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Use of Placebo Surgery in Controlled Trials of a Cellular-Based Therapy for Parkinson's Disease

Surgical procedures are frequently introduced into general practice on the basis of uncontrolled studies that are less rigorous than those required for the approval of medical interventions.[1] The standard for the evaluation of surgical therapy is lower because of the complexity of designing and conducting scientifically valid and ethically acceptable clinical trials of surgical procedures.[2] As a result, many surgical trials fail to control for investigator bias or placebo effects.[3,4]

The list of inadequately studied invasive or surgical procedures that became part of standard medical practice only to be abandoned after closer scrutiny includes bloodletting, routine tonsillectomy, routine circumcision, repeated cesarean delivery, internal-thoracic-artery ligation, gastric freezing, jejunoilial bypass for morbid obesity, glomectomy for asthma, prophylactic portacaval shunting, laparotomy for tuberculous peritonitis or pelvic inflammatory disease, adrenalectomy for essential hypertension, and extracranial or intracranial bypass for carotid-artery occlusion. A review of coronary-artery bypass procedures showed that 38 percent of indications for the procedures are questionable.[5] Many have called for more rigorous evidence of the safety and efficacy of new surgical procedures.[1,6,7,8] In this article, we provide the scientific and ethical rationale for using an imitation operation as a placebo control in our National Institutes of Health (NIH)–sponsored double-blind trial of fetal-tissue transplantation in patients with Parkinson's disease.

Randomized, double-blind, placebo-controlled trials offer the most effective way to control for the placebo effect and investigator bias. They have become the gold standard for assessing new drug interventions.[4,9,10,11] Patients assigned to a placebo group in a pharmacologic study may incur certain risks and inconveniences, including temporarily forgoing other therapeutic options and undergoing multiple [4,12,13,14,15,16]

laboratory tests and clinical evaluations.– — — — — — Assignment to the placebo group in a surgical study may involve greater risks.[6,17,18,19,20,21] Under what circumstances are the risks to subjects assigned to the placebo group in a medical or surgical trial justified, and what risks are reasonable in order to determine the benefits and adverse effects of a given intervention?[4,12,13,14,16,22] Some physicians believe that randomized, placebo-controlled surgical studies are unnecessary, cumbersome, and ethically unacceptable.[2,9,23] It has been claimed that one cannot generalize from the results of placebo-controlled surgical trials because of differences in the skills of individual surgeons and because of the confounding effect of increasing experience in performing the procedure. Finally, it has been argued that offering a subject a placebo procedure that might induce harm without offering a compensating benefit poses ethical problems[2,9,23] and that such a practice would violate the principle of doing no harm.

The advent of cellular-based surgical therapies such as implantation of fetal tissues, trophic factors, and genetically altered cell lines calls for a critical examination of the methods used to evaluate these types of surgical interventions and a reconsideration of the virtual prohibition against the use of imitation surgery as a placebo control. We believe that many of these new therapies can and should be evaluated with the more rigorous methods typically used in pharmaceutical studies, an opinion shared by the Food and Drug Administration.[24]

Surgical procedures for administering cellular-based or pharmaceutical therapies tend to be less invasive, painful, burdensome, and risky than traditional surgical procedures, which may make the risks more reasonable in relation to the possible benefits. In addition, the procedures are easier to perform, standardize, and reproduce than traditional surgical procedures because they do not entail the manipula-tion or removal of distorted (and highly variable) tissues. Therefore, these studies are less likely to be confounded by variability in the surgeon's skill and the results are more likely to be generalizable. Finally, in many respects, the assessment of cellular therapies (which involves such variables as dose, volume of distribution, time course and magnitude of effect, toxicity, and drug interactions) has more in common with the assessment of pharmaceutical agents than with that of conventional operations.[25]

Ethics of Placebo-Controlled Trials

Researchers working in U.S. institutions that receive federal funds must comply with the federal regulations for the protection of human subjects.[26] The regulations require that the risks of a study be reasonable in relation to the anticipated benefits to the subjects, if any, and in relation to the importance of the knowledge that may reasonably be expected to be gained from the study.[26] These regulations allow for the conduct of placebo-controlled studies posing more than a minimal risk to competent adults as long as the risk is reasonable. Medical benefits do not necessarily need to accrue to all subjects.[27] Determining the reasonableness of the risks and benefits of a study is the complex task of appropriately constituted institutional review boards.

