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Surgical experimentation and clinical trials: differences and related ethical problems

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Abstract
Surgical techniques are not introduced into clinical practice as the result of randomised clinical trials (RCT), but usually through the gradual evolution of existing techniques or, more rarely, through audacious departures from the norm that are decided by a surgical team on the basis of experience. Sham surgery is held by some to be not only an ethically acceptable procedure but also a perfectly fit and proper one, as it could endow surgical experiments with the strict methodological and statistical precision typically associated with RCTs. This article first briefly examines some of the methodological aspects of both RCTs and surgical experiments and then offers a few considerations regarding the ethical issues raised by sham surgery.

Key words
• bioethics
• human experimentation
• informed consent
• placebo
• surgery

THE ROAD TO INNOVATION IN SURGERY

The profound changes that have affected all sectors of medicine in recent years have not by-passed surgery. Some interventions that were widely performed until fairly recently are now unheard-of. Until the end of the 1970s the most frequently performed surgical operation was gastric resection for the treatment of ulcers. Today ulcers are cured with antibiotics and many young surgeons probably have little or no experience of performing a gastric resection. Other interventions, such as cholecystectomy for example, that were formerly performed using invasive techniques, are now performed laparoscopically. Previously unimagined operations have become ordinary, including cardiac surgery, organ transplantation, extremity reimplantation.

New surgical techniques are often not innovations so much as the result of evolution and improvements. Successive adaptations of existing techniques lead to the emergence of new procedures that are not radical innovations produced by a specific research programme, but part of a continuum formed by the evolution of day-to-day practices. Occasionally new procedures arise in dramatic circumstances when surgeons, often in an emergency, decide to try a new approach even though there is no adequate statistical support for its efficacy. If they are successful their techniques may subsequently form the basis of new protocols and be routinely applied [1]. In other words, surgical innovation is mainly the result either (rarely) of bold experimentation or (more frequently) of historical observations that bring gradual improvements to existing techniques.

These considerations distinguish surgery from other fields of medicine, in which innovations are evaluated through randomised clinical trials (RCTs) that provide a scientifically rigorous basis for their introduction into clinical practice only when there is sufficient evidence of their efficacy.

There is also a difference in the way that surgical techniques are handed down to young surgeons compared with the methods of training adopted in other fields of medicine [2]. The various steps of each procedure are described in textbooks (and with the use of more modern audiovisual and multimedial tools), but "the picture such sources paint can be highly misleading. Like mediaeval recipe books, surgical textbooks and journals assume a huge amount of contextual knowledge in their readers. 'Take three quails and prepare as usual' spoke volumes in the 1500s, but such directions do not help today's cook" [3].

THE RULES GOVERNING RANDOMISED CLINICAL TRIALS

The general design of RCTs envisages four phases [4]:

Phase I (20-80 healthy volunteers or, in some cases such as oncology, patients in an advanced stage of disease). The goals are: to assess safety; identify side-effects; determine a safe dosage; study the pharmacokynetics and pharmacodynamics of the drug.

Phase II (hundreds of patients with the pathology under study). The goals are: further assessment of safety; to determine whether the effects are in line with expectations.

Phase III (thousands of patients with the pathology under study). The goals are: to assess effectiveness; monitor side-effects; compare the new treatment with others already in use, if any.

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Phase IV (populations). The goals are: post-marketing surveillance to collect information regarding risks, benefits and uses of the agent long after its release on the market.

Clinical trials (CTs) are regulated by three separate levels of tight rules: technical-scientific (scientific requirements impose strictly programmed procedures, usually divided into four precisely defined phases); ethical (ethical committees work in accordance with strictly regulated – and often binding – procedures); regulatory (detailed and mandatory regulations have been established by national and international regulatory authorities) [5].

A COMPARISON BETWEEN RANDOMISED CLINICAL TRIALS AND SURGICAL EXPERIMENTATION

Randomised clinical trials are the gold standard of evidence-based medicine.

The procedures for conducting RCTs can generally be applied to any field of medicine: from neurology to cardiology, from metabolic diseases to infectious diseases. But they are not easily adaptable to surgery. This is due partly to procedural factors (the double blind procedure is clearly inapplicable, deception is problematic), and partly to ethical considerations ("sham" surgical procedures would raise serious concerns). Thus surgical innovations are not based on procedures that have been strictly validated in scientific or biostatistical terms, as is the case with RCTs.

At this point it is as well to recall that while each minor modification that is introduced in a technique may contribute to the progress of surgical practice it is unlikely to lead to significant results; innovation proceeds in small steps. If even tiny modifications are made to a drug, the nature, entity and probability of its effects may vary considerably, which is why RCTs are necessary not only for every new molecule but also when minor variations are made to others that have already been studied.

The problem of applying RCT procedures to experimental surgery thus creates "a tension between the highest standard of research design and the highest standard of ethics" [6], particularly in relation to the ethical issues associated with possible control groups [7].

CAN SURGERY BE MADE MORE SIMILAR TO RANDOMISED CLINICAL TRIALS? SHAM SURGERY

Seen from a purely methodological viewpoint, sham surgery could provide surgical experiments with the methodological rigour applied to RCTs [8].

Sham surgery is analogous to placebo surgery: the patient is anesthetized, the surgeon makes some incisions, and then the incisions are sewed up: the patient will believe that the surgery really took place.

There are indeed those who hold that, notwithstanding the problems just mentioned, the use of sham surgery in surgical experiments – in other words, the adoption of procedures similar to those of RCTs – is not only ethically acceptable but a proper procedure for acquiring scientifically useful knowledge [9].

