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Review Article

Review of the Ethical Literature on Surgical Placebos in Parkinson's Disease Treatment

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ABSTRACT

In clinical trials of neurosurgical interventions for the treatment of Parkinson's disease, the ethicality of using placebo surgeries as a control in trial design is disputed. A primary issue in this dispute is the risk-benefit profile associated with such surgeries, whether the benefits of the surgery justify exposing trial participants to the potential risks. Proponents argue that the risks to trial participants are sufficiently minimized such that the surgery is ethical justifiable, while critics argue both that those risks are not minimized when compared to a no-surgery trial design and when the "basic interests" of trial participants are potentially endangered by the procedure. After considering the respective merits of the arguments advanced by both proponents and critics, this analysis finds the position of those against the ethical permissibility of sham surgery in clinical trials for PD treatment more tenable. In defense of the critics' position, this analysis develops and defends two reasons adduced by critics: first, that the risks to trial participants are not in fact minimized when compared to a no-surgery trial design and second, that the magnitude of the risks associated with the sham procedure directly endangers the "basic interests" of trial participants. Given these two reasons adduced by critics, this analysis further develops this line of argument and concludes that sham surgery in this context violates the principle of beneficence.

Keywords: Parkinson's disease; Sham surgery; Placebo surgery; Neurodegenerative disease; Placebo ethics

INTRODUCTION

One of the primary ethical concerns posed by using sham or placebo surgeries as a control in clinical trials of stem cell transplantation in Parkinson's disease (PD) patients is the risk-benefit profile of the procedure. That is the risks and benefits potentially resulting from the surgery, and the ethical question of whether the benefits justify those risks. This review understands the ethical permissiveness of sham-surgeries as a control in trial design to depend on the following question: In comparison to a no surgery trial design, are the additional risks present in a sham surgery trial design justified [1]. In other words: Is the degree of invasiveness of the surgical procedure used that is, the magnitude of the risks associated with the procedure-ethically justifiable in relation to the potential benefits, particularly when patients do not receive direct therapeutic benefit from the sham procedure itself ?

In the view of proponents, the risk-benefit profile is such that the ethical permissiveness of the procedure directly follows. In contrast, critics make two counter-claims: First, that the "baseline" by which risks are assessed do not minimize those risks to the greatest extent possible, and second, that the classification of a sham procedure as a "non-therapeutic intervention" results in the risk-benefit profile associated with the procedure being in violation of the principle of beneficence – that is, in the principle's paradigmatic formulation, the principle to do no harm, and to maximize benefits while minimizing risks [2].

Since there is no clear consensus in the literature regarding the ethical permissibility of sham procedures, the following ethical analysis as part of this review will first elucidate the main arguments of proponents and critics, and then, second, highlight the merits of the respective arguments. Ultimately, this analysis concludes that, when considering the interests of subjects, sham

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procedures should be regarded as ethically impermissible. In addition, the ethical impermissibility of a sham procedure is further supported by suggesting that the proponents' argument that the risks of such a procedure are qualitatively the same as diagnostic procedures used in clinical research fails to account for the concept of "minimal risk" as incorporated into the review process of IRBs.

ARGUMENTS OF PROPONENTS AND CRITICS

Arguments of proponents

According to proponents, sham surgery controls readily meet the following two conditions enumerated in federally regulated Institutional Review Boards (IRBs) required for a clinical study [3]. These conditions are presented below in a condensed and abbreviated form:

(1) Risks to subjects must be minimized: (i) By using procedures that are consistent with sound medical design and which do not unnecessarily expose subjects to risk, and (ii) Whenever appropriate, by 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. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research. The IRB should not consider possible long-range effects of applying knowledge gained in the research as among those research risks that fall within the purview of its responsibility.

Proponents of sham surgery controls defend its meeting the above conditions on two grounds: (i) The potential risks to trial participants have been minimized as much as possible, consistent with sound scientific design and (ii) The risk-benefit ratio associated with the procedure is reasonable that is, the risks of the procedures are reasonable in relation to the possible benefits [3].

