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The Ethical Problems with Sham Surgery in Clinical Research

The recent use of sham surgery in randomized, controlled trials raises three critical questions about research involving human subjects. The first question concerns the tension between the highest standard of research design and the highest standard of ethics.[1] When these two standards come into conflict and researchers cannot simultaneously meet both, which should prevail, and how should a balance be struck? The second question points to ongoing uncertainties and disagreements in assessing the risks and benefits of research protocols. When reasonable people — the members of well-established institutional review boards or the sponsors of research — disagree in their risk–benefit assessments, can one assessment or the other properly be considered the correct one? The third question concerns the relation between the risks of a protocol and the informed consent of research subjects. Does the requirement of informed consent imply that potential subjects should be permitted to decide what risks they are willing to take, in the hope of receiving some benefit? Or do research subjects require protection that may limit their choices?

Scientific and Ethical Standards

Situations in which scientific standards in research clash with ethical requirements are, fortunately, quite rare. The use of placebo controls in some types of research remains controversial despite the status of the placebo-controlled trial as the gold standard of research design.[2,3,4,5,6,7,8,9] Critics argue that it is difficult to justify the use of placebo controls when effective standard therapy exists.[3,6,10] Despite these criticisms, which typically target a particular study or class of studies, placebo controls in drug trials are widely accepted on ethical as well as scientific grounds. Commentators who consider the use of a placebo group unethical if there is a standard treatment that has been proved effective nevertheless find placebo controls ethically acceptable in research involving conditions for which there is no standard therapy or those for which standard therapy has been shown to be no more effective than placebo.[1,6]

At first glance, the recent studies involving patients with Parkinson's disease, in which sham surgery is used as a control and real surgery is used to implant fetal cells,[11,12,13] appear to fulfill the conditions that would make the placebo controls ethically acceptable. Existing treatments for Parkinson's disease are ineffective in helping patients regain lost motor function, which is one of the hoped-for results of surgical implantation of fetal cells in the brain. The same may well be true of clinical trials that compare the effect of arthroscopic surgery for osteoarthritis with that of a sham surgical procedure.[11,13] Why should the use of sham surgery be questioned when the conditions for the ethical acceptability of a placebo-controlled study appear to be met?

The chief reason is that performing a surgical procedure that has no expected benefit other than the placebo effect violates the ethical and regulatory principle that the risk of harm to subjects must be minimized in the conduct of research.[14] In a standard, placebo-controlled drug trial, the inert substance used in the placebo group is known to have no adverse effects. The potential harm in a placebo-controlled drug trial stems from withholding or withdrawing a standard medication that has been proved effective for the treatment of the disorder being studied. The question of how great the risks of sham surgery are in any particular trial is distinct from the question of whether a surgical intervention carries risks of harm that are greater than those associated with no surgical intervention. It is undeniable that performing surgery in research subjects that has no potential therapeutic benefit fails to minimize the risk of harm. An alternative research design that did not involve sham surgery would pose a lower risk of harm to the subjects in the control group of the study. But herein lies the tension between the scientific and ethical standards: the alternative design would be less rigorous from a methodologic point of view.

Defenders of placebo-controlled surgical trials have challenged the "double standard" for drug research and surgical research. One physician asked, "If we so well accept a placebo in . . . drug trials, why don't we accept it in surgery trials?"[13] The chairwoman of the National Institutes of Health committee that reviewed the proposal for the research on Parkinson's disease was quoted as saying, "Too many surgeries are done on the basis of anecdotal evidence and not put to the same sort of rigorous tests that drug therapies are."[11] Although this dichotomy in research design may be a double standard, it is based on adherence to an essential ethical standard for research: the requirement to minimize the risk of harm to subjects.

Assessing Risks and Benefits

The risk of harm in placebo-controlled surgical studies is not limited to the morbidity associated with the surgical intervention. In the studies employing sham brain surgery in patients with Parkinson's disease, general anesthesia was administered to the subjects in the placebo group. One bioethicist approved of the protocol for the sham surgery because the risks associated with sedation have dropped substantially in recent years.[13] This defense relies on the overall ethical judgment that the risks to the subjects who undergo the study procedure and those who undergo the sham procedure are outweighed by the benefits of the research — in this case, the contribution to medical science.

