Chapter 29
Using a Placebo or Sham Procedure as a Control: Ethics and Practicalities

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New surgical treatments are often introduced without proof of efficacy from randomized controlled trials, and some procedures that are perceived to be effective have never been rigorously tested [1, 2]. In the early 2000s the results of two particularly controversial randomized controlled trials of surgical interventions appeared in the New England Journal of Medicine, Published in 2001 the Freed trial tested embryonic stem cell implantation as an experimental cutting-edge therapy for Parkinson's disease compared to a control group without implantation. Unlike most controlled surgical trials, the control group underwent a 'sham surgery' nearly identical to the intervention procedure including four twist drill holes through the frontal bone. However, for patients in the control group, the dura mater was not penetrated. This procedure blinded study participants to whether they received the intervention or not making it possible to account for any placebo effect of the surgical intervention per se.

The following year Mosely et al. published their findings in a study which compared patients with osteoarthritis of the knee randomized to undergo arthroscopic debridement, then a commonly accepted therapy, versus patients randomized to two other groups (1) arthroscopic lavage only, or (2) a 'placebo surgery,' where the surgery was simulated in detail but the actual procedure was limited to three 1-cm incisions in the skin. While the Freed study tested a novel therapy, this study used a design with a 'placebo surgery' to test whether an accepted therapy was, in fact, effective.

Recent years have seen further randomized trials of surgical interventions using placebo or sham surgeries as the control. Two reviews published in 2015 examined randomized controlled trials of surgical procedures where the control group received a placebo, or sham, surgery [1, 2]. Both reviews found that more than half

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of the studies considered showed significant improvement among the control groups, and the treatment group was superior to the placebo in less than half of the trials. Furthermore, in most of those the difference between intervention and placebo was small. This evidence of significant effects from placebo procedures highlights the need to account for the placebo effect in surgical trials. Nevertheless, placebo-controlled surgical trials remain controversial and can be difficult to conduct.

Blinding and Placebos

Blinding of the randomly assigned treatment in clinical trials is a key design feature to protect the integrity of the trial. Depending on the level of blinding (single or double-blind), it controls for bias due to participants' (single blind) and also researchers' (double-blind) expectations [3]. It has long been recognized in medicine that some accepted therapies are observed to be more effective than no treatment at all but, after rigorous testing, are found to be no more effective than a placebo. In these cases, the effect of the accepted treatment is likely due largely to the patients' expectation of efficacy. The existence of this placebo effect highlights the importance of managing both conscious and unconscious expectations. To minimize the chance that observed differences can be attributed to the placebo effect, when a study compares two or more treatments, care should be taken for them to appear as similar as possible. In some scenarios such as in studies comparing two medications, incorporating a placebo comparator may be simple. For studies comparing two surgical techniques or a surgical technique to a nonsurgical treatment, it may be difficult or impossible to maintain blinding.

Distinctive Aspects of Sham Surgeries or Procedures

The most obvious difference between placebo-controlled trials of medications and procedures is that finding a suitable placebo becomes much more difficult with an invasive surgical procedure involving the use of anesthesia and obvious long-term effects such as scarring. Trials of therapies involving injections or infusions could use saline as a placebo without difficulty because the intrinsic harm is no greater than drawing blood for laboratory tests which is a routing part of medical testing. This qualifies these placebos as posing 'minimal risk.'

There is evidence that the placebo effect is stronger for more invasive procedures than for medications, in turn suggesting that a suitable placebo for a procedure must be more invasive than an injection, and therefore beyond what can be considered to be minimal risk [4]. Summarized evidence from various trials suggested that in placebo-controlled trials, improvement from an injected placebo was greater than from oral placebo, and that sham acupuncture had a greater placebo effect than an

oral placebo [4]. The authors presented additional evidence of various novel procedures with early anecdotal success which were later found to be unsupported by controlled trials, making a case that the placebo effect may be stronger when the intervention is more involved than swallowing a pill. They also proposed a design for a prospective randomized trial to compare a placebo procedure (sham acupuncture) to an oral placebo. Subsequently, Kaptchuk conducted the proposed trial in the context of treating arm pain and reported that the sham acupuncture was found to be more effective than an oral placebo [5]. The finding that the placebo effect may be more pronounced for interventions than for oral placebos carries the implication that the inclusion of placebo or sham procedures may be even more important for evaluating surgical interventions than they are for medical interventions. It also highlights the importance and difficulty of designing a realistic and suitable sham procedure to ensure blinding and account for benefits due solely to the placebo effect itself.