Regarding, (i) the risks has been minimized as much as possible insofar as, according to Freeman "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" amongst other therapeutic measures. Regarding, (ii) these risks are reasonable, according to Freeman in relation to the benefits of a sham surgery control, since those benefits namely, "receiving standard medical treatment at no cost, having the opportunity to obtain fetal tissue transplant at no cost if the procedure proves safe and effective, being spared the risks associated with transplantation if it proves to be unsafe or ineffective," and, most importantly, "contributing to advances in the treatment of a disease of great personal interest to not only participants," but society as a whole significantly outweigh the possible risks associated with the drilling of burr holes and the use of cyclosporine [3].

Elaborating on, the claim that the risks of study participants have been minimized as much as possible depends on, as London notes, taking "the active arm of the trial as the proper baseline to evaluate" those risks possible for those participants receiving the sham procedure. The baseline for evaluation of risks, then, is whether penetration of the dura occurs, and whether material is subsequently inserted. Since neither occurs in the sham arm of the trial, the risks are minimized to the greatest extent possible, as argued by proponents. Even though some risk is still associated with the sham procedure – namely, the drilling of partial burr holes, anesthesia, and administration of the immunosuppressant cyclosporine subjects are not, as London again notes, unnecessarily exposed to risks since those risks have been minimized to the greatest possible extent consistent with sound medical design [4].

Indeed, London highlights that sham surgery is "no different from diagnostic procedures to which subjects are routinely subjected within the context of a well-designed clinical trial." The implication of this point is that trials employing a sham surgery control do not pose any greater risks to trial participants than would a trial that did not include a sham procedure. Given this stance, sham surgeries in this case, as London tells us, do not "raise special concerns over and above those that routinely arise in the evaluation of clinical research," and thus proponents view such procedures "as largely contiguous with existing methods and practices in clinical research" and do not need any "special justification" to be included in trial design [4].

Thus, when described as above, sham procedures in this context seem to meet IRB conditions for ethical permissibility insofar as the risks are minimized as much as possible while still maintaining sound scientific design, and the benefits both to society and to medical science outweigh the possible risks of the procedure.

Argument of critics

Critics have pushed back against the risk-benefit profile of a sham procedure as a justification of its ethical permissibility. The argument of critics is twofold. First, critics maintain that the risks associated with a trial in which a sham procedure is used as a control are not, in fact, minimized since the baseline for risk evaluation is the sham procedure itself. Second, sham surgery procedures are more appropriately classed as non-therapeutic, and consequently, when viewed as non-therapeutic, the risk-benefit profile of a sham surgery procedure fails to satisfy the principle of beneficence – that is, in sum, the principle to do no harm by satisfying a favorable risk-benefit profile wherein the benefits are maximized, and the risks minimized.

Regarding the first claim, Macklin contests the use of the active arm (example the actual performance of the operation) of a trial as the baseline for risk-evaluation, noting that "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 no surgical intervention" [5]. Similar to London's view, Macklin suggests that, rather than having the baseline of risk-evaluation is the active arm of the trial, the baseline should instead be the

absence of a procedure. That is, the baseline against which to assess the degree of risk involved in the procedure should be a state in which the procedure is not performed at all. This point underlies the main thrust of Macklin's argument: namely, that surgical procedure inherently carries risks and thus having a sham arm of a clinical trial does not, according to both Macklin and other critics meet the criteria of minimizing risk to subjects.

