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Visualizing the randomized sham-controlled trial in orthopedic research: proposed steps to conducting a total knee arthroplasty randomized controlled trial

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Performed more than 600,000 times annually in the USA alone, total knee arthroplasty is the one of the most common and costly elective operations in the world. A primary total knee arthroplasty is generally an elective procedure, for which total index hospitalization costs are estimated around $30,000 USD. Roughly four in five patients declare they are satisfied postoperatively, justifying the procedure's frequency and high costs. It is sobering to realize, however, that the evidence base in favor of this procedure remains circumstantial. We as a profession lack randomized trials showing a subjective improvement over placebo intervention. We argue for the necessity of sham-controlled surgical trials in this setting and provide a surgical atlas showing how a sham operation may be performed.

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Keywords: orthopedic • placebo-controlled • randomized sham-controlled trial • sham • total knee arthroplasty

Mechanical, surgical and procedural interventions performed to alleviate subjective symptoms or concerns are susceptible to the placebo effect [1]. Sham controlled trials are often needed to reveal this finding. Consider for instance that stenting performed for chronic, stable angina found no improvement in treadmill exercise time against a sham intervention [2], though earlier studies, lacking a placebo control, had found a benefit to this procedure over medical management [3]. In the case of vertebroplasty for painful osteoporotic fractures, the injection of polyacrylamide cement was no better than a sham intervention in two randomized trials [4,5]. In orthopedic medicine, there are a number of widely performed interventions that have failed to show superiority over a sham procedure [6–8].

Total knee arthroplasty (TKA) is an orthopedic procedure that is most commonly performed for mild to moderate pain and where there is a limited range of motion of the knee. As of 2010, 600,000 TKA procedures were performed annually in the USA [9–11]. This number is projected to increase as the US population grows and ages [12,13]. TKA involves more than just a surgical procedure. Prior to surgery, patients are recommended to have preoperative education and counseling, a rigorous medical optimization checkup to identify modifiable risk factors that affect recovery time and length of stay, such as malnutrition, uncontrolled diabetes, cardiovascular disease, opioid use and physical de-conditioning [14]. After surgery, patients are typically prescribed physical therapy rehabilitation.

How much of the benefit of TKA is the surgery itself versus the pre- and postoperative interventions, and the expectation the intervention will help? A placebo or sham controlled trial could answer this question, but has not yet been undertaken. We hypothesize that one barrier to such a study is difficulty in visualizing the appropriate steps for a sham procedure arm for this complex surgical procedure. As such we propose a step-by-step illustration of the appropriate sham procedure to compare against TKA.

Use, cost, benefits & harms of TKA

TKA is predominantly performed for a subjective condition – painful osteoarthritis. The origin of TKA [15] is credited to Theophilus Gluck. In 1890, Gluck performed the first TKA on 20 May, using ivory as the replacement component of the prosthesis. Over time, advances in the prosthetic component evolved, and in the 1970s, orthopedists assessed the functionality of modern approaches in small observational trials [16,17]. These manuscripts provide design objectives and detailed preoperative and postoperative notes but lack a comparator group.

In 2005, roughly 500,000 TKAs were performed in the USA costing over $11 billion. In 2013, osteoarthritis was found to be one of the five most expensive conditions for hospital costs. These five most expensive conditions account for roughly one-fifth of aggregate hospital costs [10]. The cost of TKA procedures is commonly justified based on published rates of success. Studies suggest 80% of TKA patients are satisfied [18]. Notably among those who undergo a primary TKA, which cost roughly $30,000 per surgery, about 5% of all surgeries undergo surgical revision, costing roughly $75,000 per surgery [19–21]. Despite 50 years of studies, what remains unclear is what percent of improvement is driven by: the belief that a salutary intervention is performed; the pre- and postoperative regimen; and the placement of the metal and plastic intercalating prostheses itself.

Sham controlled trials in orthopedics

As of 2020, 14 sham-controlled trials in orthopedics have assessed a surgical or procedural intervention to treat a subjective ailment (Supplementary Table 1). These trials have examined chronic low back pain or osteoporotic vertebral compression fractures (8/14, 57%), knee osteoarthritis or meniscal tears (3/14, 14%), sacroiliac joint pain, (1/14, 7%), subacromial shoulder pain (1/14, 7%) and lateral epicondylitis (1/14, 7%). The 14/14 (100%) studies reported no concerns about the safety of the intervention.

