Travails of Surgical Trials in India: Problems and Proposed Solutions

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ABSTRACT

Clinical trials in surgical patients pose their own unique problems including difficulties in consenting, using a placebo or ‘old’ procedure, ensuring standards in novel procedures and objectivity in measurement of endpoints.In India, problems of consent are compounded by poverty, ignorance and inequality in availability of healthcare.

This article discusses the potential problems faced in conducting clinical trials on surgical patients and looks at possible solutions in the form of training, audit and improving regulation.

The evidence based medicine (EBM) movement is knocking hard at the surgeons door. [1] Exponentially increasing technology coupled with spiralling costs and the need to satisfy patients as well as payers, be it the patients themselves, insurance agencies or the tax payer, pose a special problem. Whilst attempting to provide effective and cost efficient care care evidence is required to support utilisation of any technology across all medical specialities.

Generation of evidence in surgical patients has its own challenges.

Trials involving surgeons are essentially of 3 types:

1. Those involving medical treatment in surgical patients eg adjuvant chemotherapy for cancers, testing various forms of analgesia post operatively, intraoperative fluid management
2. Those comparing various surgical techniques eg laparoscopic vs an open approach or two different types of incision or different devices or implants.
3. Those comparing a surgical intervention vs a non surgical intervention or not intervening at all eg surgery vs physiotherapy for knee pain or establishing whether surgical implantation of cells in the brain for Parkinsons disease actually helps.

The first of these essentially are medical trials. The remaining two groups provide special challenges, which are discussed in this article. Again we are faced with different types of studies, summarised by Cook. [2] Exploratory trials essentially look at short evaluation of novel procedures under development by the inventing surgical team looking at feasibility and refinement of these procedure in those most likely to benefit. Once the procedure is standardised, explanatory trials would be carried out in small groups of patients by surgeons trained in the novel procedure to establish short term efficacy often with surrogate outcomes. The final test of efficacy would be pragmatic trials reflecting the ‘real life’ situation with surgeons from multiple centres representing the broad range of experience seen in clinical practice test the procedure with long term clinical and patient reported outcomes.

Though this logical stepwise progression is ideal, the nature of surgical procedures and perhaps the surgical temperament is such that no ‘cutting edge’ centre would like to be perceived to be left behind in adopting the ‘next good thing’ leading to widespread adoption of a promising approach till it is so prevalent that evolution is difficult. This is succinctly summarised by Buxtons law[3]- ‘Its always too early (to evaluate technology) till its too late’. Though was written in the context of heart transplants, a classic example is the widespread adoption of laparoscopic cholecystectomy a scant few years after its first demonstrations. This procedure has a particularly interesting development with the ridiculing of its first proponents to rapidly capturing the imaginations of both the surgeons and public and becoming part of standard care in two to three years[4]. Such was the conviction that laparoscopy was a great thing that the proponents believed that scientific testing in the form of a randomised controlled trial to evaluate this procedure would be unrealistic! [5] In spite of this, an exceedingly well designed clinical trial was carried out. [6]

The study from Sheffield [6] highlighted one of the major problems in carrying out surgical trials- the issue of randomisation. It is intrinsically difficult to explain to the patient that a team will offer different procedures based on pure chance rather than best practice. This is an implicit admission on the part of the surgeon that he does not know something which is contrary to the traditional demigod status society offers them. Further, to completely remove bias it is necessary to blind the patient as to the technique to counter the expectations of success of a novel procedure. The Sheffield study[6] famously achieved this by putting on dressing of both the laparoscopic and open surgery and went to the extent of staining both the dressings with povidone iodine to prevent particularly clever patients from using wound soakage as a marker to deduce which dressing was dummy. Surgical studies have gone even further and included invasive procedures such as sham burr holes [7] and sham arthroscopy [8] under anaesthesia as placebo to avoid exceedingly strong bias for interventions. Interestingly all these studies using extensive masking have turned out to disprove the much touted novel treatment under evaluation!

