architecture and record limb movements: 1 night with the patient already treated with dopaminergic agonist; 1 night after treatment withdrawal; and, last, 1 night after reintroduction of the dopaminergic agonist compound. The patient had a clear benefit from pramipexol, then a major recrudescence of restlessness in both arms subsequent to pramipexol withdrawal, and was relieved again when the molecule was administrated at 12 p.m. on the following day. VPSG, as well as an electromyogram (EMG) on the extensor carpi radialis (ECR) muscle were performed to record periodic movements of the upper limbs.[5] Surprisingly, a repeated extension of the small finger was observed, especially during pramipexol withdrawal (Fig. 1A, insert 1b,c; or see Video). The upper limb movements could occur unilaterally (right or left), bilaterally, or extend to the lower limbs and were observed during periods of wakefulness and non-REM sleep. EMG activity of the ECR (Fig. 1, part 2; or see Video) fulfils the American Academy of Sleep Medicine criteria for PLM disorder, [6] apart from for their localization.

Discussion and Conclusions

Involvement of upper limbs in RLS, although poorly known, is relatively frequent.[7] We report on a case that confirms that RLS can be limited only to the arms. Remarkably, a repeated extension of the small finger, mimicking the typical extension of the hallux, characteristic of PLM, was noticed. One should be aware of the upper limb variant of this syndrome, and that treatment by dopaminergic agonists proves to be very efficient.

Legends to the Video

Video 1. Video montage illustrates periodic upper limb movements and is taken directly from the video capture during PSG. Insert shown is an enlargement of the original video of the whole body, explaining the low resolution. EEG recording: F, frontal; C, central; P, parietal; T, temporal; O, occipital; uneven numbers, left. EOGD G2 and EOGG G2: electrooculogram. Ment+Ment−: chin EMG. JbG+JbG−; JbD+JbD−: left and right anterior tibialis EMG. DelD+DelD−; DelG+DelG−: right and left deltoid muscle EMG. DphD+DphD−; DphG+DphG−: right and left extensor carpi radialis EMG. ■

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Sham Surgery Controls in Parkinson's Disease Clinical Trials: Views of Participants

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ABSTRACT

Background: Sham surgery controls are increasingly used in neurosurgical clinical trials in Parkinson's disease (PD) but remain controversial. We interviewed participants of such trials, specifically examining their understanding and attitudes regarding sham surgery.

Additional Supporting Information may be found in the online version of this article.

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Methods: We conducted semistructured qualitative interviews with participants of 3 sham surgery–controlled trials for PD, focusing on their understanding of sham design, their reactions to it, its impact on decision making, and their understanding of posttrial availability of the experimental intervention and its impact on decisions to participate.

Results: All subjects (n = 90) understood the 2-arm design; most (86%) described the procedural differences between the arms accurately. Ninety-two percent referred to scientific or regulatory reasons as rationales for the sham control, with 62% specifically referring to the placebo effect. Ninety-one percent said posttrial availability of the experimental intervention had a strong (48%) or some (43%) influence on their decision to participate, but only 68% understood the conditions for posttrial availability.

Conclusions: Most subjects in sham surgery–controlled PD trials comprehend the sham surgery design and its rationale. Although there is room for improvement, most subjects of sham surgery trials appear to be adequately informed.

Key Words: sham surgery; gene therapy; Parkinson's disease; bioethics

Sham surgery controls are increasingly used in neurosurgical clinical trials of interventions for Parkinson's disease (PD).[1–3] Unlike a pill placebo, sham surgery is invasive, usually consisting of bilateral burr holes (full or partial) with or without penetration of the dura. The use of sham controls is supported by most PD clinical researchers in North America despite these controls being exposed to invasive sham surgery because of the scientific advantages in controlling for placebo effects.[4] A recent review noted that there have been 6 surgical interventions for PD that had initially shown promise in open-label trials but that later proved to be no more effective than placebo surgery.[5] In 5 of 6 experimental therapies tested, the response to active therapy was 50%–70% less in blinded trials than in open trials; the open-label studies also tended to underestimate the potential risks.

Yet sham surgery controls remain controversial. Some scientists reportedly consider sham brain surgery "an expensive, potentially dangerous and possibly unethical bit of biomedical theatrics."[6] In Europe and the United Kingdom, where sham controls are deemed less acceptable than in the United States, a large clinical trial of a fetal cell transplant treatment is under way without the use of sham controls.[6] One prominent reason why sham controls have been deemed unacceptable is a concern that vulnerable, elderly patients with incurable and debilitating illnesses may be exploited in such research.[7] In evaluating the ethics of this controversial topic, it is important to incorporate the perspective of those PD patients actually involved in such trials.

