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Factors Underlying Patient and Surgeon Willingness to Participate in a Placebo Surgery Controlled trial

A Qualitative Investigation

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Objective: To investigate the factors underlying willingness to participate in a hypothetical trial among patients and surgeons, to inform the design of future placebo surgery controlled trials.

Background: Placebo surgery controlled trials are the gold standard for testing the efficacy of surgical procedures. However, these trials commonly fail to meet the target sample size and terminate underpowered.

Methods: From October 2019 to July 2020, eligible patients were identified from the orthopedic waiting list at a single tertiary hospital and surgeons were identified from orthopedic clinics at three tertiary hospitals in Australia. Qualitative interviews explored factors underlying willingness to participate in a hypothetical trial, including understanding of trial concepts; attitudes; and trial design preferences. Data collection and analysis were conducted in parallel. Recruitment ceased when no new concepts emerged. Interview data were analyzed using reflexive thematic analysis.

Results: The majority of surgeons and only a few patients indicated a willingness to participate in a placebo surgery controlled trial. Factors underlying willingness were captured in four themes: (1) Understanding and attitudes toward placebo; (2) Attitudes towards randomization/perception of equipoise; (3) Perception of risk; and (4) Ethical concerns.

Conclusions: To optimize recruitment in the future, trialists may consider embedding strategies into the recruitment process that validate patients' symptoms, encourage an altruistic mindset, address surgeon biases, and involve surgeons in explaining trial concepts to patients. Trialists may also consider designing three arm trials that meet surgeons' preferences for a "low" and "high" fidelity placebo.

Key words: placebo surgery controlled trial, qualitative research, feasibility, trial recruitment, trial design

INTRODUCTION

The vast majority of surgical procedures are not supported by evidence from randomized controlled trials and as such the efficacy of most surgical procedures has not been tested.[1] Can we justify the continued widespread use and cost of these procedures without rigorous testing? The gold standard for testing the efficacy of a surgical procedure is a placebo surgery controlled trial.[2] While consensus definition for a placebo surgery trial is lacking, it can be described as a trial in which a surgical procedure is compared with a blinded procedure involving anesthesia and skin incision only.[3]

A recent systematic review found that of 24 placebo surgery controlled trials which compared the efficacy of an invasive surgical procedure to a placebo procedure and had a published protocol available, only three trials reached the target sample size within the projected timeline.[3] On average, trialists took 88% more time than anticipated to reach the recruitment target. Among the nine orthopedic trials, none reached the target

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sample size within the projected timeline and trialists took on average 120% more time than anticipated to reach the recruitment target. Poor recruitment puts trials at risk of being underpowered. Underpowered trials may not adequately test the underlying trial hypotheses. Lengthening the timeline of a trial and adding sites increases trial costs. Terminating a trial before reaching sufficient power wastes valuable research funding and raises ethical concerns for the participants who enrolled in the trial for no potential knowledge gain.[4]

Feasibility testing is required to ensure that trials are optimally designed to reach the target sample size before running out of time or money.[5] Previous research points to low willingness among patients and surgeons to participate in placebo surgery controlled trials.[2, 6] Understanding and addressing the factors underlying willingness to participate may optimize recruitment in future trials. Therefore, the aim of this qualitative study was to investigate the factors underlying patient and surgeon willingness to participate in a placebo surgery controlled trial.

METHODS

Ethical approval was granted by the lead Human Research Ethics Committee at St Vincent's Hospital Melbourne, Australia (Reference 072/19).

Design

Factors underlying patient and surgeon willingness to participate were investigated in the context of a hypothetical placebo surgery controlled trial in orthopedics. A qualitative research paradigm involving reflexive thematic analysis was adopted.[7] This enabled the research team to interpret the participants' perceptions and attitudes through their "lens" as clinician-researchers with backgrounds in psychology, orthopedic surgery, clinical trials, and qualitative research.