Regarding the second claim, some critics suggest that sham procedures be classed as a non-therapeutic intervention that is, an intervention in which the subject receives no direct therapeutic benefit, and that serves only to provide an answer to a particular scientific question, e.g., in this case, whether stem cell transplantation is therapeutically efficacious for Parkinson's. As Clark elaborates, sham procedures are more accurately regarded as non-therapeutic primarily for two reasons. First, the various procedures administered to address the major risk factors associated with the surgery namely, drilling of partial burr holes that do not penetrate the dura, general anesthesia, low-dose of the immunosuppressant cyclosporine, and PET (positron-emission topography) studies – are performed only for the purpose of sound trial design. And second, the magnitude of the risks associated with the procedure for example, death (though remote)-outweighs the magnitude of the benefits that may result. Consequently, a sham procedure in this context fails, according to critics, to satisfy the principle of beneficence [1,3,6].

In sum, the argument against the ethicality of sham surgery in this case rests on two claims that surgery carries inherent risks, that would not be present were the control arm of a trial not to include surgery and thus the risks to trial participants are not minimized; and sham procedures in this case are more aptly characterized as non-therapeutic procedures and thus fail the principle of beneficence insofar as the risks to trial participants are not minimized, and the procedure itself has no direct therapeutic effect for participants [5,6].

ETHICAL ANALYSIS

The lack of consensus in the literature regarding the ethicality of sham surgery in this case is a result, in part, of IRB guidelines being amenable to the positions of both critics and proponents, as London and Kadane note [7]. The goal of this analysis, however, is to provide support for the claim that the ethical underpinnings of the critics' position of sham surgery conform more with the intent of IRB guidelines than does the position of sham surgery proponents. The intent of IRB guidelines, so understood, is to balance the intent of research to advance scientific/medical knowledge and what is permissible to subject trial participants to.

As described in the previous section, the use of sham surgery in this case appears to be ethically permissible since, as noted above, the procedure seems to readily satisfy the two ethical conditions stipulated by IRBs. As London notes, generally the greater the minimization of risks to study participants while remaining consistent with a sound study design, the stronger the ethical justification of that study. This case seems to conform to that guiding thought regarding the ethicality of clinical studies. For, as has been noted, the risks to study participants are minimized as much as possible by using only partial burr holes and substituting placebo substances for risk-mitigating antibiotics, while remaining consistent with sound scientific design as London points out, and reasonable to the importance of the scientific knowledge that may result namely, an efficacious therapy for Parkinson's [4].

Still, the arguments of critics suggest theoretical issues that may undermine the prima facie support for sham procedures in this case. These theoretical issues principally concern the justificatory strength of a risk-benefit assessment. For instance, the risk-benefit conditions stipulated by IRBs and other ethical review boards are not met by either the quantitative and qualitative nature of the risks associated with a study. That is, the ethicality of a study is not settled on the basis of a risk-benefit assessment when that assessment considers only the quantity and quality of those risks. There must be, in addition, a relation of reasonableness established between those risks and possible benefits to ethically justify a study, as many critics of these procedures have noted [4]. This concept of "reasonableness" is articulated in IRBs as solely determined by the qualitative nature of the risks benefits being weighed that is, how respectively great the risks and benefits are.

This concept of "reasonableness" invoked in the idea of "reasonable risk" is partially filled out by turning to London's framework of patient interests when assessing the ethicality of sham procedures, particularly the notion of patients' "basic interests". Basic interests, according to London, are that set of interests a subject has "in being able to cultivate and exercise their rudimentary intellectual, affective, and social capacities in the pursuit of a personally meaningful plan of life." This concept of "basic interests" supports London's elaborated concept of reasonable risk: "reasonable risks are those that are necessary to generate important scientific information and that are consistent with an equal regard for the basic interests of study participants." This elaborated concept of reasonable risk is not solely a calculus balancing the magnitude of risks and benefits but rather situates those risks and benefits within the context of the basic interests of trial subjects. When elaborated in such a way, the potential risks incurred by trial subjects do not support the ethicality of the sham procedure insofar as the procedure unequivocally endangers those basic interests of trial subjects. That this is the case is particularly evident when considering that those basic interests of trial subjects are endangered without the prospect of direct personal therapeutic benefit and only for the sake of future persons. As London helpfully puts it, "the same concern to advance the interests of future patients that underwrites the research enterprise as a social institution cannot be withheld from present, prospective research participants" [4].