In the words of G.F. Gillet, "We need innovation in surgery to make techniques safer. We need good research to check on what we are doing and to refine our indications for using surgery in various clinical situations. Surgeons and their patients need to go into these trials and undertake their respective roles in these developments with an open mind and a careful attention to the need for the rigor that is to be had in a primarily healing art" [10]. F.G. Miller takes a similar but even more emphatic approach: "It would be truly fraudulent for a clinician to perform a fake therapy in the guise of competent medical care. In contrast, sham procedure trials are scientific experiments in which the active deception is methodologically necessary to produce valid results. Understood as research interventions that carry risks to individuals without a prospect of compensating benefit to them, sham procedures are no different in principle from common research interventions for determining outcomes such as blood-taking, lumbar puncture, or biopsy. Most importantly, the use of sham interventions does not violate the rights of patient-subjects provided that they have been adequately informed that they will receive either a real or a sham intervention and that efforts will be made to make the sham procedure indistinguishable from the real treatment under investigation. The authorization beforehand by research subjects makes the difference between legitimate and unethical deception" [11].

The advocates of this approach emphasise that, by accepting the possibility of undergoing sham surgery as part of a programme of randomised clinical trials, patients would be making a gesture of great generosity that could lead to the acquisition of useful knowledge. They further hold that, from the ethical viewpoint, it is preferable to expose a few individuals to slightly burdensome sham surgery than to expose numerous individuals to practices that have not been rigorously validated and may therefore be highly onerous and detrimental. In other words, they are inviting us to move on from a concept of ethics based on an assessment of risks and benefits to the individual to one of ethics based on an assessment of risks and benefits to the community.

SHAM SURGERY AND RCTS USING PLACEBOS: ETHICAL ISSUES

Two further types of consideration need to be examined: methodological and ethical [12].

In methodological terms, experimental protocols that bring surgery closer to RCTs could endow new techniques with the biostatistical solidity that is so fundamental to biomedical experiments, as well as help to avoid some of the bias frequently found in surgery. They could, for example, help to overcome the so-called "Pygmalion effect" (after the comedy by George Bernard Shaw), as a result of which investigators are predisposed to see the outcome they seek even when it is objectively absent [13].

However, even if the procedures adopted for RCTs were extended to surgery (including sham surgery) problems would remain that would undermine methodological rigour.

Only the patient-subject is kept in ignorance, and the clinician, who can distinguish active from inactive treatment,

may be required to engage in active deception [14].

There would then arise the problem of equipoise, which would be virtually impossible to guarantee. Charles Fried first introduced this term to the ethical debate in 1974 to refer to one of the scientific and ethical pre-requisites for the conduct of clinical trials, namely that the mental approach of the physician-researcher conducting a trial should be totally free from any kind of prejudice as to the possible therapeutic benefits of the experimental and control treatments under evaluation [15]. But this definition of equipoise, which appears to apply only to the attitude of the physician or researcher, is itself open to question because of the difficulty of ensuring that an individual's equipoise remains constant. As success follows success for some patients, or as others suffer adverse effects, an investigator may, even unwittingly, adjust his or her approach. In 1987 Benjamin Freedman proposed the definition of equipoise that has since become the most widely accepted: he introduced a concept of "clinical (or collective) equipoise". This posited the acceptability of randomised clinical trials provided there was no general recognition among the experts of the most effective treatment for a particular disease. This approach places medical practice in a collective context rather than in an individual light [16].

From the ethical point of view sham surgery is thus extremely problematic, but it is nonetheless considered both reasonable and acceptable in some quarters. In certain cases it has led to improvements in both knowledge and techniques. Data from observational studies, for instance, appeared to support the considerable efficacy of some orthopaedic surgical interventions, but sham surgery revealed that this was due largely to the placebo effect [17].

However, in general, the ethical issues raised by placebo, or sham surgery, are extremely serious.

Informed consent is a cornerstone of human research ethics. Informed consent in surgery may raise legitimate ethical concerns: "Curiously, perversely, where doctors are at their most invasive, inflicting deliberate wounds upon their patients, consent has often been a formality" [18].

The use of treatment with a placebo gives rise to problems not only in surgery, but even in traditional RCTs, where it is considered acceptable only in specific circumstances. Article 32 of the World Medical Association's Declaration of Helsinki states that: "The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option" [19]. All the key documents regarding the ethics of trials agree that placebos may only be used as the control method under strict conditions – *i.e.* when there are no methods of proven effectiveness, or when the withdrawal or withholding of such methods does not present an unacceptable risk or burden. No other reasons would be ethically acceptable [20]. The ethical problems are compounded in the case of sham, or "placebo surgery" [21], which could clash seriously with the duties imposed on physicians by medical ethics, as patients would be subjected to real but therapeutically useless invasive surgical interventions [22].

Attempts to extend to surgical experimentation and innovation the various authorisation procedures that apply to RCTs, including rules for assessment and authorisation, thus seem out of place.

Recommendations for the assessment of surgery based on a multi-stage description of the surgical development have been proposed [23, 24].

Ethics committees should instead be intellectually ready to express opinions (which need not necessarily be binding) on experimental surgical protocols, very few of which are currently subject to such scrutiny [25]. Nor are the ethical issues involved in surgical experiments often addressed in the reference manuals used by members of these committees [26-30] or by researchers [31, 32]. Evaluation by an ethics committee, where possible, could promote both the scientific soundness and the ethical validity of new techniques, particularly in regard to the balancing of risks and benefits.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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