Recruitment

Recruitment took place between October 2019 and July 2020. Patients were identified from the orthopedic waiting list at a single tertiary hospital in Australia with a large geographically, socioeconomically and culturally diverse referral base. English speaking adults aged >18 years, consented to undergo a major orthopedic surgical procedure were eligible. Eligible patients, purposively selected based on age, sex, education level, and orthopedic condition to ensure that a range of perspectives were represented in the final sample, were contacted via telephone. All practicing orthopedic surgeons in three Australian hospitals were invited to participate through an email from their respective Head of Department. Interested surgeons contacted the researchers and were provided with the study information sheet. Surgeons from each site who opted-in were enrolled consecutively.

Consistent with the qualitative approach, sample size was guided by thematic saturation, enabled through concurrent data collection and analysis. For patients, recruitment continued until sufficient diversity was captured in the sample and thematic saturation was reached. This occurred at 20 interviews, with no new concepts identified in the final (21st) interview. For surgeons, recruitment continued until each site was roughly equally represented and thematic saturation was reached. This occurred at 18 interviews, with no new concepts identified in three further interviews.

Data Collection

Data were collected through semistructured phone interviews conducted by one of two female researchers (EN, a psychologist and SB, a physiotherapist, and experienced qualitative researcher). Separate interview guides were used for patients and surgeons (see Tables S1, http://links.lww.com/AOSO/A78 and S2, http://links.lww.com/AOSO/A79). Both guides explored factors underlying willingness to participate in a placebo surgery controlled trial, including questions related to understanding of trial concepts and perceptions and attitudes toward placebo surgery trials. The patient guide used vignettes that were co-designed with a consumer representative who had experienced joint replacement but had no medical background or pre-existing knowledge of placebo trials. The vignettes functioned to introduce and explain in lay language, concepts that appear in participant trial information and consent forms such as "placebo," "placebo effect," and "randomization."[8]

Interviews were audio recorded, transcribed, and uploaded into a qualitative data management software (Nvivo data management package, version 12.0) to facilitate analysis.

Data Analysis

Patient and surgeon transcripts were analyzed separately. Two researchers (E.N., S.B.) identified initial codes in each transcript shortly after each interview was completed and met regularly to develop a coding framework. Through this process, codes were collapsed and expanded as necessary through discussion between the two researchers, resulting in a refined framework. Any questions or conflicts in the process of developing the refined framework were resolved through consensus discussion with a third researcher (M.D.). One researcher (S.B.) then applied the framework to all transcripts on an ongoing basis throughout the data collection. A subset of transcripts was cross-coded by a second coder (E.N.) to check that the framework was applied correctly. Emergent patterns were identified and grouped into themes by two researchers (E.N., S.B.), through an iterative process involving cycling back to transcripts to ensure interpretations "rang true" to the participants' perceptions.[9] Through discussion with the wider research team, emergent themes from patient and surgeon data were compared, contrasted, and critically challenged in the context of existing evidence in the broader fields of placebo, surgery, and clinical trials. Final testing and definition of themes was conducted through specific questioning in later interviews.

RESULTS

Fifty-two patients were approached and 21 consented to participate. Thirty-one declined due to commitment with work/family (n = 8); being medically unwell (n = 5) and without providing a reason (n = 18). Of 60 eligible surgeons who received an email from their Head of Department, 21 consented to participate (8/25 from Hospital 1; 5/15 from Hospital 2; 8/20 from Hospital 3). Interviews lasted on average 30 minutes (range 15–45 minutes).

Among patients, 11 were women and the median age was 57 years (range 24–78 years) (see Table S3, http://links.lww.com/AOSO/A80). Two had previously participated in a placebo drug trial. Among surgeons, the majority (11/21) specialized in hip and knee surgery and mean years of surgical experience was 14 (range 4 months–42 years) (see Table S4, http://links.lww.com/AOSO/A81). None had previously participated in a placebo surgery controlled trial.

Four patients and 16 surgeons suggested that they would have an "open mind" about participating in a placebo surgery controlled trial. "Open minded" participants did not differ from other participants based on demographics. Four overarching themes described the reasons underlying patient and surgeon willingness to participate: (1) Understanding and attitudes toward placebo; (2) Attitudes toward randomization/perception of equipoise; (3) perception of risk; and (4) ethical concerns.