We interviewed persons who had agreed to participate in sham-controlled surgical trials for PD, examining their understanding and attitude toward sham surgery controls, as well as toward the availability of the experimental intervention to those in the sham arm after the trial, a usual part of sham-controlled studies that has created controversies of its own, as subjects have sought the experimental intervention even in negative trials.[8]

Patients and Methods

Participants

Participants were recruited from 3 sham-controlled intervention trials for PD. We recruited 31 of 56 enrollees (55%) at 5 sites from the STEPS trial[1] and 30 of 43 enrollees (70%) at 7 sites of the CERE-120 trial[3]; they were interviewed retrospectively, after their surgery (details of their recruitment can be found in an earlier report[9]). In the GAD study, sponsored by Neurologix, Inc.,[2] we interviewed 29 of the 45 enrollees (64.4%) from 5 sites, of whom 24 were interviewed prospectively, before surgery. All interviews were conducted via telephone and were recorded and transcribed. Interviewer notes were used for 1 interview because of technical difficulties in recording. The institutional review boards of the University of Rochester and the University of Michigan reviewed the study and deemed this study exempt from U.S. federal regulations.

Measures and Analysis

Conditional Probe Interview

The Conditional Probe Interview (CPI) is a semistructured qualitative interview guide designed to elicit how the subjects made their decisions about participation.[10] This article focuses on those questions in the CPI that specifically address the subjects' understanding and attitudes toward the sham placebo design (listed in Appendix 1). After all transcriptions were checked for accuracy, standard content analysis procedures were used, developing and refining codes in an iterative fashion and resolving coding discrepancies through group discussion.[10]

Results

Of the 90 subjects, most were white (n = 88 [98%]), male (n = 64 [71%]), married (n = 66 [73%]), and well educated (n = 52 with college degree or higher [57%]). Average time since PD diagnosis was 11.7 ± 4.6 years.

Understanding Sham Surgery Research Design, Rationale, and Procedures

All subjects showed a basic understanding of the sham control design, that is, that there were 2 arms in

their study, a placebo arm and a treatment arm. When asked about the purpose of the control arm, the answers varied in specificity (see Table 1).

Whereas some merely said that the FDA requires it, others articulated the generic need (without specifically mentioning the placebo effect) for a comparison arm:

"I mean I'm not a world-renowned scientist or something, but I know basically that to confirm it to be a success, you have to have a control group" (STEPS, S23).

Others specifically mentioned the need to control for the placebo effect in PD clinical trials:

"The placebo effect is extremely strong in Parkinson's for some reason in some individuals. So, you've got to have a placebo group. The whole...All twelve of those people in the phase I study could have been affected by the placebo effect" (CERE-120, S7).

Overall, 92% of subjects provided an answer that referred to the scientific or, less commonly, the regulatory rationale for the sham control arm.

Eighty-six percent of subjects described the procedural differences between the study intervention and the sham surgery groups accurately. These subjects correctly contrasted the treatment arm, which involved injection with the study agent into the brain, with the placebo arm which involved only burr holes (and a saline injection into the scalp for the GAD study). Approximately 77% of subjects stated that the study intervention arm has greater risks than the sham surgery arm.

Attitudes Toward Sham Surgery Design

Overall, half the subjects reported that they initally had a negative reaction to finding out that there would be a sham surgery arm (see Table 2).

They mentioned being disappointed, concerned, or apprehensive when they learned of the sham surgery design: "[T]hat part of it is really a turn-off, a real big one" (CERE-120, S18), "I had to think about that for a little bit" (CERE-120, S2), and "I was discouraged" (GAD, S15). Surprisingly, 6 subjects had a positive reaction after being informed that there would be a sham surgery arm: "All good studies should be done that way" (STEPS, S12), "...[T]he fact that there was a placebo and it was double-blind...it did make me more confident that...[i]t's a professional study as opposed to nonprofessional" (GAD, S5). Most of the subjects with an initial negative reaction who indicated the influence of this initial reaction on their decision (15 of 21 [71%]) said it did not negatively influence their decision to participate.