A major criticism of results of surgical trials by those against the conclusion have been that skill sets differ. If the trial is negative, the critics say that not enough training was present with the team for the novel intervention and if the intervention was positive, critics would say that the level of skill at the trial centre was much beyond what would be available in routine clinical practice and therefore the results are not generalisable. Good surgical trials always mention the degree of training achieved by the team in the novel procedure. For this it is also important to understand the learning curve for not just the surgeon but the whole team. The Dutch Surgical group is an excellent example of this, the LEOPARD studies comparing laparoscopic and open pancreatic resections [9,10] ensure that each surgeon has performed at least 20 such surgeries which have been mentored or peer reviewed by unedited recordings to ensure quality. For this reason the premature cessation of the LEOPARD 2 study [10] evaluating pancreatico-duodenectomy needs to be taken seriously as surgeons were trained and had increased leaks and mortality inspite of this.

A practical problem in carrying out surgical studies is determining a valid endpoint. A good endpoint needs to be objective, measurable, easily reproducible and practical. Clearly it is not practical to have 5 year survival benefit as an endpoint for technical trials as such a study would take many years to carry out delaying the introduction of potentially useful technology. This would be a good marker for audit once it has been demonstrated that the technology is at least as safe as the standard of care- the example here being laparoscopic surgery for rectal cancer. [11]

Objectivity of the endpoint cannot be overstressed. A single centre randomised study from India [12] showed efficacy of laparoscopic pancreatectomy over the open approach by using hospital stay as the endpoint, one which is easy to bias.This is clearly demonstrated by the aforementioned Sheffield study. [6] The patients were given the liberty of deciding when to rejoin work so the median time off work was 4 weeks - a figure that would be considered laughable today. The LEOPARD study[9,10] on the other hand uses an array of objectively verifiable factors which are more difficult to bias.

As in medical trials long term risks may not be apparent. an example of this is the product withdrawal of the hip implant by Johnson and Johnson. [13] Once the data was looked into closely multiple issues emerged. Regrettably the cost of surgical trials is huge as it involves expensive technology as well as expensive surgery in contrast to pill popping. further, if something goes wrong, corrective procedures and potential litigation too are expensive. Conversely the rewards are huge so there is a lot at stake for the industry. This may encourage interesting practices if not strongly regulated.

Our own ICMR guidelines have an interesting take on these trials. The guidelines do not demand novel devices to be provided free, as would be ethical, but at a subsidy if possible.[14] This dubious stand would certainly help in cost cutting in trials using expensive devices and implants. This has been highlighted in the lay press [15] by criticism of a surgeon at a large teaching hospital for prescribing his own implants which were under evaluation at a considerable cost to poor patients visiting the public hospital.

The Indian environment generates its own problems. It is beyond doubt that india specific solutions are required rather than just the adoption of products developed in the West. The Jaipur foot is a classic example of this taking into account the need of Indians to squat and therefore flex their ankles- a movement not really required by Western counterparts using a Western toilet and not working in fields. Further the boot on the Western SACH (Solid Ankle Cushioned Heel) prosthesis is totally out of place in Indian culture where walking barefoot or in slippers is the norm. The ingenuity of Dr Sethi and his colleagues in developing this excellent prosthesis from bicycle spare parts at a fraction of the cost of the standard prosthesis must be acknowledged.[16]

Besides cultural and environmental issues, poverty and ignorance is a major drawback in successfully carrying out clinical trials in India. Surgeons are rarely questioned and patients assume that their best interest are being guarded. Further poverty leads to incentivisation- the procedure will be offered to the patient free of cost only if they agree to participate in the clinical trial. The very process that makes the trial ethical- not making participants pay for research- encourages recruitment of a vulnerable population. The poor development of healthcare in the public sector brings its own issues. In a country struggling to provide the most basic of care, are we justified in spending millions on complex technology which for example, has benefit in reduction of hospital stay by a day or two- the cheapest resource in a government hospital, unlike in the Western world where many thousands of dollars are saved by insurance companies. Practical India specific endpoints need to be used in Indian studies instead of blindly following Western studies.

Follow up of these patients is also a problem. The rural poor travel long distances to avail of healthcare. Often there is no proper address and it is unethical to demand regular follow up without adequate compensation for loss of work. On the other hand free handouts encourage trials moving to LMIC countries at a far lower cost as compensation and running cost is far less than in developed countries.

