of the *BMJ*'s content has influenced authors' perceptions of the journal, and whether the introduction of further access controls would influence authors' perceptions.

Design Cross sectional electronic survey.

Participants Authors of research articles published in the *BMJ*.

Results 211/415 (51%) eligible authors responded. Three quarters (159/211) said the fact that all readers would have free access to their paper on bmj.com was very important or important to their decision to submit to the *BMJ*. Over half (111/211) said closure of free access to research articles would make them slightly less likely to submit research articles to the *BMJ* in the future, 14% (29/211) said they would be much less likely to submit, and 34% (71/211) said it would not influence their decision. Authors were equally divided in their opinion as to whether the closure of access to parts of the journal since January 2005 had affected their view of the *BMJ*; 40% (84/211) said it had, 38% (80/211) said it had not. In contrast, 67% (141/211) said their view of the *BMJ* would change if it closed access to research articles. Authors' comments largely focused on disappointment with such a regressive step in the era of open access publishing, loss of a distinctive feature of the *BMJ*, a perceived reduction in the journal's usefulness as a resource and global influence, restricted readership, less attractive to publish in, and the negative impact on the journal's image.

Conclusions Authors value free access to research articles and consider this an important factor in

A copy of the electronic survey and details of all responses as received are on bmj.com.

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