Table 1. Understanding of sham control rationale and procedures

	n = 90[a]
What is the purpose of having a sham surgery group?	
Need to control for placebo effect	55 (61.8)
To make study legitimate/rigorous (no specific mention of placebo effect)	25 (28.1)
Cannot determine from text if subject understands purpose of sham surgery	3 (3.4)
FDA requires it	2 (2.2)
Subject not sure	2 (2.2)
Other	2 (2.2)
Describe the difference in procedures between those who receive sham surgery and those who receive the [study intervention].	
Describes differences accurately	67 (85.9)
Does not describe differences accurately	4 (5.1)
Subject cannot recall/not sure	6 (7.7)
Other	1 (1.3)
How are the risks faced by those in the [study intervention] group different from the risks faced by those in the sham surgery group?	
Those in [study intervention] group face greater risks	44 (77.2)
Those in sham surgery group face greater risks	—
No difference/face same risks	10 (17.5)
Not sure	2 (3.5)
Other	1 (1.8)

[a]Numbers may not add to 90 for every question because of missing data for some questions.

When asked to comment on the invasive nature of the control condition, most of the subjects' comments (79%) expressed views to the effect that they understood the need for sham surgery, felt the risk was acceptable, trusted the researchers, or felt it was acceptable in light of the later offer of the study intervention. However, 14% of the comments from subjects expressed some residual negative sentiments about the sham arm.

Understanding and Attitudes Toward Later Offer of Study Intervention

All 3 clinical trials offered the subjects in the sham surgery arm the experimental intervention at the end of the study period, with the condition that the study intervention was proved to be safe and effective. Although the majority of subjects understood the conditions under which the study intervention would be made available, a sizable minority (32%) wrongly assumed that it would be offered without condition, were not sure of the conditions, or expressed themselves in a way that did not allow a clear determination of whether they understood the conditions (Table 3).

The later offer of the experimental study intervention had a strong impact on the enrollees' decision to participate, with nearly half (48%) saying that it was a necessary or strong reason for his/her decision to participate and an additional 43% saying it had some influence.

Table 2. Attitudes toward sham surgery controls (n = 90[a])

What was your initial reaction to finding out there would be a sham surgery group?	
Negative reaction (disappointed, concerned, surprised, etc.)	42 (47.2)
Neutral reaction (not surprised or concerned, etc.)	41 (46.1)
Positive reaction (strengthens study, makes study more rigorous, etc.)	6 (6.7)
What influence did this initial reaction have on your decision, if any?	
Negative influence on decision/made subject more hesitant regarding participation	7 (15.6)
No negative influence on decision/neutral influence	35 (77.8)
Positive influence on decision	3 (6.7)
Usually placebos are risk-free (like taking a sugar pill), but sham surgery placebos involve a neurosurgical procedure. What do you think about the fact that sham surgery involves an invasive procedure?[b]	
Understood need for control group, so accepted this	42 (42.0)
Risks of sham surgery seemed acceptable	22 (22.0)
Trusted researchers and so accepted this/deferred to researchers	11 (11.0)
Acceptable in light of later offer of [study intervention]	4 (4.0)
Understood need for control group, but disagreed with inclusion of sham surgery	8 (8.0)
Understood and accepted need for control group, but still has some negative feelings concerning invasiveness	6 (6.0)
Other	7 (7.0)

[a]Numbers may not add to 90 for every question because of missing data for some questions.
[b]For this question, numbers refer to comments, not subjects, and exceed the total number of subjects because some subjects made more than 1 comment.

Finally, 89% of subjects (among whom data were available, 64) said it would be better to be in the study intervention arm. Interestingly, 4 of the 6 subjects who had a positive reaction to the sham design still felt that the study intervention arm was the preferable arm to be in. For example, although GAD S24's initial reaction to sham design was that "that was the best...a marvelous way of handling it," he still preferred "the gene transfer....I would think that the genes have the best chance of doing something for me to help out."

Discussion

Unlike a pill placebo, placebo surgery in a randomized controlled trial is not benign. Although to date there appears not to have been serious adverse effects from sham surgeries,[11] an invasive control condition in studies involving elderly persons with incurable illnesses requires close ethical scrutiny. To inform this issue, we examined the level of understanding of participants of actual sham-controlled trials regarding key design elements of a sham-controlled clinical trial. There are several key findings. First, overall the subjects were well informed regarding the sham surgery design and its rationale. About two thirds of our subjects articulated the rationale for the sham condition with a fairly high degree of specificity (the need to control for placebo effects), and the rest of the subjects provided less specific but still accurate rationales for sham surgery. A large majority of enrollees (86%) also understood the differences in procedures between the 2 arms. That nearly half the subjects (47%) initially had a negative reaction to the sham design suggests that the subjects appreciated the implications of a sham control design—especially because most also understood that the study intervention arm is more risky than the sham arm. Further, even those few who had a positive reaction to the sham design provided a sound rationale for their opinion. On the other hand, there is room for improvement, as 14% of subjects did not adequately describe the difference in procedures between the sham arm and the intervention arm, and 18% stated that the risks of the 2 arms were the same.