Ethics

Reports of preliminary results of the Parkinson's trial sparked an ethical controversy precisely because the sham procedures could not be considered to be harmless, raising questions about whether and in what circumstances sham surgeries could be considered to be ethical and appropriate [6, 7]. The critical analysis by Ruth Macklin identified three main ethical issues to consider: (1) Finding a balance between the highest standards of research design and the highest standards of ethics; (2) uncertainties and disagreements in the analysis of risks and benefits of research; and (3) issues of informed consent.

The first issue, finding a balance between research and ethical standards, considers when placebo controls may be appropriate in surgical trials. There is a general consensus that as with medical trials placebo controls may be acceptable when there is no standard effective therapy. Others add that there may be a stronger argument for a placebo control when the major outcomes are subjective and self-reported such as pain, which is known to be susceptible to the placebo effect [8, 9]. Even in cases where a placebo control seems ethical and the strongest design, the fact that a placebo surgery undeniably causes harm without the expectation of therapeutic benefit seems to conflict with the mandate that ethical research should minimize risk of harm. Macklin [6] concludes that the duty to minimize harm is paramount and that placebo surgery is not ethical. Others argue that in the presence of genuine equipoise, the placebo surgery causes no more harm than the experimental surgery, and possibly less if the experimental surgery is found to be ineffective [8, 10]. They conclude that risk should be minimized within the context of answering the scientific question. The arthroscopy trial is a good example of minimizing harm within the context of the study. Participants randomized to the placebo group were not placed under general anesthesia or intubated and received

only three 1-cm skin incisions, and were thus subjected to a less-invasive procedure than the intervention groups [11].

The second issue pertains to analyzing and comparing the risks and benefits of the proposed research, particularly with respect to the risk to the subjects in the placebo group. Here, the opposing viewpoints differ in weighing the risk to the individual versus either that individual's potential benefit or the potential benefit in terms of the knowledge to be gained. In Macklin's analysis of the Parkinson's trial from the individual standpoint, the risk–benefit ratio is at best uncertain and at worst unfavorable [6]. However, others consider the benefit more in terms of the knowledge to be gained, and the potential number of future ineffective surgeries avoided, thus ultimately reducing risks for many [9, 12]. Some authors even suggest considering the expected benefit of the placebo surgery rather than considering only the surgical risks [13]. While there is consensus that the risk of the placebo procedure should be reduced as much as possible without sacrificing the validity of the experimental design, there is little agreement among ethicists on how to decide when the potential benefits outweigh the risks. This is further complicated by the variability in severity of proposed placebo procedures that can range from superficial skin incisions to drilling holes in participants' skulls.

The third issue in Macklin's critique considers whether informed consent in studies using sham procedures is adequate to protect the patient's interests. One point is that informed consent is necessary, but not sufficient for research to be considered ethical. Institutional review boards (IRB) are charged with judging whether the risks are justified by potential benefits and could decide in some cases that they are not, even with consent. A more troubling concern is whether participants are truly capable of rationally providing informed consent to a sham procedure. There is some evidence that patients who seem to have been properly consented do not understand their role in the study. Macklin notes "In one study, people who had been research subjects told interviewers that they had trusted their doctors, believed that their physicians would do nothing to harm them, and thought that the physician–researchers had always acted in their best medical interests." Macklin further reports that patients in the Parkinson's study were told that if randomized to the sham procedure, they would be offered the intervention if it proved to be effective. Ultimately, the intervention resulted in more serious adverse events than expected and was not offered. When told they would not be able to receive the real intervention, some participants expressed anger rather than relief that they had been spared a possibly dangerous and ineffective procedure.

Trials with placebo procedures may subject participants to a problematic degree of deception beyond disclosing the randomized and blinded design at the time of consent. In the Parkinson's study, the surgeon asked patients undergoing the sham tissue transplantation "Are you ready for the implant now?" This active deception, even in the context of the study, could mislead patients into thinking that they had actually received the intervention despite the randomized design. This highlights variability among sham procedures. Such a statement would not be relevant in the arthroscopy trial where all procedures were done with the participant under sedation or anesthesia. The Parkinson's study could also have used more neutral terminology

asking instead 'Are you ready to proceed' to minimize any specific deception. It is thus unclear whether participants truly understand their role in the study, the possibility that the procedure received may not be in their best interest, and the full extent of blinding. Thus, even seemingly satisfactory informed consent procedures may fail to ensure that participants understand the risks and benefits of the study.