These themes are described in narrative form below, supported by quotes numbered consecutively in Tables S5, http://links.lww.com/AOSO/A82 and S6 http://links.lww.com/AOSO/A83 (i.e., patient quote 1 [PQ1]; surgeon quote 1 [SQ1]) and indexed by participant number (i.e., patient 01; surgeon 01). In Tables S5, http://links.lww.com/AOSO/A82 and S6 http://links.lww.com/AOSO/A83, each quote is presented as a belief or attitude, classified as either a barrier or facilitator to participation.

Theme 1: Understanding and Attitudes Toward Placebo

While almost all patients were familiar with the term "placebo" and "placebo effect," perceiving them to be concepts involving the mind/brain, psychology, or positive thinking about treatment outcomes, the concept of placebo surgery was novel to most. Only a couple of patients were familiar with the concept due to their professional background in clinical science and medical law, however both expressed negative attitudes toward placebo surgery controlled trials. When presented with a vignette in the context of a pharmacological trial, many patients described the placebo effect as a positive phenomenon that illustrated the brain's influence over the body (PQ1). However, when presented with a vignette in the context of a surgical trial, the placebo effect was usually perceived to be negative; as a sign of weakness indicating that symptoms were "all in the head." Patients who endorsed this belief perceived the purpose of a placebo trial was to "catch out the fakers," that is, to distinguish between pain of structural or psychosocial origin, also referred to as real or fake pain (PQ2). People who distinguished between real and fake pain expressed an unwillingness to participate in a placebo surgery trial as they perceived their own pain as "real" and thus considered themselves to be unsuitable candidates (PQ3).

Consistent with this, several surgeons perceived that the placebo effect had a limited role in orthopedic surgery, arguing that surgery worked through mechanical rather than psychological processes (SQ1). However, most surgeons perceived that placebo effects played some role in their patient outcomes, suggesting that the surgeon-patient relationship was central to this effect (SQ2). All surgeons were familiar with at least one published placebo surgery controlled trial, most commonly involving knee arthroscopy. While all perceived that the outcome of these trials had significantly impacted on clinical practice, many surgeons raised concerns about the validity of the trials. They perceived a lack of equipoise in the procedure under investigation; that the inclusion criteria were too broad; that patient selection had not been informed by imaging findings; that the participating surgeons lacked experience or that variability in surgical technique rendered comparisons between surgeons difficult (SQ3). The reputation of the research team appeared to play an important role in the perceived credibility of the trial outcomes (SQ4). It was acknowledged that the outcomes of a high quality trial conducted by a high quality team could have a powerful effect on behavior by making some surgeons feel ashamed to continue performing a procedure that was found to be no more effective than a placebo (SQ5).

Theme 2: Attitudes Toward Randomization/Perception of Equipoise

Most patients appeared to understand the concept and purpose of randomization. Many patients perceived that randomization was acceptable, as long as people clearly understood the purpose of the trial (PQ4). Half of the patients expressed negative attitudes toward randomization, emphasizing that they would personally want to have a choice over treatment options rather than being a "research guinea pig" (PQ5). When presented with a hypothetical placebo surgery controlled trial, all patients expressed a preference for the "active" surgical arm. Anecdotal evidence of surgical efficacy came from "success" stories among friends and family (PQ6). A couple of patients reported that they were at the "end of the road" (PQ5) and had no choice but to undergo surgery for their condition (PQ5). A few suggested that random treatment allocation would go against their doctor's recommendations (PQ7).

