Placebo Trials in Orthopaedic Surgery

The authors of "Sham Surgery Studies in Orthopaedic Surgery May Just Be a Sham: A Systematic Review of Randomized Placebo-Controlled Trials"[1] cast a critical eye on placebo surgical trials. We applaud any attempt to identify the methodologic limitations of scientific research and to ask researchers to aim higher. We do, however, have concerns about the recommendations made and the conduct and conclusions of the study.

The study hypothesis is that "these studies would have multiple significant limitations that invalidate their conclusions." This hypothesis was not tested, nor was it accepted or rejected (i.e., were the findings of placebo trials invalidated or not). Instead, the study concludes that there were methodologic limitations that "may" invalidate the conclusions. The same could be said of any published research, as no research is perfect.

We disagree with the claims that studies performed in certain countries such as Finland and Denmark are not generalizable due to high levels of resilience in these populations. For example, the participants in these studies were not resilient enough to avoid complaining of pain and seeking treatment. We also warn against any reliance on per-protocol analyses, as they do not allow casual inference. Intention-to-treat analysis is a key part of experimental research, as it maintains the randomized treatment assignment to ensure balanced groups

The scientific principles underlying research can be seen simply as methods of error reduction that reduce bias and improve accuracy. We expect the authors to agree that the best test of any surgical procedure is to compare it with not performing the procedure. Further, the 2 treatment groups should not be systematically different (achieved by randomization) and, preferably, the patients and outcome assessors should not know the treatment allocation (to reduce performance and detection bias). We agree that there are other methods (e.g., the method and timing of randomization, blinding the statisticians, ensuring high rates of follow-up) that would add to the reduction of error, but to "invalidate" such high-level (by the authors own ratings) research implies that we should instead rely on studies that do not include blinding, are not randomized, or do not contain a comparator. To do so is to accept inferior methods of measurement, simply because the best methods are not perfect.

Fortunately, for the conditions most commonly studied in placebo trials of surgery, the results are entirely in keeping with the results of high-quality, non–placebo-controlled trials, particularly after taking into account the overestimation of benefit inherent in open trials with subjective outcomes.[2-4] There is also an overemphasis on a "placebo effect," which is largely due to natural history and regression to the mean; using a placebo control is just a good way of blinding patients, and therefore reducing error.

Rather than asking us to aim higher, we feel the message of this critique may be interpreted as asking us to aim lower.

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Review of Randomized Placebo-Controlled Trials

We read the recent review by Sochacki et al.[1] with great interest. The authors' main conclusion is that major orthopaedic trials involving sham surgery have methodologic deficiencies that may invalidate their conclusions. Considering that no rigorous evidence supports the use of interventions included in these trials, we find the authors' conclusions incongruous.

Evidently, no study is perfect. But do the suggested limitations invalidate the results of sham-controlled trials? The assumption that the included interventions provide benefits is based on data from observational studies that lack even the simplest concept in efficacy analysis, a control group. The authors seem to be implying that we are supposed to rely on observational data or expert opinions rather than data from placebo-controlled studies.

One of the criticisms concerns the lack of analysis of genetic markers for placebo effect. This critique is not valid for 2 reasons. First, there is no reason to presume that knowing the "placebo genes" of the trial population is needed to reduce bias. On the contrary, randomization is the best tool we have to avoid such bias since randomization will distribute hidden covariates efficiently. Second, the study of the genetics of the placebo response is in its infancy and should so far be considered basic research.[2] The results have not yet been applied in clinical studies in any field of medicine. Considering the current status of the "placebome" research, it is a gross overstatement to demand the analysis of genetic markers for placebo response in orthopaedic or any other clinical trial.

Another criticism concerns 2 studies performed in Finland. According to the authors, *sisu*, a mystic cultural characteristic defining the resilience of Finns, invalidates the generalizability of the study results. Here the authors refer to 2 articles. The first one is a review describing the potential advantages the Nordic countries have for pioneering in genome-wide association studies.[3] It describes the collaborative initiative called SISu (Sequencing Initiative Suomi [=Finland in Finnish]). Here, SISu is simply an acronym that has nothing to do with sisu, the "*form of courage, grit, and determination*" in Finland. Nowhere in this paper do the authors claim that studies including patients "*born and raised in Finland*" could not be extrapolated to the rest of the world. The second reference is to a short story of an elderly man with metastatic melanoma written by his treating doctor after the patient's death.[4] The man certainly displayed *sisu* during his life, but again, the story provides no justification for the claims made by the authors.

Finally, authors state that "no patients underwent psychiatric or psychologic evaluation to test their competence to participate in a randomized sham surgery trial." They seem to imply that consenting to a potentially harmful surgical procedure that has not been rigorously evaluated does not require psychiatric evaluation but consenting a study evaluating such a procedure does.

Regardless of the presented shortcomings, sham-controlled studies provide the greatest level of evidence we can currently deliver to our patients. While any improvement in methodology should be embraced, the claims made by authors are not supported by their analysis.

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