

Surgical “Placebo” Controls

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Objective

To set ethical guidelines on the use of surgical placebo controls in the design of surgical trials.

Background Data

Ethical concerns recently arose from surgical trials where subjects in the control arm underwent surgical procedures that had the appearance of a therapeutic intervention, but during which the essential therapeutic maneuver was omitted. Although there are ethical guidelines on the use of a placebo in drug trials, little attention has been paid to the use of a surgical placebo control in surgical trials.

Methods

The Council on Ethical and Judicial Affairs developed ethical guidelines based on a wide literature search and consultation with experts.

Results

Surgical placebo controls should be limited to studies of new surgical procedures aimed at treating diseases that are not amenable to other surgical therapies, and are reasonably anticipated to be susceptible to substantial placebo effects. If the standard nonsurgical treatment is efficacious and acceptable to the patient, then it must be offered as part of the study design.

Conclusions

Surgical placebo controls should be used only when no other trial design will yield the requisite data and should always be accompanied by a rigorous informed consent process and a careful consideration of the related risks and benefits. The recommended ethical guidelines were adopted as AMA ethics policy and are now incorporated in the AMA’s *Code of Medical Ethics*.

Before new drugs, devices, or procedures are used in the clinical setting, it is important that they be validated.¹ This can be accomplished through clinical trials, which help gather information on their safety and efficacy. Retrospective or historical trials occasionally permit investigators to compare the experimental intervention to a standard treatment from data previously gathered. Prospective trials are relied on primarily to establish causal relationships between a variable and an outcome.² This design makes it particularly easy to compare the outcomes in two groups that receive different interventions, where one arm of the study undergoes a standard procedure and the other undergoes an

experimental procedure. The reliability of the data derived from such trials is further improved when subjects are randomly assigned to either arm, and when subjects and investigators are not informed of the assignment. This design, the randomized, double-blind study, is considered the gold standard of clinical research because it minimizes random errors, eliminates bias, and thereby limits the risk of reaching an incorrect conclusion.³ In some of these studies a placebo is used in the control arm as a substitute for an active intervention.^{4,5} Use of a placebo enables investigators to measure absolute efficacy of the experimental intervention, whereas other types of controls support judgments about comparative efficacy.

Recently, renewed concern about the use of placebos has resulted from reports in the media and the medical literature of surgical trials that included “sham” surgery.^{6–9} Although investigators conducting such trials have referred to them as

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placebo surgery,⁸ this report generally uses the term surgical placebo control to refer to the control arm of studies where subjects undergo surgical procedures that have the appearance of therapeutic interventions, but during which the essential therapeutic maneuver is omitted. This recent trend in surgical research requires careful ethical analysis, beginning with a brief review of the current standards that are used to evaluate the ethical soundness of research designs. From a detailed examination of placebos and their use in surgical research it is then possible to derive guidelines for surgical investigators in the design of trials.

CLINICAL RESEARCH: GENERAL CONSIDERATIONS

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research has defined research as “activities designed to develop or contribute to generalizable knowledge.”¹⁰ It is widely accepted that such activities are necessary to foster treatment advances that will benefit future patients. However, it is equally acknowledged that almost all clinical research involves a certain degree of risk, and that safeguards must be applied to protect subjects.¹¹ To that effect, the federal regulations (“Common Rule”) require that Institutional Review Boards (IRBs) review protocols to ensure that:

- 1) Risks to subjects are minimized (i) by using procedures which are consistent with sound research design and that do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, using procedures already being performed on the subjects for diagnostic or treatment purposes.
- 2) 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.¹²

The Council on Ethical and Judicial Affairs of the American Medical Association (AMA) has previously discussed safeguards in the context of clinical investigation. In particular, it stated that a physician-investigator is responsible for assuring that a study is “competently designed, under accepted standards of scientific research, to produce data which are scientifically valid and significant.”¹³

However, the methodological design of clinical trials can raise complex scientific and ethical issues. One such issue is the requirement that a trial should be undertaken when there is genuine uncertainty regarding the comparative merits of two treatments.¹⁴ Furthermore, it has been argued that randomizing subjects to either the experimental or the standard treatment is ethically acceptable only when there is “equipoise,” or a belief within the general medical community that the experimental intervention will provide at least equal or greater benefit than the standard therapy.^{15,16} Most studies that meet this requirement compare two active treatments. But there are instances when equipoise may exist between a placebo and a new intervention or between a placebo and an established procedure whose effectiveness has been called into question. For example, there may be no

proven effective therapies to treat a particular condition, or an otherwise effective therapy may not be appropriate for a particular patient population. The use of placebos also may be justified when the standard treatment poses risks to the subjects, or when the condition being studied is relatively minor.