Strong preferences for the "active" surgical arm were also expressed by surgeons. The surgeons who suggested they were unlikely to participate in a placebo surgery controlled trial all perceived a lack of equipoise in the orthopedic procedures they performed, reporting that they only performed procedures which they "knew" would benefit patients (SQ6). When discussing equipoise, a culture of anecdotal over clinical trial evidence in surgery was described. A few surgeons cited "the parachute trial" in support of anecdotal over clinical trial evidence in surgery. In this fabled trial, people are randomized to jump out of an aeroplane with a parachute or placebo because there is no good scientific evidence that parachutes work (SQ7). One surgeon distinguished between clear cut "parachute" areas of surgery like repairing broken bones or torn ACLs, and areas of surgery which had experienced "mission creep", whereby indications for surgery had broadened, such as trimming a torn meniscus (SQ8). The perception of equipoise in the procedure under investigation was central to willingness to participate in a hypothetic trial. Several surgeons suggested that they would feel guilty operating on someone randomized to the placebo arm of trial if they perceived that they would have benefited from the real procedure (SQ5).

Theme 3: Perception of Risk

All patients raised the issue of risks associated with placebo surgery. While over half suggested that they would be willing to participate in a placebo controlled pharmacological trial, only four expressed willingness to participate in a placebo surgery controlled trial. This discrepancy was predominantly attributed to the perceived "risky" nature of surgery. The majority of patients perceived that "interfering with somebody's physiological anatomy" in a surgical trial took things "a step too far" (PQ8). Several cited the risks associated with anesthesia and felt this "dangerous" procedure was unjustified in the context of placebo surgery where there was no potential for therapeutic benefit (PQ9). A couple of patients felt that these risks were outweighed by the potential to further medical research and suggested they would feel satisfied knowing they had contributed to "the greater good" (PQ10).

The surgeons described themselves as risk adverse. All commented on the risks involved in placebo surgery, including infection, scarring, and complications from the anesthetic. A couple perceived the level of risk involved in a placebo surgical procedure was unacceptable, given that there was no potential for benefit (SQ8). Most suggested that they would only be willing to participate in a placebo trial involving minimally invasive procedures such as arthroscopy (SQ9). When discussing preferences for what a placebo procedure should look like, the surgeons were divided. Around half of the surgeons preferred an anesthetic and skin incision only, perceiving that any additional steps, such as introducing instruments into the body, exposed patients to unnecessary risks (SQ10). However, the other half felt that it would be difficult to maintain blinding in a placebo procedure involving an anesthetic and skin incision only, as postoperative signs and symptoms such as swelling and pain would be significantly different between the placebo and index procedure (SQ11). The need for a surgical placebo to be minimally invasive so as to reduce risks, but at the same time invasive enough to enable blinding, presented a paradox that raised doubts about feasibility among some surgeons (SQ12).

Theme 4: Ethical Concerns

Several patients expressed ethical concerns toward placebo surgery controlled trials. The idea that surgeons would subject patients to risks for no potential therapeutic benefit to the individual patient appeared to be at odds with the Hippocratic notion of "do no harm". One patient went so far as to liken the concept to unethical medical experiments in Nazi Germany (PQ11). Several patients reported that this would negatively impact on the patient-surgeon relationship. They used terms such as "cheated", "ripped off", "taken advantage of" and "cloud your judgment" to describe this feeling of compromised trust (PQ12). When presented with the option of cross-over, that is, being offered the "real" surgery at the end of the blinding period if randomized to the placebo surgery arm, one patient suggested that they would no longer have trust in their surgeon. On the other hand, a few patients suggested it was unethical to continue to use medical procedures without evidence of efficacy, simply because its "just the accepted thing to do" (PQ13).

The surgeons similarly cited their mandate to "do no harm" with a few also likening the concept of a surgical placebo to Nazi Germany experimentation and "patient abuse." One described the sacred bond surgeons had with their patients and felt a general unease at the thought of "fooling" someone (SQ13). Most surgeons had never considered participating in a placebo surgery controlled trial and some suggested that they would need time to process the idea. A few surgeons appeared to "talk themselves around"; having "mulled over" the idea during the course of the interview, they described themselves as "more open to the idea" of participation by the end. This attitudinal shift was accompanied by an acknowledgement that potential risks could be offset by the potential for trial outcomes to contribute to the "greater good" by reducing thousands of unnecessary surgical procedures in the future (SQ13, SQ14). Indeed, several surgeons suggested that performing procedures, which lacked research evidence of efficacy (as opposed to anecdotal evidence) went against the pillars of beneficence and nonmaleficence (SQ15).

