

Informed Consent and Sham Surgery as a Placebo in Fetal Cell Transplant Therapy Research for Parkinson's Disease

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ABSTRACT

Fetal cellular transplantation therapy research in Parkinson's Disease has raised important ethical questions from its beginning. One of the most hotly debated aspects of the recent clinical research has been the use of sham surgery as a placebo for the control group. Ethicists and researchers have focused on the unique risk surgical placebos pose to research subjects as compared to conventional, medical placebos. This review will deal with informed consent and the use of sham surgery in the placebo arm of recent fetal tissue transplantation randomized, placebo controlled, double blind, clinical trials. Do current procedures for obtaining informed consent meet the challenge of adequately informing patients enrolling in experiments with significant risks not only in the experimental group but also in the placebo group?

INTRODUCTION

Parkinson's Disease (PD) is a disorder of movement characterized by bradykinesia, "resting tremor," postural changes, and instability. Pathologically, PD is due to a loss of dopaminergic neurons in the substantia nigra pars compacta, other pigmented nuclei of the brainstem, and the basal ganglia. The disease is common, affecting approximately 1 million people in North America, about 1% of the population over age 65 (Victor and Ropper, 2001).

Current treatment for PD involves both medical and surgical approaches, with medical management being the most widely used. Effective medical treatment usually constitutes dopamine replacement therapy using dopamine receptor agonists or dopamine precursors, most notably L-dopa. Surgical therapy can be either ablative or stimulatory, generally with the same targets. Both medical and surgical therapies can offer substantial improvement for a period of time but their effectiveness eventually wanes, often coinciding with an upswing in side effects. In the case of L-dopa therapy, severe side effects include dystonia, dyskinesia, nausea and vomiting, and the possibility of drug induced psychosis.

NOVEL APPROACHES TO THE TREATMENT OF PARKINSON'S DISEASE

One of the most promising approaches towards the treatment of PD has been the transplantation of fetal

nigral tissue in affected areas of the brain. Open label human trials and animal experiments have shown that implanted fetal nigral tissue can survive after transplantation, reinervate affected areas of the brain, and have a positive effect of PD symptoms (Freeman et al., 1999).

Based on these results, the National Institutes of Health (NIH) funded two randomized, double blind, placebo controlled, fetal nigral transplantation studies randomized controlled trials (RCTs), in the mid-1990s after the ban on federal funding for fetal tissue research was lifted. The placebo arm of the studies consisted of sham surgery, which involved the drilling of burr holes through skull but not past the dura. Follow-up care for the placebo group was the same as for the active group in one of the studies, involving low doses of cyclosporine and positron emission tomography (PET) imaging at various stages in the study (Freeman et al., 1999). Follow-up care in the other study did not involve immunosuppressive drugs (Freed et al., 2001). The first study, begun in 1993 and conducted at the University of Colorado by Curt Freed and Columbia University by Stanley Fahn, published its results last spring. Results for the second study, begun in 1995, were published this past September.

The results of the Colombia/Colorado study showed some promising improvement with transplantation. Patients were evaluated on a subjective scale, which they graded themselves, and on a variety of objective assessments performed by the research staff. All these evaluations were done throughout the year after their surgery. The results of these evaluations showed improvement in the transplant group compared with the placebo group. But along with the positive results severe dystonia and dyskinesia were noted after one year in 5 of the 33 (15%) patients in the active arm of the study (Freed et al., 2001). The second study, which used the change in the subjects score in the motor component of the Unified Parkinson's Disease Rating Scale between baseline and final visits as its primary endpoint, failed to demonstrate a significant overall treatment effect. Additionally, 56% of the transplanted patients developed dyskinesia that persisted after withdrawal of dopaminergic medication (Olanow et al., 2003).

INFORMED CONSENT

Individuals' consent for participation in clinical trials has been at the forefront of biomedical ethics since the

Informed Consent and Sham Surgery as a Placebo in Fetal Cell Transplant Therapy Research for Parkinson's Disease

Nuremberg Trials detailed the horrifying abuse of prisoners in Nazi concentration camps for medical research purposes during World War II. In the years, since, informed consent in the research setting has evolved to serve two purposes. It was originally developed as a mechanism to ensure the protection of research subjects from undue risk and exploitation. In later years, it has become a central component in the concept of patient and research subject autonomy in medical decision-making (Beauchamp and Childress, 2001; Meisel and Kuczewski, 1996). Although the ideal of informed consent has been well established in the medical community, research dating back to the late 1960s has shown that its goals are rarely attained. Researchers have detailed problems with informed consent in research regarding: 1) patient and research subject understanding of the procedures and/or trials they have consented to and their associated benefits and risks; 2) the complexity and length of consent forms; and 3) patient and research subject understanding about the nature of informed consent – its purpose in informing patients and research subjects about the procedures or research they are consenting to and providing them with an account of the options available to them.