A double-blind, placebo-controlled trial should address an important research question that cannot be answered by a study with an alternative design that poses a lower risk to the subjects.[12,13,26] There must be preliminary but not conclusive evidence that the intervention is effective,[12,28] and the treatment should be sufficiently developed that it is unlikely to become obsolete before the study has been completed.[8,23,29] The risks to

the subjects should be minimized whenever possible in a manner that is consistent with sound research design.[26] The study intervention should be provided in addition to standard therapy, unless there is no safe and effective standard therapy or unless the withholding of such therapy does not pose an unreasonable risk to the subjects.[4]

The study design must be sufficiently rigorous to ensure the blinding of subjects and investigators, accurate and complete data collection, and sufficient statistical power to provide a reasonable assurance that the study will answer the research question.[30] Finally, the consent process must clearly identify the risks of participation, including the risks associated with assignment to the placebo group.[12] Potential subjects must meet a high standard of comprehension, be informed about alternative medical and surgical therapies, and be advised that they will not be refused medical care if they decline to participate.[26]

A Placebo-Controlled Trial of Fetal Nigral Transplantation in Parkinson's Disease

Parkinson's disease is a disorder of motor function characterized by tremor, rigidity, bradykinesia, gait disturbance, and postural instability.[31] The main pathological features are a loss of dopaminergic neurons in the substantia nigra pars compacta and a consequent reduction in levels of striatal dopamine. Replacement therapy, with the use of the dopamine precursor levodopa combined with a decarboxylase inhibitor, is the standard medical treatment for Parkinson's disease. However, long-term treatment with levodopa may have adverse effects, and new features of the disease that are not satisfactorily controlled with available medical therapies may emerge.

Fetal-tissue transplantation for the treatment of Parkinson's disease is based on research demonstrating that implanted embryonic dopaminergic neurons can survive, reinnervate the striatum, and reverse motor abnormalities in animal models of parkinsonism.[32] At least 18 centers throughout the world have introduced clinical transplantation programs for the treatment of Parkinson's disease. The results have been variable,[32] but several centers have observed consistent and clinically meaningful benefits in open-label trials.[33,34,35,36,37] Further evidence of the potential value of this procedure comes from reports of statistically significant increases in striatal fluorodopa uptake on positron-emission tomography (PET)[32,33,34,35,36,37,38] and robust graft survival with extensive striatal reinnervation at autopsy[39,40,41]; these findings are correlated with the clinical benefits.[37,39,40]

Placebo Effects in the Treatment of Parkinson's Disease

Although we and others have demonstrated the clinical benefits of fetal nigral transplantation in open trials, we cannot exclude the possibility that these benefits are due to a placebo effect or investigator bias. Long-lasting and powerful placebo effects have been reported in Parkinson's disease. In one large, double-blind pharmacologic study, patients assigned to the placebo group had a 20 to 30 percent improvement in motor scores, which persisted throughout the six months of the trial.[4] Significant improvement and deterioration have been observed after the introduction and discontinuation, respectively, of placebo in patients with Parkinson's disease.[42,43] Placebo effects are a particular problem because of the marked variability in the magnitude and duration of responses to antiparkinsonian

medication.[44] Furthermore, the magnitude of the placebo response increases with the extent of the placebo intervention,[4,6] suggesting that the response to any surgical procedure might be particularly pronounced.

It is not possible to test adequately for a placebo effect in a laboratory setting, since animals are not known to have responses to placebo.[45] Moreover, the response to implanted cells in animal models may differ from that in patients. We therefore concluded that in order to determine the safety and efficacy of fetal-tissue transplantation in patients with Parkinson's disease, it was necessary to perform a double-blind, placebo-controlled study. This study would control for placebo effects, as well as the effects of patient selection, treatment, and bias on the part of the evaluator.

The Trial Design

Thirty-six competent adults with advanced Parkinson's disease whose symptoms could not be satisfactorily controlled with medical therapy consented to be randomly assigned to undergo one of three study procedures: bilateral fetal nigral transplantation with tissue from one donor per side, bilateral transplantation with tissue from four donors per side, or bilateral placebo surgery. Calculations based on our open studies[34] indicated that a total sample of 36 subjects (12 per group) would provide the study with more than 80 percent power to detect differences between the groups with an alpha level of less than 0.05 and an independent-sample two-tailed t-test.

According to the protocol, subjects in both transplantation groups undergo two surgical procedures separated by approximately one week. Subjects randomly assigned to the control group undergo two placebo surgical procedures that are designed to provide an equivalent experience for the subjects and their family members. Each placebo procedure includes the placement of a stereotactic frame, target localization on magnetic resonance imaging, the administration of general anesthesia with a laryngeal-mask airway, and a skin incision with a partial burr hole that does not penetrate the inner cortex of the skull; there are no needle penetrations into the brain, and no fetal tissue is implanted. The duration of the surgical procedures and the perioperative care are identical in all groups. All patients receive low-dose cyclosporine for six months and continue to receive medical therapy. Subjects are evaluated in an identical manner at three-month intervals. At the conclusion of the study, if fetal-tissue transplantation is found to be safe and effective, subjects in the placebo group will be offered the better of the two transplantation procedures (with tissue from one donor per side or four donors per side).

