

An Approach to the Ethical Evaluation of Innovative Surgical Procedures

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Abstract

While there is an ethical obligation to improve clinical outcomes by developing better therapies, surgical innovation has largely progressed without the strict regulations required of novel pharmaceutical products. We explore the reasons why new surgical techniques are frequently introduced without the benefit of randomised controlled trials, and present an approach to the ethical evaluation of novel surgical procedures.

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Introduction

Innovative surgery is perhaps best defined as “a novel procedure, a significant modification of a standard technique, a new application of or a new indication for an established technique, or an alternative combination of an established technique with another therapeutic modality that is developed and tested for the first time.”¹ Unlike the clear policies regulating the human testing of new drugs and medical devices, there is currently no established protocol for the introduction of new surgical therapy.^{1,2} Often, modifications to established techniques are instituted in an ad hoc manner by a surgeon or a group of surgeons either due to the immediacy of need, or as a planned attempt to achieve a more efficient or effective surgical outcome. In other instances, surgeons proficient in a technique may extend its use for new indications. As most of such modifications are the natural evolution of the practice of surgery and have marginal or incremental impact on outcomes, it is debatable if all such innovations need to be governed by the same standards mandatory for novel pharmaceutical products. Is it practical for a surgeon to always require formal approval from an Institution Review Board (IRB) before performing an improvisation of an established surgical technique? Should all new surgical

techniques be subject to the rigours of a randomised trial for validation of safety and efficacy prior to implementation and dissemination? Given the large numbers of new and alternative surgical techniques, their potential demands on healthcare resources and for harm, adequate regulation would seem necessary. We explore the reasons why many surgical techniques have been adopted without supporting prospective randomised trials, and propose a practical and ethically sound approach to the evaluation of novel surgical procedures.

The Challenges of Evaluating New Surgical Techniques

The prospective randomised controlled trial (RCT) is the gold standard validation of the safety and efficacy of a therapeutic intervention. Almost all novel drug treatments are subject to this robust scientific evaluation prior to their introduction to the general public. However, a review of “surgical research” by Horton³ revealed that nearly half of all reported data on novel surgical techniques comes in the form of case series, with barely 10% derived from a randomised trial. Evidently, the RCT is not the requisite scientific study design prior to the introduction of a new surgical technique. Why are new surgical techniques not

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subject to the same robust scientific analysis? A more practical question is perhaps: need they all be?

The challenges of a surgical RCT are well recognised. Briefly, patient accrual for surgical trials is frequently slow – the number of patients who receive surgical treatment will always be vastly less than those treated with drugs. Recruitment is particularly difficult if the two treatment methods differ significantly, such as in a medical versus surgical trial.⁴ The capacity to complete a trial of significance in a timely manner is also often beyond a single institution, and many surgical trials lack sufficient statistical power to refute the null hypothesis in question.⁵ In addition, the design of a RCT for surgery is frequently more complex. Blinding is a common problem, especially if the surgical technique is compared with a non surgical intervention. Even if two surgical techniques are to be compared, blinding is oftentimes not feasible, and placebo surgeries are rightfully deemed unethical.⁶

Perhaps more unique in surgical trials is the absence of a true position of equipoise in many innovative surgical procedures. Equipoise, defined as a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each treatment, is a prerequisite for the ethical conduct of a randomised controlled trial.⁷ The innovative surgeon-investigator in all likelihood developed the new surgical technique because he or she had reason to believe in its superiority, which implies that clinical equipoise can no longer be present in his or her mind. Even if the investigator was not the innovator, a surgeon often has strong preferences for a procedure, not least due to his or her specific expertise. This proximity of the surgeon with the intervention, and indeed the surgeon as an experimental variable, also limits the easy conduct of randomised surgical trials.⁸

Another difficulty of evaluating new surgical techniques is the timing of evaluation. New surgical procedures, whether with new devices or a modification of an established technique, evolve with constant refinement. If a technique is new, an individual surgeon's learning curve also plays a factor in the surgical outcome. As Reeves⁹ writes, "doing an evaluation too early may preclude acceptance, since the technology may not have evolved sufficiently and surgeons may not have mastered it; conversely, doing an evaluation too late may make the evaluation moot, since the technique may have already become established and withholding it may be deemed unethical".

Assessing a New Technique

The regulatory approach to new therapeutic devices by the Center for Devices and Radiological Health (CDRH) at the US Food and Drug Administration (FDA) is a commonly

adopted model for such regulation. In general, the CDRH considers the available scientific evidence and determines the safety and effectiveness of each new device, and provides information on the intended use. Locally, the Health Sciences Authority (HSA) has introduced the Medical Product Act "to regulate the manufacture, import, supply, presentation and advertisement of health products". These regulatory controls ensure that new devices, when used as intended, have a minimum standard of efficacy and safety.

The CDRH similarly offers a good model for the evaluation of novel surgical techniques. Evidence for the efficacy and safety of a new surgical technique often comes in the form of case reports or case series. In the surgical literature, case studies with outcomes compared to "historical data" are also common. Such observational studies, although prone to bias, do provide important information on efficacy, safety and risk profiles. They also have an important role in evaluating treatment for rare diseases or conditions with high mortality for which the affected numbers are small. However, in the hierarchy of evidence available, the prospective randomised trial is supreme. A well-designed RCT controls for selection bias and other confounders, and allows for differences in outcome to be attributed to the new intervention.