Large surgical trials in the Western world are carried out by collaboration facilitated by professional bodies such as the Dutch Pancreatic Cancer Group.[9,10] Within our country professional bodies do not commonly meet for such scientific aims - conferences being more a social occasion over weekends, often with family in attendance and with direct or indirect sponsorship by industry.

It would be unfair to conclude an article on this subject without offering potential solutions.

1. Start young: Surgeons are not appropriately trained in research methodology, ethics, epidemiology and data collection. The thesis as currently produced is a sad reminder of a bygone era of descriptive prose rather than an attempt to train young surgical minds in the scientific method and principles of evidence based medicine. More importantly, the curriculum places no emphasis on critical analysis of published papers. This deprives future surgeons of understanding of appropriate trial design even if they have the ideas and resources in future to carry them out. This is easily remedied by a change in the syllabus and examination pattern.

b) Audit and performance evaluation: Newer procedures should be subjected to a process of audit and surgeons can be evaluated in carrying these out. The audit process if carried out in a structured and anonymised manner with an aim to gain knowledge rather than punish the surgical community could provide a large volume of information on the efficacy of novel procedures without complex trials being carried out. Performance evaluation is easily carried out with most laparoscopic endoscopic and robotic procedures as the facility of unedited recording is easily built into the equipment. this information can easily be stored as well as transported for peer review.

c) Partnership: Various stakeholders need to collaborate to achieve success in surgical innovation. A surgeon with an interesting idea should be able to access appropriate help within the industry to develop new technology. Associations such as the Indian Institute of Technology can provide knowhow in materials and engineering to facilitate innovation and forums for interaction between diverse specialities need to be regularly held. The huge divide in healthcare isn India is evident. The vast majority of patients are in the public sector wherein innovations are maximally valued in the private sector by the affluent population actively seeking cutting edge technology. It is indeed unfair to use the low cost public sector to develop expensive technology accessible beyond clinical trials only by the wealthy few. A public private partnership can be worked out wherein even the poor can benefit with provision of this technology at subsidised rates, reducing the need for expensive disposables and development of low maintenance devices for less accessible areas of our country.

d) Involvement of Medical Associations : Cooperation between a large number of surgeons belonging to a scientific body is essential to enable good recruitment and conduct of surgical trials in a real world environment. Professional associations need to set up databases and prioritise research ideas to get such professionals together to address the lacunae in their field. Professional bodies would also be able to set their own guidelines in an attempt to maintain a uniform standard of quality care and also formulate guidelines for absorption of novel technology into standard practice. The National Cancer Grid [17] is an excellent example of this effort. Funded by the Department of Atomic Energy, the grid hopes to standardise cancer care across the subcontinent and proved a platform for collaborative trials. Workshops on protocol development conducted by senior faculty would ensure research is of high quality and a stamp of approval from the National Cancer Grid would also facilitate funding.

e) Strong regulatory guidelines: To ensure good quality ethical research a strong and fair regulatory environment is essential. Regulatory mechanisms are finally being put into place. The Medical Devices Rules 2016 and the new Drugs and Clinical Trials Rules 2018 provide well defined guidelines for ethical conduct of clinical trials and patient protection. The development of a structured registered Ethics committee to oversee protocols and monitor these trials should ensure patient protection as well as good science. The Clinical Trials Registry of India (ctri.nic.in) ensures that protocols are freely available for all to see what trials are being conducted. Further the protocol presented cannot be subsequently tweaked at the time of publication ensuring good science. Negative studies, even if not published can be visible to all, preventing unnecessary duplication of futile research.

f) Punitive measures also need to be strong ensuring compliance to principles of good clinical practice. Strengthening the regulatory authorities and arming them with measures to tackle offenders is essential for effective policing of research.

In summary, there are many problems facing the surgeon attempting to conduct a well designed ethical clinical trial. Regulatory guidelines are changing in the country. With the increasing involvement of professional bodies and co-operation between various professional groups, the government and industry, the future is possibly brighter for the conduct of quality surgical trials.

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