ETHICS OF SURGICAL RESEARCH IN TANZANIA

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Summary

Surgical procedures have often been introduced into practice without rigorous clinical research to check on safety and proof of cost-effectiveness as is done when researching on a new drug. This is because clinical research involves an inherent tension between the ethical values of pursuing rigorous science and protecting participants from harm. The latter may be particularly challenging when surgery is involved. However, clinical trials are unethical if they are not designed to answer valuable scientific questions with the use of valid research methods. In addition to having scientific merit, clinical trials must present a favorable risk–benefit ratio: the risks to participants must be minimized and justifiable by the benefits to them, if any, and the potential value of the scientific knowledge to be gained from the study. It is also essential that investigators obtain informed consent from participants and have an ethical responsibility to act in their best interest.

A randomized, controlled clinical trial carried out in the surgical field, is not a form of individualized surgical therapy; it is a scientific tool for evaluating innovative procedures in groups of surgical research participants, with the aim of improving the care of similar patients in the future. Such clinical trials are not designed to promote the best interests of enrolled patients and may expose them to risks that are not outweighed by known potential benefits. Furthermore, the use of placebo (sham) surgery in controlled clinical trials has been controversial resulting in a lot of debate because the fundamental ethical principles of beneficence and non-maleficence appear to be violated. Patients could be exposed to complications of surgery with no prospects of possible benefits. It is therefore imperative that the use of placebo surgery must be evaluated in terms of the ethical principles appropriate to clinical research. As technology is expanding and health care resources becoming more limited, surgeons are compelled to evaluate surgical procedures and technology to ensure they are safe and effective.

In conclusion, trials of surgical procedures including those involving the use of placebo surgery whenever required, should be conducted before new surgical procedures become standard treatments, provided that these trials meet the ethical requirements that are appropriate for clinical research. These ethical issues and requirements in surgical research and their relevance to a developing country like Tanzania is discussed in this paper.

Key words: Ethical, Surgical Research

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Introduction

Ethical considerations in biomedical and surgical research are becoming increasingly important for the academic surgeon. With advances in surgical technology taking place especially in the developed world, the new knowledge and understanding will raise some critical and unique ethical concerns. However, in a developing country like Tanzania, economic hardships and lack of technology make it very difficult for our surgeons to match progress being made in surgical research in developed countries.

Yet research remains a pivotal part of an academic surgeon's career and, in striving for success, surgeons face the pressure to "publish or perish". Consequently, there is a danger of violating some ethical principles including fabricating results. Inadequate funding of a study may force researchers to behave unethically by only considering positive findings and ignoring ambiguous or inconclusive data. Similarly, research residents are often compelled and rewarded by their supervisors for producing manipulated results without scrutinizing the methodology used in the research project. Like any scientist, a surgical investigator should be cognizant of the ethical issues associated with researching on a new technology and not leave such considerations only to philosophers or ethicists.

Some institutions tacitly allow the use of new surgical procedures in series of patients without informing individuals that they are participating in a scientific study, as long as no written protocol or hypothesis exists and the study has not been submitted to the scrutiny of an ethics or institutional review board. This jeopardizes patients' rights and risks losing public confidence in how biomedical research is conducted. Though enforcing more rigid and less ambiguous guidelines of human research may curtail enrolment into some studies, it will also protect patients from being used as subjects without their knowledge. It is also true that the inconveniences, administrative problems and bureaucracy in preparing and getting approval for a randomized controlled trial together with pressure of hospital beds and operating time discourages surgeons from going through the process. In a survey, 61% of surgeons in the USA felt their patients could not be enrolled in

randomized controlled trials for reasons including the surgical condition being uncommon; there was no community equipoise and patient preference.[1]

This review attempts to discuss and highlight areas that are important regarding ethics in surgical research to guide Tanzanian surgeons to do their clinical research in an ethical manner. Surgical research in Tanzania is minimal partly due to shortage of surgeons in the country who are busy in their clinical work. This paper also reviews ethical issues concerning endoscopic surgery, as this will be increasingly performed in Tanzania. Use of sham surgery controls in randomized clinical trials, which is a topic of considerable ethical debate in the current medical literature, has also been addressed briefly.