DISCUSSION

To our knowledge, this is the first in-depth qualitative investigation of the factors underlying willingness to participate in a placebo surgery controlled trial. While negative attitudes toward randomization and preferences for one intervention arm over another contribute to low recruitment rates in surgical trials more broadly,[10–12] recruitment may be more difficult in trials involving a placebo arm.[13] To enhance recruitment in future placebo surgery controlled trials, based on these findings we recommend incorporating strategies into the recruitment process that validate patients' symptoms; target patients' and surgeons' understanding and perceptions around equipoise; encourage an altruistic mindset; in addition to incorporating surgeons' preferences for trial design (see Table 1).

Our findings suggest that validating patients' symptoms may be an important component of the recruitment process in a placebo surgery controlled trial. Patients in our study held strong biomedical beliefs that their symptoms were caused by an underlying structural-anatomical problem which needed to be fixed. While strong expectations that fixing the structural-anatomical problem will resolve symptoms may provide some explanation for the placebo effect observed in previous placebo surgery controlled trials,[14] results from our study suggest that being invited to participate in a placebo trial could be viewed by patients as questioning the legitimacy of their symptoms. To validate patients' symptoms during the recruitment process, we recommend linking a biopsychosocial explanation of symptoms to potential treatment mechanisms (see Box 1). Ensuring patients understand that it is the procedure, rather than the validity of their symptoms under question, is also likely to be important.

Surgeons are likely best placed to provide explanations about symptoms, treatment mechanisms and what participation in a placebo surgery trial means for the individual patient. Patients typically place a high level of trust in their surgeon[15, 16] and our findings validate concerns expressed by surgeons in previous studies that difficulty grasping trial concepts may lead patients to lose trust in their surgeon.[17, 18] Ensuring that surgeons are well trained to deliver these explanations and that they themselves accept the notion of equipoise will be critical as patients may pick up on differences in tone and the quantity of information provided between study arms.[2] A robust recruitment process may involve the implementation of a surgeon-led "explanation process" in addition to a trialist-led consent process.

Our findings suggest that "anecdotal evidence" of treatment efficacy is important to both patients and surgeons. For trialists explaining the rationale for a placebo surgery controlled trial, disentangling anecdotal from scientific evidence is likely to be challenging, particularly when it comes to high volume surgical interventions. For surgeons, involving "champions" who are respected leaders in their field as advocates for evidence based decision making may enhance perceptions of equipoise. For patients, education tools to support the delivery of trial information such as video animation and decision aids may be useful.[2, 6, 19, 20]

TABLE 1.

Recommendations for Future Placebo Surgery Controlled Trials in Orthopedics

Barrier/Facilitator	Recommendations for Future Trials
Patient belief that placebo trials are designed to "catch the fakers"	Validate the patients' pain experience during the recruitment process (see Box 1). Reinforce that the trial does not question the patient's symptoms but rather questions the effectiveness of the treatment. Communicate to patients that it would be unethical to consider including a patient in a clinical trial if they did not have the condition for which the procedure is normally performed. Involve surgeons in the recruitment process and train them to explain trial concepts to patients.
Patient understanding of trial concepts including surgical placebo, randomization, and equipoise	Use of education tools such as video animation and decision aids to support explanations from surgeons and trial staff.
Patient altruistic mindset	Explain that patients are being exposed to the risks of surgery everyday for procedures that may be no more effective than a placebo procedure. Explain how outcomes from a placebo surgery controlled trial can advance patient care in the future. Provide patients a personalized explanation of the risks involved in participation.
Surgeon perception of lack of equipoise in surgical procedures	Screen surgeons for perceptions of equipoise around the research question. Engage with "champion" surgical leaders to help disentangle anecdotal from scientific evidence.
Surgeon lack of confidence in the validity of evidence from placebo trials	Involve "champion" surgical leaders in trial design. Engage with credible surgical professional bodies during design, data collection and dissemination phases of trial.
Surgeon preferences for the design of the placebo procedure	Involve surgeons in trial design. Consider a three-arm trial including both a high fidelity and low fidelity placebo arm.
Surgeon commitment to beneficence and nonmaleficence	Engage with "champion" surgical leaders. Provide education sessions on the ethical principles of placebo trials in surgery. Use motivational interviewing techniques to encourage surgeons to reflect on the role scientific evidence should play in everyday practice.

