

COMMENTS

Ethical issues in randomised trials in surgery

GEORGE THOMAS

Abstract

Clinical trials are required in surgery to evaluate existing procedures and to assess the value of new techniques. Except for observational studies which are considered useful only to propose a hypothesis, all study designs require a comparator group. The randomised controlled trial (RCT) is recognised as the most robust study design. There are specific ethical difficulties in conducting RCTs.

Keywords: surgical trials, sham surgery, informed consent, equipoise, therapeutic misconception.

Why do we need trials in surgery? One would suppose that an invasive and often irreversible procedure would not be performed without compelling evidence that it works. Unfortunately, in the development of surgery, this is not always true. For example, in the past, ever more extensive surgery was carried out for cancer of the breast in the belief that cutting out all the tissue which was potentially diseased would lead to better outcomes. This belief was found to be false through a trial comparing extensive surgery with more simple surgery (1). Trials have helped define appropriate surgery in quite a few instances.

The randomised controlled trial

There is no doubt that the study design which provides the most compelling evidence in clinical medicine is the randomised controlled trial (RCT) (2). This is the best study design to reduce the potential for bias. In recent years, the idea of a hierarchy of evidence has become prevalent, and the RCT occupies the very highest level, often called level one evidence. However, it is widely recognised that double-blinding, that is blinding the identities of both the researcher and the trial participant in the intervention, is most often

impossible in surgical trials. The alternative is to conduct RCTs of different kinds, for example, single-blinded or even non-blinded trials.

Trials, treatment and therapeutic misconception

One of the fundamental conditions required to be satisfied in the ethical conduct of a trial is that the trial participant must be aware that he or she is participating in a trial. The researcher must make every effort to avoid the therapeutic misconception (3). In other words, the surgeon /researcher must ensure that the participant is completely aware that the treatment is experimental and may have no beneficial effect. Once we accept this principle, it is possible to argue that the principle of beneficence, that is the requirement that the procedure be helpful to the patient, is no longer applicable. Indeed, it is impossible to simultaneously state that it is an experiment and that we do not know whether it will work, and also that it is beneficial. Most certainly, in medical treatment it would be unethical for a doctor to do something to a patient which he or she did not believe to be helpful. This fundamental difference between research and treatment is often not appreciated and is the cause of much acrimonious debate. When a patient is under the treatment of a medical practitioner, it is understood, even if not explicitly stated, that the patient is being offered the best standard of care possible. When the patient is being enrolled into a study as a trial participant, it is an ethical imperative that the participant is explicitly told that he or she is participating in an experimental process because there is uncertainty about the treatments available. The question, of which Institutional Review Boards (IRB) must be acutely aware, is whether the researcher is making sufficient effort to avoid the therapeutic misconception in the mind of the trial participant. The Indian Council of Medical Research guidelines for ethical research emphasise the requirement for full disclosure that the participant is in a trial and that there may be no benefit (4). The real question is whether, in spite of having all this covered in the information sheet, the researcher is *truly* informing the trial participant. To ensure this, we need a level of trial oversight that is simply not available in most places where research is being done in India, at present.

Communicating equipoise

One of the fundamental requirements for a randomised trial is

Authors: **George Thomas** Head of Orthopaedics and Emergency Services, St. Isabel's Hospital, Mylapore, Chennai, Tamil Nadu 600 004 INDIA

To cite: Thomas G. Ethical issues in randomised trials in surgery. *Indian J Med Ethics*. 2021 Jan-Mar; 6(1) NS: 39-41. 2020. DOI:10.20529/IJME.2020.099.

Published online first on September 5, 2020

Manuscript Editor: Sandhya Srinivasan

© Indian Journal of Medical Ethics 2020

equipoise. That is, there should truly be a belief in the mind of the researcher that the intervention is at least as good as the standard against which it is being compared. Ethical practice demands that the researcher inform the participant about the presence of doubt. In other words, the researcher needs to inform the participant that he or she, by chance, may fall into a group which is not the currently practised standard of care. Are participants capable of understanding this situation? What makes them agree to participate in such a trial? At the best of times, patients are naturally anxious about surgery. It seems almost certain that this anxiety will increase if they are informed that the doctor is not certain that the procedure will help. Are participants really aware that they are participating in an experiment? Is their consent truly voluntary? At present we cannot be certain. Faced with this uncertainty on the one hand, and the need to improve medical knowledge on the other, ethics committees do well to approve such trials only when the risk of harm is very low. There are reports in the literature when ethics boards have approved risky trials with disastrous consequences (5).

