Journal of Clinical Epidemiology 83 (2017) 18–23

Sham surgical procedures for pain intervention result in significant improvements in pain: systematic review and meta-analysis

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Accepted 1 December 2016; Published online 4 January 2017

Abstract

Objective: To perform a systematic review and meta-analysis to study the magnitude of the placebo effect associated with sham surgery procedures.

Study Design and Setting: We conducted a systematic search for randomized controlled clinical trials comparing any type of surgery to a corresponding sham placebo group and compared improvements in the sham treatment arms in subjective, objective, categorical, and continuous outcomes, as well as complication rates and mortality. Effect sizes were reported as standardized mean differences (SMDs). This is a systematic review and meta-analysis.

Results: The overall effect size for pain improvement after sham surgery was SMD = 0.22 (95% confidence interval [CI] = 0.08–0.35) with improvement most marked at 1 month (SMD = 0.34, 95% CI = 0.26–0.43). There was a higher rate of improvement in subjective outcomes compared to objective outcomes for both dichotomized (number of patients with improvement) (42.8% compared to 27.1%) and continuous outcomes (SMD = 0.12, 95% CI = −0.05, 0.30 vs. SMD = −0.01, 95% CI = −0.05, 0.03). There were no deaths in the sham treatment arms and major complications were very rare (0.2%, 95% CI = 0.0–0.6%).

Conclusion: Sham surgery is associated with a large improvement in pain and other subjective patient-reported outcomes but with relatively small effect on objective outcomes. Sham surgeries are overwhelmingly safe. The magnitude of this effect should be used when planning future sham-controlled surgery trials.

Keywords: Sham; Surgery; Sham surgical; Sham effect; Placebo; Placebo effect; Systematic review; Meta-analysis; Randomized; Pain

1. Introduction

Quality, up-to-date sham-controlled randomized trials can effectively guide decision making for surgeries in individual patients [1–4]. This form of evidence-based medicine, when deemed ethically appropriate, can help prevent patients from receiving surgical interventions that have no proven therapeutic benefit or that can even be harmful [1,2,5]. However, sham surgical trials have been controversial [2,3,6,7]. Several authors have suggested that sham trials jeopardize the safety of patients by subjecting them to unnecessary risk and invasive procedures [7–9]. However, others suggest that sham interventions can be ethical and clinically meaningful [1,3,5,10,11].

Despite the ethically charged obstacles, sham clinical trials have made key contributions in the past decade. There is rising evidence that some surgical interventions have a sizable "placebo effect" on patients [1,3,10,12–16]. The placebo effect and other nonspecific effects complicate the interpretation of the surgery's therapeutic effect [1]. These effects suggest that the difference in treatment between surgery and sham placebo may not be large or significant [1,17]. In other words, the clinical effect of the surgery may not be better than the sham placebo effect.

Although many sham-controlled clinical trials have demonstrated a "placebo effect" associated with sham surgery, the magnitude of the placebo effect in sham surgical trials remains unclear. Understanding the magnitude of the sham effect and determine what factors can affect the magnitude of the sham effect is important for those who are interpreting sham-controlled randomized controlled trials as well

Funding: None.
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http://dx.doi.org/10.1016/j.jclinepi.2016.12.010
0895-4356/

What is new

- This is the first systematic review and meta-analysis evaluating the magnitude of the placebo effect associated with sham surgery procedures.

as for appropriately powering future trials. We conducted a systematic review and meta-analysis of sham-controlled surgical studies to study the magnitude of effect associated with sham surgeries. For this study, we only included data from the sham arm of these trials as we were attempting to understand the magnitude of the sham effect. We studied differences in sham effect by outcome studied (i.e., pain, subjective outcomes, objective outcomes) and by time (i.e., within days, weeks or months after the sham procedure) to better understand what variables can affect the magnitude of the sham effect.

2. Patients and methods

2.1. Literature search

To identify randomized clinical sham surgery trials, we conducted a systematic search in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials from January 1, 2000 to July 8, 2014. This time period was chosen so that we would focus on studying more modern interventions. We defined a ''sham surgery trial'' to be a randomized clinical trial comparing the efficacy of surgery to a placebo surgery, a faked surgical procedure designed to mimic a true therapeutic surgical intervention. We also defined a surgery as an intervention that alters the anatomy, including incisions and implants and stimulators that were left in the body for at least 1 day. A search in clinicaltrials.gov and of independently identified systematic reviews was also conducted to identify additional sham trials.

2.2. Study selection

Identified articles were screened based on the inclusion criteria: randomized controlled clinical trial comparing any type of surgery to a corresponding sham placebo group. Exclusion criteria included the following: (1) nonrandomized trials; (2) no true sham group (i.e., pharmacological treatment as placebo); (3) having results in a later publication; (4) results that were not yet available; and (5) nonsurgical interventions in the treatment group (i.e., lidocaine or steroid injections).

We studied the sham effect for (1) pain improvement in studies in which pain was reported as an outcome, (2) improvement in subjective patient-reported outcomes, and (3) improvement in objective, measurable outcomes.

2.3. Data abstraction

Two reviewers independently reviewed the titles and abstracts and then evaluated the full articles for potential eligibility. Both reviewer assessed the inclusion of each of the relevant trials and agreed on a final list of trials. We extracted characteristics of each published article using a standardized data collection form. For each trial, we documented author; journal; year of publication; type of procedure studied; number of patients in the sham group; primary outcome(s); improvement in outcome; length of follow-up; major complications; and the study outcome assessing which study arm (intervention or sham) had the more improved outcome (as determined by achieving statistical significance in the primary study outcome as determined by the two reviewers). Major complications were defined as those that resulted in death, prolonged hospital stay, or any additional medical or surgical intervention to reverse the complication.

Any primary outcome, whether dichotomized (number of patients with improvement), continuous, subjective, or objective, was included in this study. Subjective outcomes were defined as patient-reported measures such as quality of life, pain, symptom improvement or worsening, and social health. Pain was included whether it was the primary or secondary outcome. In cases where the primary outcome(s) were not clearly delineated, two readers read the study and determined which outcomes were the main outcomes that were reported in the study and defined those as the primary outcome. This was done by consensus. Objective outcomes included outcomes that could be measured through standard diagnostic testing, such as imaging, blood tests, hemodynamic measurements, pressure measurements, or pathologic studies (i.e., ejection fraction, perfusion defects on single-photon emission computed tomography, sphincter pressures). It is important to note that for studies which specified an objective outcome such as ''50% improvement in pain,'' this study was analyzed as having a binary outcome.

Outcomes were only abstracted from the sham groups in the trials as the focus of our study was the safety of the sham procedures and magnitude of the sham effect. The rationale for studying objective and subjective outcomes separately was based on our hypothesis that measurable/objective outcomes would be less prone to suffer from a substantial treatment effect from a sham procedure, whereas subjective/patient-reported outcomes would be more prone to do so. We chose to study pain, in particular, because it was the most commonly reported outcome of the included studies. Double counting of subjects was allowed as long as the outcomes reported between studies were different.

2.4. Outcome variables

Our primary outcomes in this meta-analysis were (1) improvement in pain on a 0–10 analogue scale, (2) improvement in any subjective outcome, and (3) improvement in any