In a trial of a treatment for pain in patients with cancer, the investigators inserted capsules into a space at the base of the spine by means of a lumbar puncture. In some subjects, the capsules contained an inert substance,

and in others it contained an analgesic that could alleviate the pain. According to one estimate, 10 percent of patients undergoing this procedure experience a severe headache that can last a day or two after the procedure. In addition, there is a risk of permanent nerve injury or paralysis.[11] These risks can hardly be considered minimal. Although the probability of nerve injury or paralysis may be low, the magnitude of the harm is great. In addition, standard treatments for cancer-related pain exist, so it is questionable whether this experiment meets the condition regarding alternative treatments that the critics of placebo controls in medical studies insist must be met.

Assessments of risks and benefits are difficult enough to make when substantial evidence of a treatment's efficacy exists and when subjects in the placebo group are not exposed to harm from the intervention. Controversies about both the magnitude of the potential harm and the risk–benefit ratio have surrounded the trials involving sham surgery in patients with Parkinson's disease. In these trials, the risk–benefit ratio is at best uncertain and at worst unfavorable. The institutional review board at Columbia–Presbyterian Medical Center would have accepted the sham surgery but stopped short at approving the administration of real antibiotics to subjects in the placebo group.[11] A group of researchers at Yale University decided to omit sham surgery from their study design on the grounds that drilling holes in a patient's head without providing treatment would require further studies in animals and humans in order to be ethically acceptable.[11] Yet one investigator who performed the sham surgery likened the risk involved to that of going to the dentist.[12] This comparison suggests that the risk is minimal, according to the definition in the federal regulations on research involving human subjects: "Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[14] Most people, however, would probably consider the risk associated with drilling holes in the skull greater than that associated with drilling holes in teeth.

If there were some objective way of assessing the magnitude, as well as the probability, of harm caused by these surgical interventions, the determination that there is a favorable ratio of benefits to risks in the studies involving sham surgery might be credible. However, the difficulties that institutional review boards have in making consistent, reliable assessments of benefits and risks are well documented.[15,16,17] As the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research reported:

> It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible.[18]

The controversy that has arisen over the use of sham surgery in studies of Parkinson's disease demonstrates the wide variation in judgments of what sorts of "risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."[14]

Informed Consent in Research Involving Sham Surgery

In the era before informed consent to participate in research was an ethical and legal requirement, some researchers performed sham surgery without obtaining informed consent from subjects.[10] One article reporting the results of coronary-artery surgery in patients with angina stated, "The subjects were informed of the fact that this procedure had not been proved to be of value, and yet many were aware of the enthusiastic report published in the *Reader's Digest.* The patients were told only that they were participating in an evaluation of this operation; they were not informed of the double-blind nature of the study."[19]

Today, of course, patients entering trials that are randomized, blinded, and placebo-controlled are informed of these aspects of the research. This information does not diminish their hope that they will receive the experimental treatment rather than the placebo. A patient who underwent sham surgery in a study of Parkinson's disease said she knew there was a 50-50 chance that she had not received the real treatment, but when she was informed of that fact one year later, she said she thought she had received the real treatment. In fact, she perceived small improvements in her condition after the operation.[11] Disclosure of the research design evidently does not eliminate the known placebo effect of surgery,[20] nor does it deter patients from enrolling in the study. Yet these findings do not by themselves justify the exposure of patients to risks that would not be imposed by an alternative research design. Researchers have an obligation to minimize the risks to their subjects, and institutional review boards are charged with ensuring that the risks are reasonable in the light of the anticipated benefits. There would be no need for a system of institutional review boards to protect subjects if their informed consent were the only ethical requirement for conducting research.