When faced with such trials, institutional review boards must ensure that the board itself (not the institution) has sufficient capacity, ability and authority to monitor the trial and halt it if harms occur. In my opinion, there is no IRB in India that can fulfil this requirement.

Sham surgery

Another ethical conundrum in randomised trials in surgery is whether to permit a trial arm in which no real surgery is performed. The fundamental reason why such trials are necessary is to answer the question whether no surgery will give equal or better results than the proposed surgery. In other words, the equipoise is between the procedure and not doing the procedure. One such trial was performed on elderly people with osteoarthritis (6). One arm had arthroscopic debridement of the knee and the other had a sham procedure. In such trials the participant's identity is blinded, and therefore, the well-known "halo effect" of having undergone a supposedly useful procedure is counteracted, because no participant is aware whether he or she underwent the debridement or a sham procedure. The results of this trial showed conclusively that the procedure is useless. This has saved a lot of patients worldwide from a useless procedure. The conundrum is whether it is ethically correct to subject a participant to a procedure, sham surgery, which definitely has no benefit. Many international guidelines for research, including the latest version of the Declaration of Helsinki permit such trials (7). The Indian Council of Medical Research guidelines take the view that sham surgery can be allowed in certain situations (4: p 82). This is based on the idea that research is different from treatment, and as long as the participant is not under the therapeutic misconception, it is the autonomous choice of the participant to enroll in the trial and this must be respected. The problem is that in India, many participants in clinical trials are not very well educated and

one is not sure whether the consent for participation is truly voluntary (8,9).

The case of joint replacement surgery

Most surgical innovations have been introduced based on case series without any control groups. The major reason for this practice is pragmatic – multiple factors make controlled trials in surgery far more problematic than in pharmaceutical interventions (10). The story of the replacement of joints is no different.

After many false starts, replacement of the hip joint was put on a firm footing by John Charnley. In his design, a metal component was introduced into the canal of the femur to replace the head of the femur. The size of the head of the femur was kept at 7/8 inches (22.225 mm) to reduce wear of the acetabular cup which was made of high molecular weight polyethylene. Both components were attached to the bone using bone cement (11). This joint design has had a very high success rate. The two major problems are that the joint will become loose over a period of time and secondly, the range of motion of the hip is limited because of the small size of the replacement femoral head. Improvements in design focus on increasing the life of the joint and on increasing the range of motion of the joint. One of the ideas to simultaneously tackle both loosening and range of motion was to design a surface replacement of the head of the femur, so that the size was the same as the native hip; and to use metal on both joint surfaces, the so-called metal on metal design (12). Early success with the Birmingham Hip Replacement (BHR) prompted other companies to develop and introduce competing products. One of these, the Articular Surface Replacement (ASR) demonstrated an unacceptable rate of loosening at five years (13).

The long-term effects of a surgical procedure like joint replacement are difficult to predict. New joint designs are approved by licensing authorities based on laboratory data which show a projected failure rate of five percent or less after ten years of use (14). Such data are accepted because innovation would otherwise come to a standstill and better designs may never see the light of day. This is a compromise, and careful follow up is required to ensure that the device performs as expected. Such surveillance is difficult even in the developed West, and is certainly not possible in India at present. Presumably, the ASR satisfied this criterion.

The need for an evidence based approach to surgical innovations has been recognised and has led to the suggestion of several guidelines, for example the IDEAL collaboration (Idea, Development, Exploration and Long term follow up), the step-wise algorithm of Malchau and the guidelines of the Royal College of Surgeons of England (15).

The ethical transgressions in the ASR case were:

- introducing an experimental design worldwide, including in countries like India with poor regulatory oversight and poor

protocols for the management of patients with faulty implant designs.

- continuing to promote the implant in India even after it was known that the design was faulty.
- failure to contact all patients who had the implant.
- failure to arrive quickly at a fair compensation package and resorting instead to litigation.

At present, in India, the authorities should permit the use of such new implants only in select centres with the ability to follow up the patient for a sufficient period of time and intervene quickly if things go wrong.