These 14 trials assessed the difference between the mean changes of assessment scores in intervention and sham arms. These scores assess either pain (often assessed by the visual analog scale and/or Short Form-36BP) and/or disability and physical function (often assessed by the Short Form-36-PF and/or Oswestry Disability Index). Ten out of 14 studies (71%) failed to demonstrate that the proposed intervention improved outcomes compared with the sham arm. In five of ten (50%) negative studies, both intervention and control arms improved from baseline. This suggests that some interventions are beneficial, in other words, better than not performing them, but that benefit is a placebo effect.

Of the four studies (29%) that reported a significant treatment effect, all four assessed interventions on either chronic low back pain or sacroiliac joint pain. All four positive studies used either per protocol analysis or did not specify the type of analysis (intention-to-treat vs per protocol) used. Otherwise, intention to treat analysis was performed in eight out of 14 studies (57%).

Approximately 20% (3/14, 21%) of studies permitted crossover in the study after 1 month had elapsed. In the manuscripts, authors cite that it was not ethical to prolong or delay the surgical intervention if subjective pain had not been achieved by a predetermined time (ranging from 1 to 6 months). The use of crossover in these studies is a confounding event that precludes meaningful analysis of long-term efficacy outcomes.

Collectively these studies suggest null to modest effect sizes and call into question the value of these surgical interventions. Simultaneously, they highlight the ability for trials to be performed in orthopedics.

When are sham trials necessary?

Sham trials are necessary for interventions that purport to improve subjective end points, for which at least some of the benefit may be due to the placebo effect or the pre- and postoperative therapy. TKA meets this precondition.

Sham trials have historically been limited for large, complex surgical operations, due to the risk of harm to participants. However, this limitation lacks a rational basis. For instance, in any sham trial, there are risks to participants on both arms – intervention and control arms – due to anesthesia, incision and wound healing. But the purpose of the sham trial is to minimize the risks to society, if interventions are pursued that are ultimately no better than placebo [22]. In the case of larger, more invasive surgeries, these risks, if the interventions are ineffective, are an order of magnitude larger than for minor surgeries. Thus, we believe not performing sham trials in these situations is concerning [23].

Proposal of a sham-control trial

We believe that one potential barrier, among others, to conduct a randomized, sham-controlled trial of TKA is difficulty in visualizing the necessary steps to performing a feasibly blinded sham arm. In the Figures 1 & 2), we