Experimental Surgery

Experimenting an innovative surgical procedure can be challenging and differs from experiments involving new drugs for treatment of medical conditions. In the latter situation, in case of an adverse event, the drug can be stopped and the medical therapy changed but in surgery it may not be possible to reverse an innovative surgical procedure. It follows that surgical patients must exercise considerable trust in their surgeons when consenting for an innovative surgery. The procedure will often be carried out with the patient unconscious (anaesthetized) and it is therefore essential to obtain patient's prior written consent to preserve autonomy and fulfill strong moral and legal obligations. "Informed" (valid) consent assumes that adequate information has been given to the patient to make a rational decision as to whether to undergo the innovative surgery. However, sometimes due to lack of modern diagnostic facilities in the majority of hospitals in Tanzania, a surgical patient cannot be given all the facts pre-operatively. Frozen section biopsy facilities are usually not available to assist intra-operative decision when required. To overcome this dilemma for the surgeon it is appropriately added on the consent form that "the surgeon can perform any other procedure that may be found necessary during the operation only pertaining to the surgical condition being dealt with".

Prospective randomized controlled trials (RCTs), commonly used in testing new drugs, have also been used in surgical trials. These involve "blinding" the researcher and participants and have revealed significant placebo (non-specific) effects of surgery.[2] There are various methods of "blinding" in surgical trials, the simplest being to compare two surgical procedures done through similar skin incisions so that no difference is noted externally. An example is the placebo (sham) operation whereby in the late 1950's the internal mammary artery was tied behind the ribs to test whether it would give relief to patients with angina by diverting blood to the heart.[3] A physician who did not know which operation had been done assessed the patients and found no difference between the two groups. The surgical procedure was subsequently abandoned. Ethical issues related to sham surgery will be discussed in a separate section.

Another surgical research double-blind placebo intervention study involved laser treatment and endoscopic assessment of Barrett's oesophagus-a premalignant change in its lining.[4] As the risk of endoscopy is minimal, blinding in this study was ethical and patient autonomy was preserved. To ensure the study was ethical, those falling in the placebo group were also promised that they would receive the treatment if it proved to be effective, the only disadvantage being that the treatment would be delayed.

Other blinding methods used in surgical trials include making use of different incisions that can be concealed from patients and assessors by applying the same dressings over the wounds for example when comparing laparoscopic with minicholecystectomy.[5] Assessors can also be blinded for example when wanting to adequately assess symptoms following a surgical with a non-surgical treatment for the same condition like in gallstone disease as when lithotripsy was compared with open cholecystectomy.[6]

Apart from controlled trials to assess surgical therapies, surgical research can also be done in the immediate postoperative period and if the study is not part of the operation, separate consent must be obtained prior to surgery. Obtaining consent in the postoperative period is not appropriate as the patient may not be in the right state of mind being under the influence of analgesics and/or sedatives. Similarly any intraoperative research like physiological studies often being done by anaesthetists requires obtaining a separate consent from that for surgical treatment. When surgical research involves removal of tissue or taking a specimen that is not part of the operation, this too requires a separate consent.

Endoscopic Surgery

Endoscopic surgery has been largely accepted by patients and surgeons, however, there are some ethical issues that need to be addressed. Financial constraints of a developing country like Tanzania impose a burden that calls for a strong conviction, determination and commitment to one's belief in the benefits of endoscopic surgery. It will of course not be available to the majority of the population who need it, as they will not be able to afford the costs. Elsewhere in the developed world and nowadays in some developing countries like India, this minimally invasive surgery has been promoted with great intensity through the influence of the media, aggressive entrepreneurship of instrument manufacturers, patient demand often based on distorted information and advocacy by enthusiastic surgeons. These are of ethical concerns and need to be handled appropriately as endoscopic procedures get popular in Tanzania. Though the results of laparoscopic cholecystectomy have been very encouraging, it is imperative for surgeons in developing countries to evaluate and decide which endoscopic procedures will give real benefit to their patients as compared to the open procedure in terms of safety, efficacy, applicability and cost-effectiveness; in other words to differentiate what is truly beneficial surgery for the patient from the one done just for the sake of enthusiasm of the performing surgeon. As surgical scientists with altruistic principles, every