RESEARCH SUBJECT UNDERSTANDING OF CLINICAL TRIALS AND PROCEDURES

Significant numbers of subjects in studies regarding the quality of informed consent have been unable to articulate important aspects of their consent when tested about them. In one study of cancer patients enrolled in a Phase I clinical trials, only 33% of the participants interviewed were able to state the purpose of the trial (Daugherty et al., 1995). Other studies have also found sizable percentages of research subjects without an adequate level of understanding of the procedures they had consented to or the projects they had enrolled in. In these studies, research subject comprehension ranged from a little over 50% to almost 75% (Byrne et al., 1988; Cassileth et al., 1980; Lynoe et al., 1991). According to these figures, at the very least one-quarter of all research subjects do not understand or do not recall what they have consented to. If it is the first, lack of understanding, then those subjects do not meet the ethical criteria for what is considered "informed." The con-founding factor is subject recall.

Differentiating between recall and understanding has been problematic in informed consent research and the literature is ambiguous about research subjects' ability to retain information. Problems with long term recall and comprehension were noted in one study as research subjects' average score on a test of their recall and understanding declined from 71.6% immediately after enrollment to 61.2% after 3 months (Bergler et al., 1980). Compounding the problems of recall versus understanding are findings suggesting that research

subjects with differing severity of disease retain different information over periods of time. An examination of subjects recall over time showed that healthy subjects, or those with a less severe diagnosis, retain the most information regarding a clinical trial's purpose, benefits, and risks, while sicker subjects tended to retain the most information regarding a study's procedures (Schaeffer et al., 1996). The most relevant finding of this study was that the changes in recall and understanding do not always decrease over time. Sicker subjects displayed an increase in their recall and understanding of purposes, benefits, risks, and procedures over a four to six week period, while healthier subjects displayed only a small decrease. These findings led the authors to assert that research subjects were able to retain information over a six-week period without a significant decline and possibly a slight increase, thus casting into doubt the assumption that research subjects do not retain much of what they hear or read. Since the most notable studies regarding research subject understanding of informed consent tended to conduct their interviews within a much shorter time frame, it would appear that research subject understanding, not recall, is the major problem with informed consent.

In clinical trials the problem of poorly informed subjects is compounded by the fact that their participation will not definitely benefit them even though therapeutic benefit is often cited as their most important reason for participation. In the study of cancer patients in Phase I trials mentioned previously, 85% cited therapeutic benefit as their main reason for participation. Research has placed tumor response rates at 4% to 6% in phase I trials. No subjects in that same study mentioned altruism as their primary reason for participation (Daugherty et al., 1995).

In addition many studies have found that research subjects often recall the possible benefits of their participation with greater frequency and accuracy than the risks. One study of research subjects suffering from acute coronary syndromes employed a scoring system to ascertain subjects' knowledge of the clinical trial they were participating in. Within 14 hours of the consent process, the mean score for understanding of the possible benefits was 85%, while the mean score for possible risks was 35% (Kucia and Horowitz, 2000). In the Columbia/Colorado fetal nigral transplantation study, some subjects in the placebo group felt misled after the study had ended when they were told that they would not be eligible for the real transplant procedure due to safety concerns. "This response exemplifies the 'therapeutic misconception' – the all too common assumption that research promises beneficial treatment, even in its earliest phases" (Macklin, 1999). The "therapeutic misconception" and research subjects' tendency to emphasize benefits over risks have been cited as an important barrier to informed consent in clinical trials (Applebaum et al., 1991).

Informed Consent and Sham Surgery as a Placebo in Fetal Cell Transplant Therapy Research for Parkinson's Disease

It is important to note that a poor consent process is not the only reason behind the "therapeutic misconception" and the emphasis of benefits over risks among research subjects. In a study examining the feelings healthy patients had towards participating in clinical research, the researchers found that a significantly small number of people expressed interest in participating in trials involving experimental medications (Dazzi et al., 2001). This led the authors to reasonably assert that many patients who agree to participate in clinical trials do so for expected personal gain, or else there would be many fewer subjects participating in research today. Although poor communication on the part of medical personnel and the complexity of the material presented are often indicated as causes of poorly informed research subjects, these findings suggests that research subjects are also complicit in their lack of comprehension.