Second, the subjects' comments regarding the invasive nature of the sham surgery arm suggested that

Table 3. Understanding and attitudes toward later offer of study intervention

	n = 90[a]
How are researchers going to decide if the [study intervention] will be offered later to those who get the sham surgery initially?	
If the intervention is determined to be potentially beneficial and safe	60 (68.2)
Automatically offered/ no preconditions	13 (14.8)
Not sure what conditions must exist	10 (11.4)
Cannot determine if subject understands conditions	5 (5.7)
Please explain what influence [the posttrial offer of study intervention] had on your decision to participate, if any.	
Necessary or strong condition for participating	37 (48.1)
Some influence but not necessary	33 (42.9)
Did not influence decision	7 (9.1)
Other	—
Do you think it would be better to be in the [study intervention] group or the sham surgery group?	
Active treatment group	66 (89.2)
Placebo group	3 (4.1)
Tried not to think about it	1 (1.4)
Other	4 (5.4)
Why [would that arm be better to be in]?[b]	
Motivated by desire for direct personal benefit	33 (41.3)
Did not want to wait a year to receive [study intervention]	18 (22.5)
Did not want to go through surgery twice	12 (15.0)
Each option has advantages	6 (7.5)
Wanted to wait and see what happened to subjects who received [study intervention] before subject received it	2 (2.5)
Did not want to be influenced by expectations, so tried not to think about this	1 (1.3)
Other	8 (10.0)

[a]Numbers may not add to 90 for every question because of missing data for some of the questions.
[b]For this question, numbers refer to comments, not subjects, and exceed the total number of subjects because some subjects made more than 1 comment.

even if they had a negative initial reaction, they accepted its rationale. Only about 14% of subjects' comments (14 of 100 comments) reflected a residual negative sentiment. Of those, 8 comments reflected the view that although the subjects saw a need for a comparison arm, they disagreed with sham surgery as the proper control. These subjects knowingly accepted the sham arm despite their objections in order to participate in the trial. This raises the question of whether these subjects were therefore less (because they had to accept something they did not agree with) or more (because they might have made a knowing trade-off) "voluntary" in their decisions to participate. Third, the offer of posttrial availability of the study intervention is very important to those who enroll in sham-controlled trials in PD. Almost half said it was either a necessary or a strong condition for their participating, with another 43% citing it as having "some influence." However, a significant minority (32%) was either mistaken or unclear about the conditions for such an offer, and given its strong impact on decision making, this is clearly an area in need of improvement. Finally, the results reinforce the need to carefully distinguish between subject motivation and subject understanding,[10,12] as clearly demonstrated by those subjects who recognized the need for the rigorous study design, all the while desiring to be in the intervention arm.

The study has limitations. First, the results are based on qualitative coding of narrative texts. Although we used methods to maximize reliability and reduce bias, such coding involves judgment, and others may have coded the texts differently. Second, the time of interviews varied, so that some subjects were interviewed prospectively, whereas a majority were interviewed retrospectively, some several years after surgery. However, our sample included both prospective (n = 24 enrollees) and retrospective (n = 66 enrollees) interviews, and the responses were similar in both groups. Third, missing data were a problem for a few of the follow-up probe questions because of the nature of how we conducted the interviews—allowing the subjects to lead the discussion and thereby sometimes not asking all the probe questions. Fourth, because the informed consent process for these clinical trials was extensive, involving well-educated subjects, one should be cautious about generalizing these findings to other settings.

Most subjects in sham-controlled PD trials achieve not only factual comprehension about the special features of a sham control design—as required by informed consent—but also achieve an appreciation of the scientific and regulatory rationale for the design that goes beyond the strict requirements of informed consent. They are also able to coherently explain their decision making regarding research participation. But there is clearly room for improvement, especially regarding the conditions for posttrial availability of the study interventions. Overall, informed consent concerns regarding special features of sham-controlled trials in PD, although needing some improvement, should not be seen as a special ethical barrier to such studies. ■

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