PLACEBO CONTROLS

The precise meaning of the term placebo has varied over time,¹⁷ but generally it is understood as “a medicine given merely to please the patient.”¹⁸ Much of the controversy surrounding placebos stems from the element of deception that is present when a physician provides a placebo instead of an active treatment without informing the patient. Yet, in a number of cases, even though a presumably inert treatment is provided to patients in lieu of an active treatment, a therapeutic response has been observed—referred to as the “placebo effect.”¹⁹

Although there continues to be disagreement regarding the use of placebos in treatment, this Report focuses on the use of a placebo in the context of surgical controlled trials. Unlike the therapeutic setting, in a control trial the subject is informed about the possibility of receiving a placebo. As Robert Levine, a leading ethicist, has observed, the use of a placebo in the context of clinical trials when subjects are informed of the possibility does not include the same element of deception as the use of placebos in the clinical context.²⁰

The use of a placebo as a control usually is intended to present few physical risks to subjects, although it is acknowledged that subjects who receive a placebo may experience some negative “placebo side-effects.” Other risks involved in the use of a placebo are that subjects may be required to delay or may forego receiving a beneficial treatment. Alternatively, the placebo effect may result in some benefit to the subjects.

Placebo Controls in Surgical Clinical Trials

Starting in the 1950s, placebo use in clinical trials evolved into a common methodology as interest in the placebo effect and the double-blind procedure grew.¹⁷ With the recent development of “sham” surgery, new questions have been raised about the use of placebo in clinical trials. In the case of the transplantation of fetal nigral tissue into the brains of subjects with Parkinson’s Disease, the active arm of the study received an experimental intervention. The subjects in the control arm underwent most elements of the surgery but did not receive an injection of fetal tissue intended to produce therapeutic effects. Subjects were prepped for surgery, received anesthesia, had incisions made at the surgical site (burr hole only through the outer table of the skull, no needle in the brain), received antibiotics, etc. Unlike trials of medications in which the placebo control generally involves a sugar pill or other inert sub-

stance, subjects in the control arm of these surgical trials were exposed to many of the risks and discomforts generally associated with invasive surgical procedures. Indeed, the investigators in these trials admitted that the risks involved were greater than those incurred by subjects who receive a placebo in pharmacological studies. They further recognized that the use of a procedure that could cause harm without offering a compensating physiologic benefit poses ethical problems and might violate the principle of nonmaleficence.⁸ This led renowned ethicist Ruth Macklin to conclude that "performing surgery in research subjects that has no potential of therapeutic benefit fails to minimize the risk of harm,"⁹ and is in violation of applicable ethical guidelines. The investigators cited several potential benefits to placebo subjects: contributing to advances in treating the disease affecting them personally, receiving standard medical treatment at no cost, and obtaining the experimental treatment at no cost, should it prove to be effective.

There are strong arguments in favor of using clinical trials to evaluate the therapeutic value of surgical procedures. If a trial comparing a novel surgical procedure and a surgical placebo control reveals no benefit for subjects in the active arm, then presumably ineffective operations will be prevented from taking place in the future. In the early 1960s Henry Beecher argued that scientists should investigate the extent of the placebo effect so that dangerous operations that were no more effective than placebos would not be performed.²¹ This recommendation followed the report that internal mammary artery ligation, a popular procedure used in patients with myocardial ischemia during the 1950s, produced no greater therapeutic benefit than an incision without ligation.²²

ETHICAL DISCUSSION

How should surgical placebo controls be evaluated in light of the above considerations? The first question is to determine whether such surgery should be considered analogous to a placebo. Like a placebo, this variant of a surgical procedure enables investigators to factor out confounding variables and make judgments about absolute efficacy. A study design involving a surgical placebo control may yield data of superior scientific validity but, as stated above, placebos generally are understood to present few risks. In the case of a surgical placebo control, however, the control arm is subjected to risks associated with surgery, such as infection and anesthesia reactions. Consequently, the ethical use of a surgical placebo control may require that the informed consent process be adapted to emphasize the risks involved in both arms of the trial, along with a description of the difference between each arm of the trial in terms of the essential procedure that will or will not be performed.