CONSENT FORMS

Along with the "therapeutic misconception" and research subjects desire to experience benefits rather than risks, another reason often cited as a cause of poorly informed research subjects and patients, in both clinical trials and therapeutic procedures requiring consent, is the complexity and length of consent forms (Cassileth et al., 1980). A study dealing specifically with the length of consent forms found that comprehension of the forms was inversely related to the forms' length. Of research subjects given consent forms of varying length (short, medium, and long), those with the short form demonstrated the highest level of comprehension and those with the long form demonstrated the lowest level. In addition, all subjects given the shortest form felt the information was useful, while 23% of the subjects given the medium length form felt the information was either frightening or not useful. Forty-one percent of the subjects given the longest form felt the information was either frightening or not useful (Chaikin and Lasagna, 1969).

Another study dealing with the complexity of consent forms found that consent forms were only slightly less difficult to understand than medical journals, but much more difficult than popular media (Morrow, 1980). This finding led the authors to reasonably assert that although consent forms may thoroughly provide all the information required to inform research subjects, their complexity is most likely to be an important barrier to actually informing research subjects.

Examination of consent forms has also shown that the "therapeutic misconception" is not simply due to research subjects' desire to experience benefits more than risk, but is sometimes encouraged by the consent forms themselves. The Advisory Committee on Human Radiation Experiments, in their study of the United States government's human subject radiation experi-

ments during the Cold War and their review of current ethical issues surrounding human subject research, found that consent forms often overstate the benefits of research. "The consent forms to be used with such patient-subjects sometimes appeared to suggest a greater prospect of benefit than the research as described in the documents we reviewed warranted. In a few Phase I studies, any intimation that subjects would benefit appeared questionable (United States Advisory Committee on Human Radiation Experiments, 1996). It is impossible for subjects to accurately inform themselves about their participation in research if they are not given a complete and honest account of the possible benefits and risks. The literature has shown that the complexity of consent forms along with their length and their often inaccurate statements regarding the possible benefits and risks of participation in research imposes a great burden on research subjects, as well as a barrier to understanding.

PATIENT UNDERSTANDING OF INFORMED CONSENT

Compounding problems with consent forms is the view, among patients and research subjects, that the consent process and forms are risk management tools for hospitals, not methods for informing patient's and research subject's decision-making. Some medical and research staff also share this view (Miesel and Kuczewski, 1996). Cassileth et al., in a study of recall and understanding of informed consent in post-operative patients, found that 75% of all patients interviewed believed that consent forms were used to protect physicians' rights while only about 50% of patients believed they were used to protect patients' rights. Only 43% of the participants in the study believed that consent forms were meant as "explanations of treatment" (Cassileth et al., 1980). It is important to note that this study dealt specifically with consent to treatment not to participate in research, but the main point, that patients often misunderstand the purpose of informed consent, can be applied to all consent forms and processes including those used in research.

Since their advent, consent forms in research have been meant as tools to protect research subject rights and promote autonomy (Beauchamp and Childress, 2001). The fact that 50% or less of research subjects may not understand this creates an immense barrier to truly informing patients, as they might not use the consent process to inform themselves about what they have agreed to do, but instead focus on it as process to lessen physicians' legal risks.

IMPLICATIONS FOR FETAL NIGRAL TISSUE TRANSPLANTATION RESEARCH

Freeman et al. (1999), in their defense of the use of

Informed Consent and Sham Surgery as a Placebo in Fetal Cell Transplant Therapy Research for Parkinson's Disease

placebo surgery in fetal tissue transplantation RCTs, argue that the risks and benefits of participating in the trial, either in the transplant group or, more importantly, the placebo group are reasonable. The risks involve the actual sham surgery, including the use of general anesthesia and follow-up care, which involves the administration of cyclosporine at low doses and the use of radioisotopes for PET imaging. The benefits include the potential for contributing to advances in treatment of the disease and the possibility of undergoing the procedure if it is proved safe and effective. To further cement their claim of a reasonable risk to benefit analysis, they cite the approval of their Institutional Review Board's (IRBs), the NIH, and the consent of participants in the research.