endoscopic procedure must be evaluated and appraised not in terms of enthusiastic or even euphoric personal achievement, but rather as a pragmatic clinical study as it applies to our own conditions. Endoscopic surgery differs from conventional surgery as the latter offers wide exposure, tissue contact, binocular vision and the use of traditional equipment. Endoscopic surgery requires specialized training, which unfortunately has hitherto in other countries been imparted as a 'crash course' to surgeons in active practice, unlike the training in conventional surgery over four or five years based on the traditional principles of hands-on apprenticeship as laid down by William S. Halsted. It is recommended that a formal training in endoscopic surgery should be incorporated in the ongoing comprehensive, surgical residency program in the respective teaching hospitals. This prolonged hands-on apprenticeship combined with trainer model and diagnostic endoscopy, hopefully will be made possible by reduction in the cost of equipment thereby enabling endoscopic surgery to be an integral part of surgical training and a pre-requisite for graduation. In the training program, three essentials are emphasized for endoscopic surgery in developing countries: safety, economy and care of instruments and these are inter- connected.

Surgeons in Tanzania are often unaware of the regulations regarding the ethics of surgical research including new techniques in endoscopic surgery, and will need education about such issues. Obtaining written informed consent for endoscopic surgery, as for any other operation, requires an explanation of the indications, principles and risk of the procedure, as well as the consequences of not undergoing the proposed surgery and discussion of alternative treatments.

The learning curve for endoscopic surgery is steep and initially the risk of complications will be relatively higher, with longer time for the procedure resulting in increased cost. Neugebauer et al[7] concluded that comprehensive surveillance and monitoring of laparoscopic cholecystectomy was the only realistic method with which to assess the impact of the new technology. One should however be aware of the ethics concerning competition between fellow consultants regarding conversion rate, time required for completion of the procedure and discharge from hospital which may put the patients' lives into jeopardy. Another ethical problem to be aware of during the learning curve in our environment is patients who are from the poor social class and would otherwise not afford the costs of the surgery may be exploited and enrolled without proper consent process as surgeons use the opportunity to improve their competence in the procedure.

Endoscopic procedures generally cause less pain, small scars, early discharge and return to work, and require fewer analgesics; indications of selection of patients undergoing such procedures have therefore been expanded, which is of questionable ethics. For example, laparoscopic cholecystectomy for gallstones need scrutiny as only 1-4% of asymptomatic patients with gallstones will develop symptoms or complications of gallstone disease per year. Thus, ultrasound-detected coincidental gallstones require only watchful waiting; surgery is generally not recommended.[8] However, surgeons rarely show patience whenever a patient has an ultrasound report of cholelithiasis. This is now common because of master health check-ups conducted at various hospitals. Disposable endoscopic instruments are costly, however, re-using the instruments may be the alternative and cost-effective. Guidelines for re-use of endoscopic instruments regarding proper sterilisation and maintenance need to be adhered.

Laparoscopy for diagnosis and staging intra-abdominal malignancies avoids the need for laparotomy, however, an ethical issue in this procedure is the incidence of port-site metastases. The smoke created by coagulation contains whole cells which can be carried as an aerosol during pneumoperitoneum and could be a mechanism for tumour implantation.[9] Therefore, intentional coagulation of malignant tissue should be avoided.

The other ethical issue is to regard an endoscopic surgery procedure a "failure" if it has to be converted to open surgery as for bile duct injury during laparoscopic cholecystectomy. Such events are considered as part of surgical practice and surgeons should not be ashamed as long as they occur occasionally.[10]