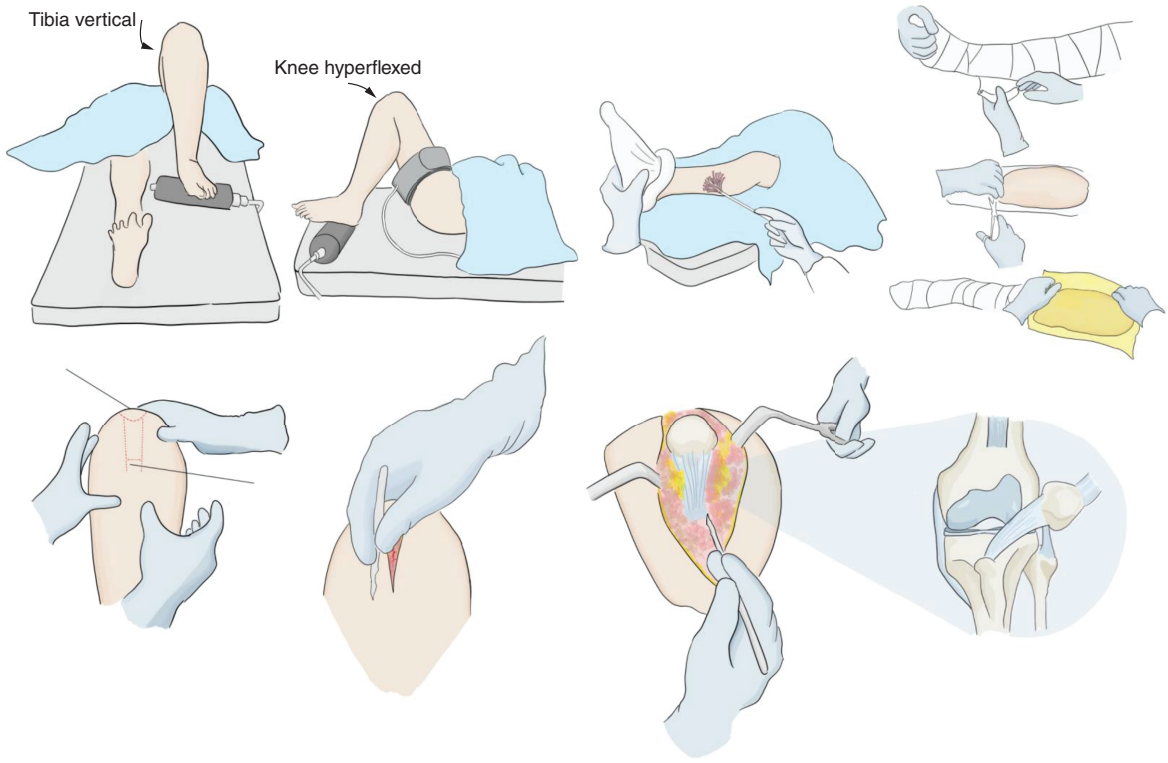

Figure 1. Surgical preparation common to both operations.

illustrate a sham procedure that contains all parts of the procedure except the critical surgical element, which in the case of the TKA, is the resection of bone and cartilage. We have chosen to illustrate a proposed TKA clinical trial with a sham-controlled placebo arm using the median parapatellar approach, the most common approach for primary TKAs. Figure 1 shows all preoperative steps up to the point of randomization. Figure 2 shows the critical surgical steps following the point of randomization. The supplementary Appendix details a step-by-step description of all surgical steps in both trial arms.

We would include those with confirmed knee osteoarthritis (a score of $\geq$2 on the Kellgren–Lawrence scale) [24]. Because, there could be differential effects due to level of risk, the study would include three cohorts of individuals – those with minimal osteoarthritis, those with moderate osteoarthritis and those with severe osteoarthritis. This would allow researchers to identify potential interactive effects.

Figure 3: Rehab post procedure will be the same for both groups.

The primary end point

By 2030, the demand for TKA is estimated to grow to 3.48 million total procedures per annum costing $13 billion dollars [14,25]. To assess for improved outcomes in knee osteoarthritis, the primary end point of our sham-controlled trial would be the treatment effect, or between-group differences in the change from baseline to 24 months, for the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and its three subscores. Experts believe the minimally clinically important difference for the WOMAC subscores are 11 for pain, 9 for physical function and 8 points for stiffness, respectively [26]. The minimally clinically important difference for the total WOMAC score is 10. Patients undergoing TKA typically improve by 20% across scores for the duration of the study period [27–29].

Concern over crossover and revision could be addressed in two ways. First, crossover, due to participants in the sham arm receiving revision procedures, could be adjusted for via statistical methodologies such as rank preserving structural failure time. Second, would be to treat the revision as an event, and the primary end point would be a composite of quality-of-life scores, where revision would be scored as a significant deterioration in quality-of-life. Alternatively, revision could be a censored event in both arms.

