INNOVATIONS IN SURGERY

A PROPOSAL FOR PHASED CLINICAL TRIALS

MIKE GROSS

From Dalhousie University, Halifax, Nova Scotia, Canada

There is an urgent need for the staged, controlled, introduction of new technology and new procedures to surgery. A classification system in four stages is proposed, which would allow for prospective assessment of new devices or methods before they are released for use by the surgical community. The proposal recognises the unique nature of a surgical operation and its learning curve. The issues of randomisation and of informed consent are discussed, and are shown not to be barriers to clinical trials, but necessary adjuncts to orderly testing. The importance of continued surveillance of innovations is emphasised.

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The randomised controlled clinical trial has become the standard by which the efficacy of treatment is assessed. Orthopaedic surgery has a poor record in this respect, although methods of initiating and conducting such trials and of analysing the data have been described (Rudicel and Esdaile 1985; Gross 1988; Laupacis et al 1989).

An increase in multidisciplinary research by surgeons, bioengineers, materials engineers, and basic scientists has produced an explosion of new orthopaedic devices and implants. This has caused rapid changes in clinical practice, not all of which have been beneficial to patients. Some devices have been introduced and failed even before they have been evaluated in controlled trials. One example was resurfacing hip arthroplasty, which was rapidly abandoned when poor four-year results were published (Head 1981). What has become almost a traditional surgical cycle is shown in Figure 1. The relationship between designers, other clinicians and the reporting of results is complex and has led to new instructions to authors in respect of possible conflicts of interest.

Another factor is the general success and continued improvement of surgical techniques, which have resulted

in ever lower complication rates. This increases the need for larger sample sizes to establish statistical significance (Herberts et al 1989). It is unlikely that any single author or institution will be able to conduct the research necessary to show that significant differences are produced by changing methods (Bonchek 1979).

There is need for a more systematised approach to the design, evaluation, implementation and general release of new surgical procedures or implants.

TYPES OF CLINICAL TRIAL

Conventional clinical trial. One of the earliest major randomised clinical trials involved the testing of drugs for tuberculosis, and was conducted by the British Medical Research Council (Hill 1990). The method has also been extensively used to assess various chemotherapeutic agents for the treatment of cancer patients and any new therapeutic agent now goes through four phases of trial before its general release.

Phase 1. A feasibility study investigates several dose regimens of a new drug to assess toxicity and therapeutic effect. The maximum tolerated dose for humans can be calculated from animal experiments by indirect extrapolation in terms of dose per unit surface area.

Phase 2. An efficacy study determines whether a particular dose regime is effective. Chemotherapeutic agents do not act in an 'all or none' fashion; but an improvement of results in as few as 25% may be significant. Therefore,

Fig. 1

The cycle of use of a surgical innovation (A, revised version; B, indications limited; C, procedure abandoned).

M. Gross, MD, FRCS, FRCS C, Associate Professor
Suite 4135, Dickson Centre, Victoria General Hospital, 1278 Tower
Road, Halifax, Nova Scotia, Canada B3H 2Y9.

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relatively small numbers of patients may be required for such a study.

Phase 3. Comparative trials are used to test the hypothesis that the new agent assessed in phase 1 and 2 is superior to the current conventional treatment. It is at this stage that randomised controlled trials with larger numbers of patients are needed.

Phase 4. A surveillance study follows patients who have received the treatment and measures factors, such as comorbidity, not necessarily directly related to the initial disease.

Proposed surgical trial. New surgical equipment or implants require a parallel series of trials.

Phase 1: Laboratory study. This is an exploratory investigation of the principles involved in a new implant, or a new method of fixation. It may require equivalent animal models for the biological response and human cadavers for the study of biomechanics.

Phase 2: Cohort study. This involves a strictly controlled prospective investigation in selected consenting patients. It is designed to determine the value and viability of the new procedure according to a predefined set of end-points.

Phase 3: Randomised controlled trial. This tests the hypothesis that the new procedure, method or implant is superior to the current standard treatment in a much larger predefined population, treated by surgeons other than the originators.

Phase 4: Surveillance study. This continues the careful assessment of a treated population by follow-up of all patients to detect any unexpected complications. The length of time will depend on the procedure or device. For total joint replacements, it would be reasonable to make a preliminary assessment at five years and again at ten years.

DISCUSSION

Each of these four phases of the surgical trial requires some further amplification.

Phase 1: Laboratory study. Many animal models have been employed in surgical research. Rodents are used for transplantation, tumour, and immunological studies, but not all animals are equivalent to the human subject in their tissue or biomechanical response. Dogs or sheep are more commonly used for implant analysis because they have similar bone architecture and the results are more easily extrapolated to the human situation.

The use of synthetic materials in patients requires regulatory approval, usually based on toxicology testing in animal models. The study, however, of the use of a synthetic material in a particular configuration, such as a ligament replacement, is also necessary since the response to biomechanical stress and deterioration may alter the toxicological results. An example is seen in reactions to cobalt-chrome alloy. Heath, Freeman and Swanson (1971) reported the carcinogenic properties of

wear particles from such a prosthesis in a mouse model; the implantation of whole prostheses of the same material in the same model probably would not have had this tissue effect (Lewis et al 1991).

In future, animal models should be used to test not only the materials but also the scaled configuration of new and, equally importantly, of modified implants. Though small variations in current designs for arthroplasty or fracture fixation may not require animal experiments, they all require justification from appropriate biomechanical testing in cadaver specimens.