To maintain the blinding of investigators, the surgical and evaluation sites are in separate locations. The evaluation sites identify participants, obtain informed consent, and perform all study evaluations. The same blinded evaluator carries out all clinical evaluations for each subject throughout the study. Clinical care is provided by a separate blinded investigator. PET studies are performed by a separate group of blinded investigators. The surgeon is the only member of the research team who is aware of an individual subject's group assignment. All surgical records related to the study are sequestered in a locked cabinet, and all the surgeons' communications with subjects or investigators follow a standardized script. Statistical and data-management practices are designed to maintain blinding throughout the course of the study. The study is

monitored by an independent performance and safety monitoring board appointed by the NIH. To assess the integrity of the blinding, subjects and investigators complete a questionnaire at the conclusion of the study.

This study is not designed to control for any clinical changes due to the surgical lesion itself, since to do so would entail substantial additional risk for the control group. Existing data suggest that surgical trauma itself is not likely to account for the benefits we observed in our open trial. Surgical trauma or implantation of biologically inactive tissue does not result in significant improvement in primate models of parkinsonism.[45] Adrenal transplantation causes more surgical damage but does not provide lasting clinical benefits or improvement on PET.[46,47] Sprouting of endogenous dopamine neurons has never been observed in the putamen (the target of our grafts) after transplantation or surgically-induced trauma. Furthermore, we saw no evidence of host-derived sprouting in two postmortem studies of patients who had received fetal nigral transplants.[39,40,41] In our study, any differences in outcome between subjects who receive tissue from one donor per side and those who receive tissue from four donors per side can be due only to the amount of tissue implanted, not to placebo or lesion effects. Although lesion-controlled surgical trials have been conducted in other circumstances,[6,17,18,19,20,48,49,50,51,52] we do not believe that a lesion-controlled study of fetal-tissue transplantation in patients with Parkinson's disease is necessary or appropriate at this time.

Risks and Benefits of Participating in the Placebo Group

In considering a placebo-controlled trial, it is important to balance the risks to participants against the potential benefits of developing a superior therapy or determining that an unproved therapy is ineffective or harmful. The risks of participating in the placebo group in this study are not trivial; there is the remote possibility of death or harm from a study-related intervention. Risks are associated with the placement of the stereotactic equipment, the scalp incision, the burr hole (even though it does not fully penetrate the skull), general anesthesia, intravenous antibiotics, low-dose cyclosporine, and the radioisotopes used for the PET studies. Subjects also have the inconvenience of multiple clinic visits and, in some cases, long-distance travel. Their access to the study treatment, if it is beneficial, will be delayed, and they may forfeit their eligibility to participate in other clinical trials. The risks have been minimized as much as possible. For example, subjects continue to receive standard medical therapy for Parkinson's disease, a partial burr hole is used to minimize the remote risk of intracranial bleeding, renal function is monitored for cyclosporine toxicity at routine intervals, adverse events are regularly reviewed, and rules were established in the protocol for stopping the trial early.

The benefits of participating in the placebo group include contributing to advances in the treatment of a disease of great personal interest to the participants, receiving standard medical treatment at no cost, having the opportunity to obtain a fetal-tissue transplant at no cost if the procedure proves to be safe and effective, and being spared the risks associated with transplantation if it proves to be unsafe or ineffective.

In our judgment, as well as in the judgment of the institutional review boards at the institutions involved in this study, the NIH study section, the performance and safety monitoring board, and the 36 persons who agreed to participate, the risks of participating in our double-blind, placebo-controlled surgical trial of fetal-tissue transplantation are reasonable in relation to the possible benefits. In addition, we believe that we have met all the ethical conditions outlined above. The patients have a progressive neurologic disease that

cannot be satisfactorily controlled with existing medical therapy. Laboratory studies and pilot clinical trials indicate that the procedure has the potential to provide a meaningful clinical benefit, and the risks of participation are reasonable and have been minimized insofar as possible. We extensively reviewed risks, benefits, procedures, and other therapeutic options with each patient and gave each an opportunity to have all questions answered. Subjects signed consent forms that were approved by the institutional review board at each institution involved in the study and by the performance and safety monitoring board appointed by the NIH to oversee it. Subjects in all groups continue to receive medical therapy, and those in the placebo group will be offered transplants if the procedure is proved safe and effective.

Conclusions

Randomized, double-blind, placebo-controlled trials are the gold standard for evaluating new interventions and are routinely used to assess new medical therapies. Surgeons have been reluctant to use imitation surgery as a placebo control in the evaluation of new procedures. It is estimated that only 7 percent of surgical investigators use a randomized study design of any type.[7] Cellular-based surgical therapies have much in common with pharmacologic treatments and lend themselves to evaluation in randomized, double-blind, placebo-controlled trials.

We elected to use this study design in our assessment of fetal-tissue transplantation before recommending its routine use. The inclusion of a placebo group in our study of 36 subjects will permit us to establish whether the benefit observed to date can be attributed to an effect of treatment apart from a placebo effect. If fetal-tissue transplants are found to be safe and effective, thousands of patients with Parkinson's disease stand to benefit, and further research will be encouraged. If the transplants are found to be unsafe or ineffective, or if they offer nothing more than a placebo effect, hundreds or even thousands of patients will be spared the risks and financial burdens of an unproved operation.

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