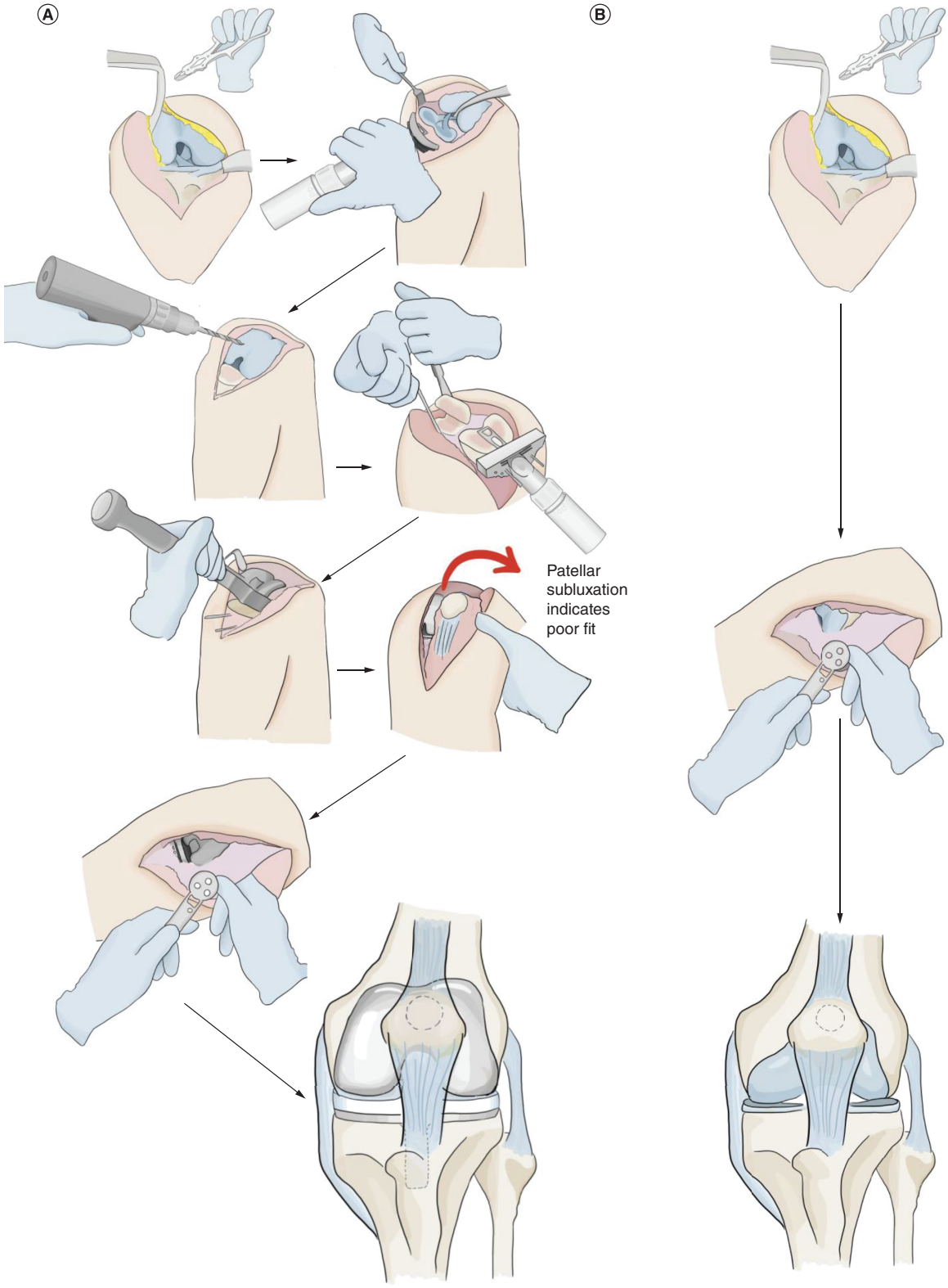

Figure 2. Critical surgical steps following randomization.

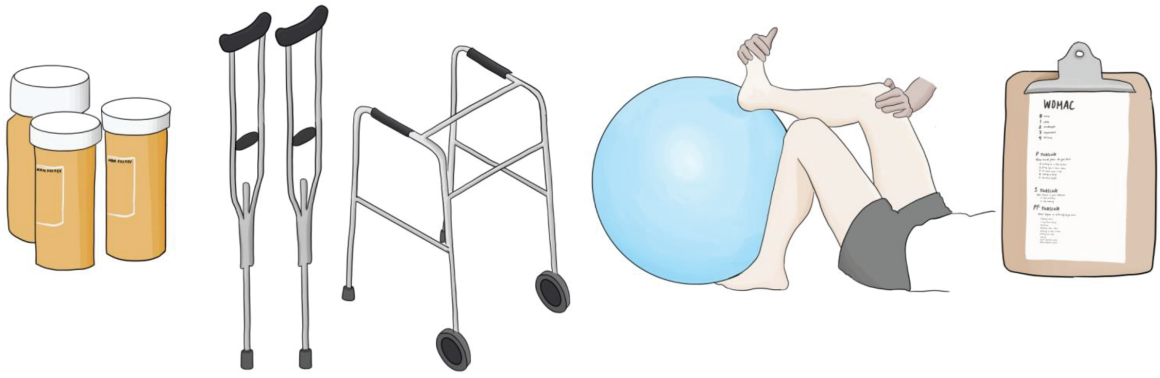

Figure 3. Follow-up, post-operative care and physical therapy exercises.

We propose that double binding in the follow-up period could be maintained for 3 months, and single blinding (the doctor will know) would occur for another 3 months. Based upon these data, a trial with 75 people per arm would have 90% power to rule in this meaningful difference with 5% alpha error. In other words, our proposed trial would require hundreds of participants instead of millions who will undergo this procedure as matter of routine care. The cost of our trial would be in the millions, but that also compares favorably against the billions that will otherwise we spent on this trial. We believe that such a trial must be performed.