The use of placebo controls in surgery should be carefully delineated. First, they should be used only when no other trial design will yield the requisite data. Such a determination should be guided by the Common Rule, which requires

that risks be minimized and that those remaining risks be reasonable in relation to the importance of the knowledge to be derived and in relation to the benefits, if any, that subjects may realize.¹² In some instances, it will be preferable to compare a new surgical procedure to an existing standard procedure, using a randomized trial.³ This will typically be the case when a surgical technique is developed as an innovative modification of an existing surgical procedure. A hypothetical example would be a randomized trial of laparoscopic cholecystectomy compared with cholecystectomy through a standard laparotomy incision.

When a new surgical procedure is developed with the prospect of treating a condition for which no known surgical therapy exists, using surgical placebo controls may be justified, but only when it is known that the disease being studied is associated with symptoms that are susceptible to placebo effects; that is, can be significantly influenced by psychological factors. For example, the use of a surgical placebo control in the Parkinson's Disease study was justified by the documentation of significant (20–30%) improvement with pharmacologic placebo treatment in earlier studies.²³

Moreover, before a surgical placebo control is included in the experimental design, the risks of the surgical placebo control operation must be balanced against the potential scientific knowledge to be gained by the study, and must be found to be low enough to justify inclusion. For example, the classic study of the effectiveness of internal mammary artery ligation to treat angina compared the established procedure (which had come into question) with a surgical placebo; the placebo thoracotomy demonstrated a beneficial effect nearly equal to that of ligation. On balance, untold numbers of patients with angina were spared a physiologically useless operation at the cost of a sham thoracotomy incision in a small number of volunteers.²⁴

If a new surgical procedure promises better results than an existing medical treatment for a particular disease, the effectiveness of the medical treatment may be relevant to the design of experimental control arms. If the medical treatment is very effective, it must be included as a control. If it is less effective or unacceptable to the patient (e.g., side effects, personal beliefs), it might not be included. Any medical treatment could be continued as needed in both of the surgical arms of a placebo controlled surgical study, as was done in the Parkinson's disease study. One measure of the effectiveness of the surgical interventions could be the extent to which medical treatments could be discontinued after the effects of the surgical intervention have had sufficient time to become manifest. The critical criterion for including a surgical placebo control is the likelihood of a placebo effect from the surgical procedure itself, as was the case in the Parkinson's disease study. In other words, how the investigational surgical procedure is compared with existing nonsurgical treatments has no bearing on whether a surgical placebo is used. The surgical placebo control is

related only to the surgical arm: it controls for beneficial psychological effects of the operation as a surgical procedure.

Studies of new operations that contain a surgical placebo control can be single or double blind (the patient only or the patient and the investigator blind to the patient's group). Double blind studies are preferable, and are possible even though the surgeon will always know what was done in the operating room. The group of investigators can be blind to the study groups if the surgeon, in follow-up, closely follows a prepared script with each patient, and if all of the follow-up measurements are done at an outside institution by investigators otherwise unconnected to the study. In this way, double blind investigations can be achieved in the setting of surgical placebo controlled studies.

CONCLUSION

The use of placebos in randomized, double-blind clinical trials is widely held to be a gold standard of research design. Recently, similar methodology has been used in the context of surgical trials. Surgical placebo controls as described here raise ethical issues generally associated with the use of placebos, such as deception and informed consent. In addition, however, the use of surgical placebo controls requires a careful assessment of the specific scientific benefits as well as surgical risks, such as anesthesia or infection, which should be as low as possible.

Recommendations

The AMA's Council on Ethical and Judicial Affairs has made several recommendations regarding surgical placebo controls.

The term surgical placebo controls refers to the control arm of a research study where subjects undergo surgical procedures that have the appearance of therapeutic interventions, but during which the essential therapeutic maneuver is omitted.

The appropriateness of a surgical placebo control should be evaluated on the following basis:

- 1) Surgical placebo controls should be used only when no other trial design will yield the requisite data.
- 2) Particular attention must be paid to the informed consent process when enrolling subjects in trials that use surgical placebo controls. Careful explanation of the risks of the operations must be disclosed, along with a description of the differences between the trial arms emphasizing the essential procedure that will or will not be performed. Additional safeguards around the informed consent process may be appropriate such as using a neutral third party to provide information and get consent, or using consent monitors to oversee the consent process.
- 3) The use of surgical placebo controls is not justified when testing the effectiveness of an innovative surgical technique that represents a minor modification of an existing surgical procedure.

4) When a new surgical procedure is developed with the prospect of treating a condition for which no known surgical therapy exists, or when the efficacy of an existing surgical procedure comes into question, a study design using surgical placebo controls may be justified if it is known that the disease being studied may be susceptible to a placebo effect and the risks of the surgical placebo control operation are relatively small.