Box 1. Example Explanation for Patients

Validation: A range of factors can influence the pain experience including anatomical structures and inflammatory responses driven by genetic and lifestyle factors; beliefs about the meaning of pain and what we do about pain. While traditional thinking is that surgery works by targeting anatomical structures, it may also work by targeting these other factors that influence the pain experience. For example, surgery may work by changing our inflammatory response. Or surgery may work because we believe that our anatomy has been fixed so we start exercising more. This does not mean that the pain experience is not real or is "all in the mind." It just means that a wide range of factors can influence the pain experience.

Equipoise/Altruistic mindset: Placebo surgery trials are a way to determine how effective a surgical procedure is. Surgery is not without risk to patients, for example, the risks of an anesthetic and the risk of infection. To be sure that the benefits of surgery outweigh the risks, researchers test the surgical procedure against a placebo surgery (anesthetic and skin incision alone) to see if the outcomes are different. Based on the best scientific evidence, we do not currently know if [the surgical intervention] is more effective than placebo surgery. This means that patients may be being exposed to unnecessary risks of surgery. It is important to note that there is no clear direct benefit to participants who volunteer in this type of research. However, volunteering will lead to improved knowledge in the field of surgery and provide benefits to patients suffering from pain in the future by informing evidence-based treatment decisions.

However, understanding the need to advance the scientific evidence base may not be enough to motivate patients to participate in a placebo surgery controlled trial. It may be that altruistic motivations are secondary to perceptions of personal risk and benefit.[21] In our study, both patients and surgeons perceived the risk associated with a general anesthetic to be high. Further research could explore whether the recruitment rate is lower in surgical trials involving general anesthesia compared with trials involving, for instance, regional anesthesia. Significant debate exists around what constitutes a "surgical placebo."[3] A so-called "low fidelity," or minimally invasive placebo procedure, involves an anesthetic and skin incision only. A "high fidelity" placebo procedure involves all the components of the procedure with only the supposed key therapeutic surgical step omitted.[2] The surgeons in our study were divided in their preferences for a low fidelity placebo procedure in which the perceived risks were lower, or a high fidelity placebo procedure in which the perceived likelihood of effective blinding was higher. Future trials might consider a three-arm design in which the index procedure is compared to both a low and high fidelity placebo procedure.

In interpreting these findings, it is important to consider that the participants in our study knew there were no immediate plans to conduct a placebo surgery controlled trial at their hospital. We acknowledge that behavioral intention is not the same as actual behavior[22,23,24] and thus it is possible people who indicated willingness would not consent to participating in an actual trial. The nonrandom sampling strategy we employed is consistent with the qualitative study design and enabled us to include diverse perspectives. However, our patient and surgeon samples may have differed from the wider population in important ways. For example, while the orthopedic service from which we recruited has a socioeconomically and culturally diverse referral base and this diversity was reflected in our sample, we did not include patients from linguistically diverse backgrounds. Given the under-representation of people from diverse linguistic and cultural backgrounds in medical research,[25] this would be a fruitful avenue for future investigation. Recruitment of surgeons involved an opt-in process and reasons for declining to opt-in were not recorded. When questioned about their motivation for participating in our qualitative study, the majority of surgeons offered; "because the Head of Department asked them to." While this supports our view that involving respected leaders in the field can facilitate trial recruitment; it also suggests that our sample represents surgeons who are more generally agreeable to participate in research. Future qualitative studies are needed to understand the transferability of our findings to other nonorthopedic surgical settings. By addressing feasibility in the study design, future placebo surgery controlled trials may counter the issues that have left previous trials underpowered.

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