Objections

There are several objections to our proposal. We have grouped these into three categories: ethical, practical and philosophical. Ethical objections include the risk of performing the sham-controlled trial, which include but are not limited to the risk of infection, thrombosis, bleeding or vascular injury [30]. Yet these complications are generally rare with TKA occurring in 1–2% [31], 2.4% [32], 0.0044% [33] and 0.03–0.2% [34], respectively, and will only be lower in the sham arm. Moreover, the risks to society if this procedure is in fact no better than a sham intervention are larger, simply because each year this procedure is offered to many more patients. Put another way: in a randomized study, it is the trial participants who are subject to risk, but without randomized data, every person undergoing the procedure annually is subject to both risk and uncertainty. Thus, we believe it is unethical not to perform this study [23].

Practical objections include the difficulty in performing the sham operation. In Figure 2, we show how patellar eversion would occur with button placement, but the articulating surfaces would not be altered. A patient would have difficulty in unblinding themselves, and the surgery is feasible, as all included steps are part of normal TKA operations. Figure 3 shows the follow-up treatment, including post-operative care and physical therapy exercises for both groups. Whether or not patients will enroll in this study is a legitimate concern; however, the field has shown that for pressing questions we are capable of enrolling in sham anginal studies, among other situations, which arguably pose higher psychological barriers. Philosophical objections include the lack of a need for such a study, as the uncontrolled experience is persuasive. We reject this view. Many other sham controlled trials reach unanticipated results, as detailed, and only a sham-controlled trial can clarify what value the surgery itself provides and what its true effect size is, which is needed for cost–effectiveness considerations. We believe that orthopedic surgeons will be favorable to this type of trial, because they have always demonstrated a commitment to evidence-based practices, especially in areas where there is equipoise.

In conclusion, TKA makes physiological and anatomic sense, is commonly and generally safely performed, is a costly healthcare service, and one that patients are generally satisfied by. Yet, whether or not the intervention itself is superior to a sham intervention, or instead if its benefit is driven by perioperative management and rehabilitation and the placebo effect is unknown. We believe that after five decades, we must hold surgical procedures to the same standard we apply to medications – these interventions must be subjected to a placebo controlled randomized trial. Millions of patients deserve the answer to this question.

In summary and Conclusion

The history of orthopedic research has been uncontrolled and not historically been subjected to randomization, likely due to the assumption and overreliance on the biomechanical model. As a result, surgical interventions and medical devices are held to a lower standard of evidence than drug development. These studies should be held to the same burden of proof as other areas of clinical research before being adopted into clinical practice. With such rigor, we worry we may deprive tens of thousands of future patients, an order of magnitude larger than those who may be subjected to a randomized sham-controlled trial, of the benefit of the truth that such interventions truly work. The results of sham-controlled trials could give patients clarifying information about the procedure's risks and benefits that can help them make a truly informed choice. For while, it is physicians and orthopedists who carry the burden of proof, it is patients who bear the consequences.

Future Perspective

Future research should explore the interaction between disease severity and potential benefit from the procedure. Which patients with structural instability and pain benefit most from total knee arthroplasty, if any. Researchers should imagine and envision ways to apply sham controlled trials to other aspects of biomedicine.

Executive summary

- Sham trials are essential to discern the true benefit of orthopedic surgeries beyond the placebo effect, by allowing comparisons between experimental arms and sham arms.
- An updated review of the 14 orthopedic randomized trials with appropriate sham control demonstrated that ten of 14 (71%) of placebo/sham arms are reported to have no different outcomes than surgical arms, which puts the efficacy of surgical intervention into question.
- Although placebo-controlled trials are necessary, sham trials may still be thought of as controversial which may likely be a barrier to adoption in the literature.
- We argue that ethically sound sham surgery procedures, as proposed in this analysis, are feasible and adhere to the principle of non maleficence, especially when considered from a population-level assessment of risk. After studying multiple orthopedic surgical manuals, we offer proposed illustrated steps to help visualize an appropriate and ethically sound sham surgery procedure.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://bpl-prod.literatumonline.com/doi/10.57264/cer-2022-0275

Author contributions

V Prasad conceived the idea and has written previously on this topic. AA Tran undertook the primary research and drafted the first manuscript. V Prasad critically reviewed the manuscript, provided additional references and assisted in redrafting the manuscript. V Prasad is the guarantor who accepts full responsibility for the finished article, had access to any data from literature searches and controlled the decision to publish. AA Tran is a medical student and V Prasad is an academic physician who has written extensively on non evidence-based care in medicine.

Financial & competing interests disclosure

V Prasad discloses: research funding from Arnold Ventures; royalties from Johns Hopkins Press, Medscape, MedPage; consulting fees from UnitedHealthcare; speaking fees from Evicore, New Century Health; and Plenary Session podcast has Patreon backers. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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