Keeping in mind the difficulties of conducting a surgical RCT, there are 3 scenarios for which we propose that prospective randomised trials should be available.

The first instance would be at the introduction of a radically new surgical procedure. As is the case for pharmaceuticals, a totally new technique should be assessed in comparison to the currently accepted standard treatment. This would allow for definitive assessment of the efficacy and risks of the new surgery as compared to current treatment, and importantly, shed light on the potential advantages of the new technique. Such rigorous testing ought not to be optional, but a fundamental ethical obligation. In fact, for radically new surgical procedures, non-human testing to ascertain feasibility and safety should precede introduction to humans, even in a trial setting. For instance, in the development of aortic endovascular stent grafts, initial experiments in animal models showed that it was possible to deploy the stents after introduction via the external carotid artery, demonstrated the formation of a vascular lumen by neo-intimal proliferation upon the synthetic scaffold and established graft patency.¹⁰⁻¹² Only after safety had been established in animals did the technique progress to trials in humans.¹³ Initial reports in the form of retrospective case series demonstrated, repeatedly, the benefits of the new technique.^{14,15} Taken alone, it may have appeared that endovascular stenting was superior to the conventional open repair of an abdominal aortic aneurysm. However, a well-designed, large, multicentre randomised controlled trial concluded that although endovascular repair was associated with a lower operative mortality than

open repair, no differences were seen in total mortality or aneurysm-related mortality in the long-term. Endovascular repair was also associated with increased rates of graft-related complications and re-interventions, and was more costly.¹⁶ This example clearly demonstrates that a well-designed randomised controlled trial provides evidence of the advantages and disadvantages of a new procedure as compared to the gold standard current treatment. And such is an instance where robust scientific evidence is ethically required prior to adoption of a new surgical technique.

A second scenario where randomised trials would be beneficial would be in the assessment of the use of an established technique for an indication that the technique was not originally developed for. We see the broadening of indications for existing techniques invariably as we gain experience. For instance, the classical indication for bariatric surgery is morbid obesity of a BMI greater than 40 or a BMI greater than 35 with significant obesity-related morbidity. However, since bypass procedures have been shown to be associated with rapid improvement of type 2 diabetes mellitus, the experimental use of bypass procedures in non-morbidly obese diabetics have been published.^{17,18} Immediate term success is reported, but long-term efficacy and risk profile remain unknown. In such a setting, we have an ethical obligation to demonstrate efficacy and safety for the expanded indications, and inferences from observational studies should not suffice.

The last instance where it would be ethically sound to have randomised studies occurs when the novel surgical technique potentially involves a large number of patients. If significant numbers of patients may be affected by a shift in surgical technique, it follows that the new treatment ought to be rigorously tested against the current accepted standard therapy. Well-conducted large randomised trials have allowed for the use of breast conserving surgery (combined with radiation therapy) instead of a mastectomy for women with breast cancer, while the fervour for laparoscopic repair of inguinal hernias has waned after prospective randomised trials demonstrated the increased rate of complications and recurrences of the laparoscopic technique.^{19,20}

The onus of evaluating novel surgical techniques should not only be upon the individual surgeon. Perhaps a reasonable approach would be to stratify the degree of deviation from current surgical intervention and evaluate accordingly. A lesser modification may well be assessed by an interested group of surgeons and the institution's IRB, while a radical new development may warrant critical evaluation at a national level. In the latter instance, perhaps a workgroup comprising of surgeons, medical ethicists, leaders of professional bodies and representatives from the community should be convened to evaluate the discovery, development and outcomes of the new technique. The review

of well-designed case series may allow for validation of the technique in the absence of randomised trials. And if clear indications, contraindications and an identifiable patient population that may benefit are present, a consensus to develop the technique in the local setting may justifiably be reached.

Assessing Training and Accreditation

Surgical competence in a new technique is another important issue. With the rapid development of new techniques and advances in technology, it is likely that a surgeon becomes keen to perform a new procedure that was developed after completion of his or her formal training. Patients often trust in the diligence of their surgeons to attain a level of competence prior to performing a procedure, and there is much to be said of self-regulation. But as McKneally summarises: "When innovative surgeons who take unaccredited courses return with uncertified skills to introduce unvalidated treatment in trusting patients, we have a recipe for disaster."²¹

Clearly then, some regulation is in order. Perhaps for emerging techniques, funding for training should be focused on centralised centres of excellence to develop a local group of surgeons competent in the procedure prior to dissemination. Depending on the operation, training may take the form of working with experienced colleagues or sending the surgeon to another institution to master the technique prior to practice. Professional regulation in the form of credentialing by peers and the surgical boards will also ensure an ethical minimum standard of surgical competence.