Phase 2: Cohort study. At this stage it is necessary to demonstrate that the postulated advantages of a new procedure or implant are realised clinically. Such a trial should be prospective and based on data collected from the phase 1 trial, or from comparison with current procedures or implants in defined patient populations. This raises an important point, discussed by Chalmers et al (1983), on the need for randomisation of patients at this stage of the introduction of a new surgical treatment or component (Bonchek 1979).

A prospective cohort analysis without randomisation is acceptable only if there is no equivalent treatment already in use and if it fulfils the following criteria:

- 1) The results of a phase 1 trial have been accepted by peer review to show the potential value of the innovation.
- 2) The criteria for success or failure are strictly defined by the principal investigator.
- 3) The patients have given their fully informed consent to an independent counsellor appointed by an appropriate Ethical Review Committee (Cartwright 1988) and are to be assessed by a fully independent observer. Approval for the trial would be granted only for a limited number of patients, sufficient to prove or disprove the study hypothesis.

The cohort study might reveal the need for modifications of the technique, instrumentation or implant, before starting the randomisation of a phase 3 trial. It should also identify unexpected complications such as thigh pain after uncemented hip arthroplasty (Campbell et al 1992).

Most surgeons believe that there has to be a special bond between surgeon and patient, based on a combination of trust, respect and ability, before consent for a surgical procedure is given. Taylor, Margolese and Soskolne (1984) suggested that one of the reasons why patients were not entered into trials was the surgeon's fear of the effect on the patient-doctor relationship. The patient's assessment of the value of any intervention depends heavily on the extent of the information provided (Angell 1984). However, if a new untried procedure is presented to patients as a gamble, in that a greater chance of doing well is associated with an increased risk from the unproven technology, they are then able to make an appropriate judgement.

Such a cohort of carefully selected patients can be entered into a rigorous trial without randomisation, and

without intruding on the uniqueness of the surgeon-patient relationship. It gives the surgeon an opportunity to introduce a new technique or technology, and it gives the patient the opportunity to receive the potential benefits of such changes, all within a carefully constructed and validated framework.

Phase 3: Randomised controlled trials. Any new surgical procedure which is in competition with current practice should be subjected to a randomised controlled trial before it is available for general use (Curran 1979). This would ensure that changes in prosthetic design would undergo rigorous clinical analysis before general release and marketing (Herberts et al 1989). Historical controls or comparisons are rarely acceptable.

The classical randomised trial, as shown in Figure 2, has been criticised by Zelen (1979) who thought that consent should be sought *after* randomisation as in Figure 3. Van Der Linden (1980) suggested that surgeons should be assigned to each treatment group according to their beliefs and skills, but this implies allocation to a treatment group before the patient has seen the responsible surgeon. This is rarely possible except in a health-care system in which patients have no choice of where or by whom they are treated. Methods minimising the effects of randomisation on patients have been well discussed by Curran (1979) and Fost (1979).

These hypotheses and Zelen's subsequent modifications (Zelen 1990) may be flawed. Patients enter trials with the hope of obtaining better treatment and must accept certain risks, which vary with the severity of the illness and the side-effects or complications of the treatment offered. The patient's judgement of these risks is almost entirely dependent on the information presented and true informed consent must therefore be obtained before randomisation (Lawrence 1991). The barrier to entry to the trial should not be randomisation but the balance of choice between the two treatment arms (Angell 1984). True randomisation is essential to prevent unconscious or conscious manipulation by investigators or patients (Lavori et al 1983).

The responsibility for ensuring true informed consent should rest with an Ethical Review Committee (Moodie and Marshall 1992) which should ensure that patients participate fully in the decision-making processes (Kassirer 1983). The problems relating to the use of randomised controlled trials in surgery include the irreversibility of an operation should one of the treatments prove superior to the other, and the difficulty of ensuring comparability of procedures (Rudicel and Esdaile 1985).

An example of the need for such trials is total hip arthroplasty. The original design by Professor Sir John Charnley has been shown to function for at least 20 years and it constitutes the 'gold standard' (Herberts et al 1989). Changes in prosthetic design should be compared with the original on a long-term basis, and in a carefully defined patient population. The public often confuses the latest technique with the best, but that perception, often

Fig. 2

Classical randomised clinical trial.

Fig. 3

Double consent randomised design.

reinforced by the media, arises from lack of education and the failure to understand the process of medical progress. Such education will take place when the surgical community accepts improved standards of evaluation, implements them, and explains the need for them. The originator of a new technique should also be required to show that it can be learned and practised by other surgeons to the same standards and results.

If there is no comparable surgical option in current practice, then the comparison must be made against a non-surgical treatment. If an advantage is later shown for surgery, it will still be possible to operate on the control group, who will have contributed to proving the effectiveness of the procedure in question.

Phase 4: Surveillance study. A surveillance programme should be designed to reveal potential complications. Manufacturers are under obligation to offer implants which meet certain legal and ethical requirements, but these are not very rigorous and at present there is little incentive to set up extensive clinical trials before offering implants for sale. The frequent introduction of modified and new implants must increase unit costs to the manufacturer, costs which are ultimately paid by the patient or the health-care provider. Detsky (1989) has analysed the cost-effectiveness of clinical trials in medicine and has shown them to be a good investment. This must surely apply to surgical implants as well.

The phase 4 surveillance study should be regulated by some authority (the FDA in the USA) which should collect, collate and analyse data and make available to

all surgeons any reports of complications related to an implant or procedure. Such reports could then result in a re-evaluation by the regulatory authority in the light of appropriate advice from the scientific clinical community.

Conclusions. A classification system for surgical trials is suggested which would provide more careful monitoring and evaluation of innovations. The proposals are applicable to all surgical disciplines, but are most required in orthopaedics because of the extensive use of implants and prostheses in the specialty.

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