Conclusion

Randomised trials in surgery are very helpful in defining which procedures are truly useful. The idea of the hierarchy of evidence according to which randomised controlled trials occupy an exalted position and increase the chance of publication in a high impact journal should not pressurise the researcher to adopt this study design when the ethical challenges are extremely difficult to overcome. In India, Institutional Review Boards need to constantly keep in mind the characteristics of the study participants and ensure that information is adequate, that therapeutic misconception is avoided and that the risk from randomisation is minimal. New devices or implants should be introduced into clinical use in the country only after an appropriate lapse of time, unless there are very compelling benefits which make immediate roll out necessary for the welfare of patients. The decision for such express rollout should be made by an independent expert committee.

References

1. Newmark JJH. No ordinary meeting: Robert McWhirter and the decline of radical mastectomy. *J R Coll Physicians Edinb*. 2016;46(1):43-8.
2. Horton R. Surgical research or comic opera: Questions, but few answers. *Lancet* 1996;347 (9007);984-5.
3. Applebaum PS, Roth LH, Lidz CW, Benson P, Winslade W. False hopes and best data: *Hastings Cent Rep*. 1987;17(2):20-4.
4. Indian Council of Medical Research. 2017. National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. New Delhi: ICMR; 2017[cited 2020 Aug 30]. p 50. Available from http://ethics.ncdirindia.org//asset/pdf/CMR_National_Ethical_Guidelines.pdf
5. Teixeira da Silva JA. Ethical perspectives and ramifications of the Paolo Macchiarini case. *Indian J Med Ethics*. 2017 Oct-Dec; 2(4):270-5. doi:10.20529/IJME.2017.048
6. Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med*. 2002 Jul 11; 347(2):81-8.
7. World Medical Association 2018. Declaration of Helsinki – Ethical principles for medical research involving human subjects. Item 33. Helsinki, Finland: WMA; 1964, (amended 2018A) [cited 2020 Aug 30]. Available from <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>
8. Agu KA, Obi EI, Eze BI, Okenwa WA. Attitude towards informed consent practice in a developing country: a community-based assessment of the role of educational status. *BMC Med Ethics*. 2014 Oct 22; 15: 77.
9. Crepeau AE, McKinney BI, Fox-Ryvicker M, Castelli J, Penna J, Wang ED. Prospective evaluation of patient comprehension of informed consent. *J Bone Joint Surg Am*. 2011 Oct 5; 93(19): e114(1-7).
10. Jones DS. The history and controversies of surgical evidence pg 479-501. In: Schlich T, editor. *The Palgrave handbook of the history of surgery*. London (UK): Palgrave Macmillan; 2017.
11. Charnley J. *Low friction arthroplasty of the hip*. Berlin, Heidelberg: Springer – Verlag 1979.
12. Fawsitt C, Thom H, Hunt L, Nemes S, Blom AW, Welton LJ, et al. Choice of prosthetic implant combinations in total hip replacement: cost-effective analysis using UK and Swedish hip joint registries data. *Value Health*. 2019; 22: 303-12.
13. Weinroth M, McCormack P, Joyce TJ. Precaution, governance and the failure of medical implants: the ASR [TM] hip in the UK. *Life Sci Soc Policy*. 2014;10:19.
14. National Institute of Clinical Excellence UK. Total Hip replacement and resurfacing arthroplasty for end-stage arthritis of the hip. Technology appraisal guidance [TA304]. 2014 Feb 26[cited 2020 Aug 29]. Available from <https://www.nice.org.uk/guidance/ta304/chapter/1-Guidance>
15. Reito A, Lehtovirta L, Lainiala O, Mäkelä K, Eskelinen A. Lack of evidence — the anti-stepwise introduction of metal-on-metal hip replacements. *Acta Orthop*. 2017 Oct; 88(5): 478-83. Doi: 10.1080/17453674.2017.1353794

1. Newmark JJH. No ordinary meeting: Robert McWhirter and the decline

Be a part of IJME

IJME invites readers to submit research studies, comments, case studies, reports, reviews, letters, as also poems, short stories, original paintings and photographs of print quality (both in colour and B/W) to be considered for publication.

All submitted matter is subject to peer review.

Contributors are neither paid nor charged any fee for published matter.