5) With respect to standard nonsurgical treatment: if foregoing standard treatment would result in significant injury and the standard treatment is efficacious and acceptable to the patient (in terms of side-effects, personal beliefs, etc.), then it must be offered in all arms of the study design.

When the standard treatment is not fully efficacious or is not acceptable to the patient, the standard treatment may be foregone in any arm of the study.

This policy was adopted by the AMA in June 2000 and the guidelines in substantially this form have been incorporated into the *Code of Medical Ethics*.²⁵

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References

1. Brody B. The ethics of biomedical research. London: Oxford University Press; 1998; 140.
2. Cummings SR, Ernster V, Hulley SB. Designing a New Study: I. Cohort Studies. In: Hulley SB, Cummings SR, eds. Designing Clinical Research: An Epidemiologic Approach. Baltimore: Williams & Wilkins; 1988.
3. Solomon MJ, McLeod RS. Should we be performing more randomized controlled trials in evaluating surgical procedures? *Surgery* 1995; 118:459-467.
4. Freedom B, Weijer C, Cranley Glass K. Placebo orthodoxy in clinical research I: empirical and methodological myths. *J Law Med Ethics* 1996; 24:243-251.
5. Freedom B, Weijer C, Cranley Glass K. Placebo orthodoxy in clinical research ii: ethical, legal, and regulatory myths. *J Law Med Ethics* 1996; 24:252-259.
6. Johannes L. Sham Surgery is used to test effectiveness of novel operations. *Wall Street Journal* 1998; December 11:A1, A8.
7. Stolberg SG. Sham Surgery returns as a research tool. *New York Times* 1999; April 25:WK3.
8. Freeman TB, Vawter DE, Leaverton PE, et al. Use of placebo surgery in controlled trials of a cellular-based therapy for Parkinson's disease. *N Engl J Med* 1999; 341:988-992.
9. Macklin R. The ethical problems with sham surgery in clinical research. *N Engl J Med* 1999; 341:992-996.
10. Levine RJ. Ethics, Regulation of Clinical Trials. 2nd ed. New Haven: Yale University Press; 1986.
11. National Institutes of Health, Office for Protection from Research Risks. Protecting Human Subjects. IRB Handbook. Washington, D.C.: U.S. Government Printing Office; 1993;
12. Protection of Human Subjects, 45 CFR 46.111 (October 2000).
13. Council on Ethical, Judicial Affairs. Opinion 2.07, Clinical Investigation. In: Council on Ethical and Judicial Affairs. Code of Medical

- Ethics: Current Opinions. Chicago: American Medical Association; 2000; 11–13.
14. Chard JA, Lilford RJ. The use of equipoise in clinical trials. *Soc Sci Med* 1998; 47:881–898.
 15. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987; 317:141–145.
 16. Karlawish JHT, Lantos J. Community equipoise and the architecture of clinical research. *Cambridge Quarterly of Healthcare Ethics*. 1997; 6:385–396.
 17. Shapiro AK, Shapiro E. *The Powerful Placebo. From Ancient Priest to Modern Physician*. Baltimore: Johns Hopkins University Press; 1997.
 18. *American Heritage Dictionary, 2nd College Edition*. Boston. Houghton Mifflin; 1991; 947.
 19. Brody H. Placebo. In: Reich WT, ed. *Encyclopedia of Bioethics*. New York: Simon & Schuster Macmillan; 1995; 1951–1953.
 20. Levine RJ, *Ethics, Regulation of Clinical Trials*. 2nd ed. New Haven: Yale University Press; 1986.
 21. Beecher HK. Surgery as placebo: a quantitative study of bias. *JAMA* 1961; 176:1102–1107.
 22. Cobb LA. Evaluation of internal mammary artery ligation by double-blind technique. *N Engl J Med* 1959; 260:1115–1118.
 23. Clark PI, Leaveron PE. Scientific and ethical issues in the use of placebo controls in clinical trials. *Annu Rev Public Health* 1994; 15:19–38.
 24. Cobb LA. Evaluation of internal mammary ligation by double-blind technic. *N Engl J Med* 1959; 260:115–118.
 25. Council on Ethical, Judicial Affairs, American Medical Association. Opinion 2.076: Surgical "Placebo" Controls. In: *The American Medical Association's Council on Ethical and Judicial Affairs. Code of Medical Ethics*. Chicago: American Medical Association; 2000.