Macklin (1999) has argued that informed consent alone does not meet the ethical requirements of human subject research. She notes that researchers have an obligation to minimize the risks to their subjects and it is the charge of IRBs to enforce this. Freeman et al.'s position can be further questioned when the literature documenting the problems with informed consent is taken into account. To claim as they do, that the approval of the risk benefit analysis by subjects enrolled in their research in part validates the ethics of placebo surgery, circumvents the entire purpose of an ethical approach to human subject research, of which informed consent is one of its main foundations.

When research subjects give their consent to participate in research, they acknowledge that they have weighed the risks and benefits as they have been presented to them and judged them to be acceptable. Research has demonstrated that many research subjects informed in a conventional consent process do not fully comprehend the nature of their consent, the procedures of the trial they have entered, all the risks associated with it, and the reality that their chance of receiving benefit is often quite small. Regardless of these problems, the research community has deemed the informed consent process, as it currently stands, acceptable for patients entering medical placebo controlled RCTs. But there is a fundamental difference between medical placebo controlled RCTs and the ones used for PD fetal tissue transplantation research. The placebo arm of the former uses inert and innocuous substances or procedures, while that of latter use potentially harmful surgical procedures, anesthesia, and post-operative care. Extensive research has shown that a significant number of subjects involved in clinical research do not fully comprehend the nature of their participation on many levels. It would be unfair for researchers and IRBs to assume that current informed consent procedures adequately protect subjects involved in research that uses sham surgery as a placebo, since there is a 50% chance that the patient will be put at significant risk without receiving any experimental therapy and, therefore, have no chance of benefit.

THE FUTURE

If current consent procedures are not adequate to meet the ethical requirements of enrolling subjects in trials that use sham surgery as a placebo arm, what can be done? An ideal approach would target the areas of informed consent that help create a barrier to true patient understanding.

An important target for an enhanced consent process would be the "therapeutic misconception." Applebaum et al. (1991) propose a novel procedure where a neutral discloser, not a member of the research team, conducts the consent process, emphasizing not only the research but how research differs from treatment. In their research with this type of consent process the results were promising. They noted substantial changes in the percentage of subjects who understood the various components of research (randomization, placebos, etc.) as compared to the subjects who participated in the normal consent process. Other ideas include quizzing subjects on the information provided them during the consent process to further reinforce what was said or read and using a standard script to ensure the information provided is complete and not dependent on the subject's effort to learn about the research (Reicken and Ravich, 1982).

The legalistic nature of the forms and process is another area in which improvement might be made (Cassileth et al., 1980). That some research subjects mistakenly feel that the consent forms and process are simply risk management tools for physicians and hospitals prevents those subjects from using the consent process as a tool to ensure they are informed about their decisions. This is not just a problem for research subjects. Many physicians also see consent forms as risk management tools (Meisel and Kuczewski, 1996). Although most researchers and IRBs probably understand the purpose of consent forms, it is imperative that all members of the research staff understand that consent forms are first and foremost a tool to insure research subject autonomy and that this understanding is passed on to potential subjects.

Additionally, problems with the length and complexity of consent forms have been cited by various studies as real barriers to informing research subjects. This is an area where improvements can easily be made. IRBs and researchers can work to insure that not only are consent forms accurate and complete but that they are as brief as possible (without sacrificing important information) and that they are written on the same level as easily understandable popular media.

CONCLUSION

Informed consent in research is one of medicine's most powerful tools in ensuring that the autonomy of

Informed Consent and Sham Surgery as a Placebo in Fetal Cell Transplant Therapy Research for Parkinson's Disease

research subjects is protected. It is imperative that every effort be made to inform subjects, in terms they can easily understand, about the research they participate in. This becomes even more important when research subjects may be exposed to physical risk without any obvious medical benefit, as in the case of subjects assigned to the placebo arm of fetal tissue transplantation studies. To assume that research subjects have exercised their autonomy by signing a form or agreeing to participate in research (without ensuring that every effort has been taken to inform them of all the potential consequences, both good and bad) would be an abdication of our responsibility to the ethical practice of medicine.

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REFERENCES

Applebaum, P.S., Roth, L.H., Lidz, C.W., Benson, P., and Winsdale, W. (1991) False Hopes and Best Data: Consent to Research and the Therapeutic Misconception. In: *Biomedical Ethics*. Mappes, T.A. and Zembaty, J.S. (eds.), McGraw Hill, New York. pp. 239-245.