In sum, the positive argument for the ethical impermissibility of sham surgeries in the case of Parkinson's disease depends on conceiving the relation of reasonableness between risks and benefits as involving the protection of the basic interests of trial participants. Following from this elaborated concept of "reasonable risk," the argument advances the claim that the risks of the procedure are not reasonable in relation to the potential

benefits insofar as the magnitude of the potential risks to trial subjects directly endangers those basic interests without the possibility of direct therapeutic benefit.

It should be noted that this conclusion should not be accepted without an important qualification. The fact that trial subjects do not receive any direct therapeutic benefit – that is, because the sham surgery is classed as a non-therapeutic intervention – does not definitively count against placebo surgeries in PD therapies. Just because an intervention is non-therapeutic, in other words, does not by itself count against ethically performing such interventions? Recall that proponents of sham surgeries in PD trials make this point, noting "that there are many elements of clinical trials that subject participants to risks or burdens without the prospect of direct personal benefit" [4]. For instance, proponents note, certain diagnostic procedures (such as extra blood draws, spinal taps, etc.) that present no direct therapeutic benefit to trial participants but that are integral to sound trial design are nonetheless ethically justified. Recall that sham surgery, for proponents, is qualitatively the same as extra blood draws or spinal taps. Again, this point underlies proponents' main point that the risks of a sham surgery are not greater than any surgery trial design.

This argument of proponents, however, seemingly fails to account for the definition of "minimal risks" as stipulated by IRB regulation 45 C.F.R 46 (§46.102), which defines risks as minimal when "the probability and magnitude of harm and 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 or, diagnostic physical or psychological examinations or tests" [8]. This condition of minimal risk is applicable only to non-therapeutic procedures, a type of procedure that includes sham surgery procedures, as argued above. The point here is that sham surgeries in this case do not meet the requirement of minimal risk insofar as the risks to subjects are greater than they would otherwise be in diagnostic procedures. That is, proponents claim that, regarding potential risks to subjects, sham surgeries and diagnostic procedures are qualitatively the same. Even if the magnitude of the risks themselves were qualitatively the same in both the sham surgery and diagnostic procedures, it would still be the case that the probability of risk to subjects is much greater in the sham surgery than in diagnostic procedures.

Given the above analysis, sham surgery used as a control in trials studying the efficacy of "neurosurgical therapies" for PD may be seen as ethically impermissible [9]. This is the case for two reasons, as delineated above: (i) the relation of risks to benefits is unreasonable insofar as the magnitude of risks to subjects in sham surgery in this case is such that the basic interests of trial subjects are endangered and (ii) the risks to trial subjects do not qualify as "minimal" according to the IRB definition insofar as both the probability and magnitude of those risks rise above the risks to subjects in no surgery trials. These two points underlie the main thrust of this analysis: that a prohibition of sham surgery as a control in trial design conforms more with the ethical underpinnings of IRB guidelines namely, balancing the intent of clinical research to advance scientific/medical research to the duty to safeguard the basic interests of trial participants – than does permitting such surgeries [5].

CONCLUSION

This analysis concludes that sham surgery as a control in Parkinson's disease trials is not ethically justifiable. This conclusion rests on several interrelated points following: Macklin, surgery especially procedures as invasive as the one that would be used in a possible trial carries inherent risk and thus ipso facto the risks to trial participants are not minimized; sham procedures in this case fail to satisfy the principle of beneficence that is, the principle to minimize risks to trial participants and to maximize the benefits to themselves or others insofar as neither are the risks minimized nor are the benefits maximized since trial participants stand to receive no direct therapeutic benefit; and following London, the risks of the procedure are not reasonable in relation to the benefits insofar as the magnitude of the possible risks directly endangers the "basic interests" of trial participants.

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