Practical Considerations and Guidelines

In 2002 the Council on Ethical and Judicial Affairs of the American Medical Association published a report titled "Surgical 'placebo' controls" in the Annals of Surgery which gave a cogent overview of the ethical and practical considerations and provided a five-point recommendation [9].

First: A placebo surgery should be considered only when no other experimental design could provide the necessary evidence. It recognizes that placebo or sham procedures are ethically controversial, to be used only when truly necessary.

Second: Particular attention should be paid to the informed consent process. The risks of procedures should be carefully explained, and the randomized design emphasized. This should carefully explain the differences between study arms along with the importance of blinding and the fact that the participant should not know which treatment was received. Additional measures may be employed to ensure that consent is truly informed, such as an additional neutral witness or a trained monitor present during the consent process. The arthroscopy trial went so far as to require that consenting participants write the following statement in their own chart: "On entering this study, I realize that I may receive only placebo surgery. I further realize that this means that I will not have surgery on my knee joint. This placebo surgery will not benefit my knee arthritis" [11]. In that trial only 44% of patients consented to participate suggesting that the consent process was effective. The fact that among each of the three study arms approximately 13% of participants thought they had received the placebo procedure demonstrates both that the blinding was effective and that even with stringent informed consent procedures participants may still tend to overestimate the likelihood that they will receive the experimental treatment.

Third: The use of a surgical placebo is not justified when the experimental procedure being tested is a modification of an already accepted procedure. In this case the suitable control group is the accepted procedure. An example would be comparing robotic surgery versus laparoscopy for a standard procedure or inguinal hernia repair with and without mesh.

Fourth: A surgical placebo group may be considered when testing an experimental procedure to treat a condition that has no accepted surgical treatment or to test an accepted surgery when its efficacy has come into question. However, this is only appropriate when the relevant outcomes are likely to be susceptible to the placebo effect and the risks of the placebo procedure are relatively minor. As a general rule, outcomes that can respond to the placebo effect tend to be patient self-reported outcomes such as pain, or other related outcomes such as functional tests, which can

be influenced by patient's perceptions and expectations. This can also extend to physiological measures like blood pressure [14]. Determining whether the risks of the placebo procedure are sufficiently low requires careful thought and is ultimately subjective. The case of the arthroscopy trial where the placebo procedure involved three small skin incisions and minimized anesthesia risks presents a clear case of low risk. On the other hand, in the Parkinson's trial, the placebo procedure was more invasive, potentially pushing the boundary of acceptable risk. Whether a placebo surgery can be designed to maintain blinding and to have an acceptably low risk will depend on the procedure being tested. In the case of a complicated procedure with a prolonged recovery time, it may not be feasible.

Fifth: When there is an acceptable and effective nonsurgical treatment and withholding or forgoing that treatment could cause injury, then the nonsurgical treatment should be offered to all arms of the surgical trial. This is consistent with both the conduct of the Parkinson's trial where standard medical therapy was continued throughout the trial.

Conclusion

There is ample evidence that surgical patients can experience a placebo effect, and that this placebo effect may be even more pronounced than for a medical placebo. Some previously accepted, and seemingly effective, surgical procedures have been shown in placebo-controlled trials to be no more effective than a sham procedure. Therefore, a rigorous evaluation of the efficacy of some surgical procedures will require a carefully designed randomized trial where the control arm includes a placebo or sham procedure and appropriate blinding to account for the placebo effect. Nevertheless, although the 'best' experimental design may require a placebo surgery, the fact that any surgery causes some harm and increases the risk to control participants raises ethical concerns that must be addressed to justify the use of a placebo procedure. For a placebo-controlled surgical trial, there must be no surgical treatment that is known to be superior to placebo and there must be true equipoise between the experimental and placebo procedures. The use of placebo controls in surgical trials requires increased attention to designing a placebo procedure to maintain blinding while minimizing risk, along with scrupulous attention to the informed consent process.

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