Audit and Informed Consent

For each new experimental surgical technique, it is likely that a surgeon will be able to find a patient willing to undergo the procedure. Such patients may be driven by the severity of their medical condition, the lack of an alternative therapy, or simply be psychologically predisposed to seeking the latest innovation. Either way, unambiguous information regarding the experimental technique and unvalidated nature of the therapy needs to be provided. All available evidence, whether from animal models or reports of use in humans, should be made available to the patient. Patients should be informed that the device or technique was designed to be therapeutic, but that the immediate and long-term outcomes and complications have yet to be fully elucidated. We propose that an honest discussion of the outcomes to date and the institutions' and surgeon's experience with the innovation in question should be presented to the patient, particularly in the infancy of the adoption of a new technique.

Finally, the critical assessment of surgical outcomes in

the form of formal audit is an essential aspect of evaluating novel surgical techniques. The systematic review of key performance indicators including major complications, re-operations and mortalities will provide concrete evidence of the efficacy, costs, safety and risks of each new technique.

Conclusion

Improving clinical outcomes through developing new techniques and devices is an ethical obligation, and often, patients benefit from the thinking, innovative surgeon's daring and skills. However, unvalidated surgical techniques may potentially harm patients, and the unchecked adoption of innovative surgery may unjustifiably raise surgical costs. The responsibility for ethically evaluating novel surgeries should extend beyond the individual surgeon. We propose to stratify each new innovation based on how much it deviates from current practice, and to have the more radical innovations be audited by national boards prior to practice. The adequate assessment of each new technology by the surgical community, the evaluation of surgical competence, audit and provision of transparent informed consent should all be part of the ethical evaluation of untested, innovative surgery.

REFERENCES

1. Reitsma AM, Moreno JD. Ethical regulations for innovative surgery: the last frontier? *J Am Coll Surg* 2002;194:792-801.
2. Spodick DH. Numerators without denominators. There is no FDA for the surgeon. *JAMA* 1975;232:35-6.
3. Horton R. Surgical research or comic opera: questions, but few answers. *Lancet* 1996;347:984-5.
4. Stirrat GM, Farrow SC, Farndon J, Dwyer N. The challenge of evaluating surgical procedures. *Ann R Coll Surg Engl* 1992;74:80-4.
5. Dimick JB, Diener-West M, Lipsett PA. Negative results of randomized clinical trials published in the surgical literature: equivalency or error? *Arch Surg* 2001;136:796-800.
6. London AJ, Kadane JB. Placebos that harm: sham surgery controls in clinical trials. *Stat Methods Med Res* 2002;11:413-27.
7. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;317:141-5.
8. Fins JJ. Surgical innovation and ethical dilemmas: precautions and proximity. *Cleve Clin J Med* 2008;75Suppl 6:S7-12.
9. Reeves B. Health-technology assessment in surgery. *Lancet* 1999;353 Suppl 1:S13-5.
10. Jordan WD Jr, Sampson LK, Iyer S, Anderson PG, Lyle K, Brown RJ, et al. Abdominal aortic aneurysm repair via percutaneous endovascular stenting in the swine model. *Am Surg* 1998;64:1070-3.
11. Yoshioka T, Wright KC, Wallace S, Lawrence DD Jr, Gianturco C. Self-expanding endovascular graft: an experimental study in dogs. *AJR Am J Roentgenol* 1988;151:673-6.
12. Mirich D, Wright KC, Wallace S, Yoshioka T, Lawrence DD Jr, Charnsangavej C, et al. Percutaneously placed endovascular grafts for aortic aneurysms: feasibility study. *Radiology* 1989;170(3 Pt 2):1033-7.
13. Chuter TA, Donayre C, Wendt G. Bifurcated stent-grafts for endovascular repair of abdominal aortic aneurysm. Preliminary case reports. *Surg Endosc* 1994;8:800-2.
14. Eliason JL, Upchurch GR Jr. Endovascular treatment of aortic aneurysms: state of the art. *Curr Treat Options Cardiovasc Med* 2009;11:136-45.
15. May J, White GH, Harris JP. Endoluminal repair of abdominal aortic aneurysms — state of the art. *Eur J Radiol* 2001;39:16-21.
16. Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ. Endovascular versus open repair of abdominal aortic aneurysm. *N Engl J Med* 2010;362:1863-71.
17. Schauer PR, Burguera B, Ikramuddin S, Cottam D, Gourash W, Hamad G, et al. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. *Ann Surg* 2003;238:467-84;discussion 84-5.
18. Wajchenberg B, Cohen R, Schiavon C, et al. Laparoscopic duodenal jejunal bypass in the treatment of type 2 diabetes mellitus in patients with BMI <34. Initial results. Abstract presented at: 68th Annual Scientific Sessions of the American Diabetes Association; June 6-10, 2008; San Francisco, CA. Abstract 1454-P.
19. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. *N Engl J Med* 1995;333:1444-55.
20. Neumayer L, Giobbie-Hurder A, Jonasson O, Fitzgibbons R Jr, Dunlop D, Gibbs J, et al. Open mesh versus laparoscopic mesh repair of inguinal hernia. *N Engl J Med* 2004;350:1819-27.
21. McKneally MF. Ethical problems in surgery: innovation leading to unforeseen complications. *World J Surg* 1999;23:786-8.