Is it overly paternalistic to protect research subjects from risks they seem willing to accept? The emphasis today on respect for the autonomy of patients and research subjects creates a reluctance to question whether their choices are fully rational. In one of the studies of fetal-tissue transplantation in patients with Parkinson's disease, the subjects were told in advance that if they underwent the sham surgery, they would be eligible for the real transplantation procedure on completion of the trial, if the procedure proved to be beneficial. But because of a higher-than-anticipated incidence of death and other adverse events in the group of patients who had undergone the real surgery, the patients in the sham-surgery group were initially not offered the treatment.[11] Surprisingly, rather than being relieved that they had undergone the apparently safer, sham surgery, several subjects were outraged. They said they might not have participated in the study if they had known they would have to wait so long for the real surgery. One woman said that she and her husband, who had participated in the study, felt they had been "double shammed": first when they learned that her husband had undergone the sham procedure, and then when he was denied the real surgery on the basis of safety considerations.[11] This response exemplifies the "therapeutic misconception"[21,22] — the all-too-common assumption that research promises beneficial treatment, even in its earliest phases.

Studies of consent documents show that they sometimes overstate the benefits and understate the risks of research protocols.[23,24] But even when consent forms are accurate in describing the known risks and anticipated benefits, the expectations of research subjects may be unrealistic. 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.[23] The misconception that research is designed to benefit the patients who are the subjects is difficult to dispel. The comments of the hopeful subjects in the studies of Parkinson's disease[11,12] suggest that the informed-consent process remains less than perfect. This observation is hardly new, and the inadequacy of informed consent is by no means unique to these trials. Yet this experience provides evidence that the protection of human subjects cannot rest solely on the ethical foundation of informed consent.

One feature of the research on Parkinson's disease prompts a different question about the quality of informed consent. Critics of the use of placebos in clinical trials claim that such use is unethical because it involves the active deception of patients. Commentators on the ethics of the use of placebos in clinical trials generally argue that it is not deception that constitutes the ethically problematic feature but rather the potential harm of withholding a treatment proved to be beneficial.[7,25]

In the studies of Parkinson's disease, although the patients were informed in advance that they had a 50-50 chance of receiving sham surgery, the researchers had to engage in active deception in performing the research maneuvers. In one study, just before the surgical procedure was performed, the surgeons asked the subjects, "Are you ready for the implant now?"[11] This was a deliberate attempt to mislead the subjects. One of the researchers was quoted as saying, "We thought it might be difficult to maintain a poker face."[11] These are words people use when they are engaged in lying. Even though the lie in this case may have been harmless, since it was uttered in a context in which the truth had previously been disclosed, it cannot be maintained that no deception was involved in the use of sham surgery. To achieve the effect that a placebo-controlled trial aims for, the researchers had to make misleading statements to the subjects in the placebo group and had to make sure their facial expressions did not reveal the true situation.

Conclusions

Sham surgery is ethically unacceptable as a placebo control in trials of fetal-cell transplantation in patients with Parkinson's disease. Sham surgery, with accompanying anesthesia, poses the risks of any surgical intervention that would not be used alone for therapeutic purposes. In trials that use antibiotics to protect subjects against infection, there are the added risks associated with antibiotic treatment. In trials that forgo the use of antibiotics in the sham-surgery group, there are the added risks of infection.

One question remains to be answered. Those who defend the use of sham surgery could argue that the possibility of a strong placebo response to surgery[20] does, in fact, confer a benefit on the subjects who are randomly assigned to the control group. Might the benefit of the placebo effect outweigh the risks of the sham surgery and therefore justify its use in research? The answer is no, unless the sham surgery would be recommended solely for therapeutic purposes outside the research context.

A related question is whether it would be ethical to conduct trials specifically designed to document the placebo effect of surgery. Three groups would be needed: an untreated control group, a group undergoing sham surgery, and a group undergoing real surgery.[20] Johnson argues that "for surgical procedures, as for drugs, the placebo effect must always be taken into account if any assessment is to be objective."[20] Yet despite

the importance of the research question, Johnson contends that "none of the means of measuring placebo [effects] can be applied to surgical operations because it is unethical, for example, to make an abdominal incision and sew it up again without undertaking any procedure."[20]

Perhaps some defenders of the use of sham surgery in randomized, controlled trials would be prepared to go this far. In response to the question, "If phony operations can help people, why not just do them?" one surgeon said, "That is an important point. What to do with it, medicine is going to have to decide."[13] One cannot always predict what the medical community will decide. But one conclusion seems apparent. The placebo-controlled trial may well be the gold standard of research design, but unlike pure gold, it can be tarnished by unethical applications.

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