Beauchamp, T.L. and Childress, J.F. (2001) *Principles of Biomedical Ethics*, 5th Ed. Oxford University Press, New York.

Bergler, J.H., Pennington, C., Metcalfe, M., and Freis, E.D. (1980) Informed Consent: How Much Does the Patient Understand? *Clin. Pharmacol. Ther.* **27**:435-440.

Byrne, D.J., Napier, A., and Cuscheri, A. (1988) How Informed is Signed Consent. *Brit. Med. J.* **296**:839-840.

Cassileth, B.R., Zupkis, R.V., Sutton-Smith, K., and March, V. (1980) Informed Consent - Why are its Goals Imperfectly Realized? *N. Engl. J. Med.* **302**:896-900.

Chaikin, L.C. and Lasagna, L. (1969) Obtaining Informed Consent. *Arch. Intern. Med.* **123**:682-688.

Daugherty, C., Ratain, M.J., Grochowski, E., Stocking, C., Kodish, E., Mick, R., and Seigler, M. (1995) Perceptions of Cancer Patients and Their Physicians Involved in Phase I Trials. *J. Clin. Oncol.* **13**:1062-1072.

Dazzi, D., Agnetti, B., Bandini, L., Corradini, P., De Giovanni, F., Ghillani, M., Giacomo, G., and Pezzarossa, A. (2001) What Do the People Think (and Know) About Informed Consent for Participation in a Medical Trial. *Arch. Intern. Med.* **161**:768-769.

Freed, C.R., Greene, P.E., Breeze, R.E., Tsai, W., DuMouchel, W., Kao, R., Dillon, S., Winfield, H., Culver, S., Trojanowski, J.Q., Eidelberg, D., and Fahn, S. (2001) Transplantation of Embryonic Dopamine Neurons for Severe Parkinson's Disease. *N. Engl. J. Med.* **344**:710-719.

Freeman, T.B., Vawter, D.E., Leaverton, P.E., Godbold, J.H., Hausner, R.A., Goetz, C.G., and Olanow, C.W. (1999) Use of Placebo Surgery in Controlled Trials of a Cellular-Based Therapy for Parkinson's Disease. *N. Engl. J. Med.* **341**:988-992.

Kucia, A.M. and Horowitz, J.D. (2000) Is Informed Consent to Clinical Trials an 'upside selective' Process in Acute Coronary Syndromes. *Am. Heart J.* **140**:94-97.

Lynoe, N., Sandlund, M., Dahlqvist, G., and Jacobsson, L. (1991) Informed Consent: Study of Quality of Information Given to Participants in a Clinical Trial. *Brit. Med. J.* **303**:610-613.

Macklin, R. (1999) The Ethical Problems with Sham Surgery in Clinical Research. *N. Engl. J. Med.* **341**:992-996.

Meisel, A. and Kuczewski, M. (1996) Legal and Ethical Myths About Informed Consent. *Arch. Intern. Med.* **156**:2521-2526.

Morrow, G.R. (1980) How Readable Are Subject Consent Forms? *JAMA* **244**:56-58.

Olanow, C.W., Goetz, C.G., Kordower, J.H., Stoessl, A.J., Sossi, V., Brin, M.F., Shannon, K.M., Nauert, G.M., Perl, D.P., Godbold, J., and Freeman, T.B. (2003) A Double-blind Controlled Trial of Bilateral Fetal Nigral Transplantation in Parkinson's Disease. *Ann. Neurol.* **54**:403-414.

Reicken, H.W. and Ravich, R. (1982) Informed Consent to Biomedical Research in Veterans Administration Hospitals. *JAMA* **248**:344-348.

Schaeffer, M.H., Krantz, D.S., Wichman, A., Masur, H., Reed, E., and Vinicky, J. (1996) The impact of Disease Severity on the IC Process in Clinical Research. *Am. J. Med.* **100**:261-268.

United States Advisory Committee on Human Radiation Experiments. (1996) Research proposal review project. In: *Final Report of The Advisory Committee on Human Radiation Experiments*. Faden, R.R. (ed.), Oxford University Press, New York. p. 455.

Victor, M. and Ropper, A.H. (2001) *Principles of Neurology*. McGraw Hill, New York. p. 1128.

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