Informed Consent

Informed consent is an ethical concept that is most relevant to surgery. It is common especially in developing countries to take advantage of a patient's ignorance and not go through the consent process appropriately both in clinical care and research. The ethics of surgical research necessitates all participants provide a valid consent which requires patient capacity, adequate disclosure of information and voluntariness. Capacity is the ability to understand information relevant to decision-making. The enrollment of "vulnerable" subjects — those who may have an impaired capacity to give informed consent or who may be susceptible to "undue inducement" to participate in research should be avoided, unless the study can only be conducted on incapable persons whereby a substitute (or proxy) consent is obtained. Disclosure refers to the provision of relevant information to the patient and his/her comprehension. Providing both written and verbal information in a language best understood by the participant enhances comprehension. Most surgical research carries more than minimal risks, so the requirement for careful disclosure of these risks to potential participants is generally stringent. Voluntariness refers to the freedom of a person to make a treatment decision without coercion or manipulation. In specific circumstances related to emergency research, the research ethics committee can justify consent waiver only if the delay required to obtain consent would prevent the research from occurring and only after prior consultation with the "community" of potential research participants.

To summarize, in a valid informed consent process for a surgical procedure, patients must: (i) be provided sufficient information to make an informed decision; (ii) be competent to give consent; (iii) be aware of the right to refuse surgery; or (iv) voluntarily agree to the procedure [11]. Inadequacy in obtaining consent in many countries is potentially subject to malpractice litigation. At Muhimbili National Hospital

(MNH) in Tanzania, the informed consent form does not contain details of the information that the surgeon has to discuss with the patient. In most hospitals, it is assumed that this has been done[12] and the patient validates the process by signing on the form that he/she has agreed to be given anaesthesia and undergo surgery. The requirements for adequate informed consent are defined much more strictly when patients are asked to participate in a surgical research study. The aim of research is to obtain generalizable knowledge and does not guarantee benefit to the participant in the study. The informed consent form for research is a detailed document specifically written for a particular study and approved by a research ethics committee. Often research participants appear to confuse treatment in the scientific context of clinical trials with individualized medical care. Sometimes they overestimate the benefits of participation in a trial and underestimate the risks. These deficits in understanding make it difficult to obtain meaningful informed consent.

Apart from time constraints in busy academic institutions[11,13] including MNH, the consent process is also not optimally conducted due to inadequate understanding of surgical procedures. Such shortcomings have also been reported in Great Britain[14] and in the USA.[15] Surgical residents need thorough education on communication skills and operative procedure risks, on the benefits and alternatives to surgery in order to improve their competence in obtaining consent. Furthermore, it is deplorable to observe that due to patient ignorance and the generic nature of the informed consent form, surgical ward nurses are also allowed to obtain informed consent by witnessing the patient's signature on the form/document without appropriate explanations. Surgeons are still treated with such high respect that even if uneventualities occur, it is considered to be God's will.

Sham Surgery in Randomised Controlled Trials

Randomised double-blind placebo-controlled trials (RCT's) have been considered as the gold standard design in biomedical research and evidence-based medicine. Randomised controlled sham surgery is designed to control the placebo effects of surgery and to eliminate other forms of bias. Use of sham surgery or surgical placebo in randomized clinical trials has, however, stirred ethical concerns associated with use of control (sham) groups. Horng and Miller[16] identify three key ethical questions in placebo surgery: "First, is placebo surgery compatible with the ethical requirement to minimize risks? Second, are the risks associated with placebo surgery reasonable and justifiable in relation to the potential value of the scientific knowledge to be gained from its use? Third, can informed consent be obtained for a trial that randomly assigns patients to undergo genuine or placebo surgery?" Contrary to a placebo-controlled medical trial, the control group in sham surgery trial, apart from forfeiting the possible benefits of the innovative treatment is also exposed to additional risks of the placebo procedure, which can jeopardize the risk-benefit ratio of the clinical trial. Examples of sham surgery controlled trials include the arthroscopic treatment of osteoarthritis of the knee[17], and intracerebral fetal tissue grafts in Parkinson's disease.[18,19] The latter has raised much ethical debate as to the necessity of a sham surgery control arm. Freed et al[19] did not use general anaesthesia and immunosuppressive agents in either arm thereby minimizing risks involved. Significant placebo effect of sham surgery was noted in the initial months after the procedure.[20]

Debating in favour of sham surgery in clinical trials, Freeman et al[18] deplored the common practice of introducing surgical techniques into clinical practice without thorough evaluation resulting in patients being exposed to significant risks with no benefit achieved while consuming valuable societal resources. They recommended three criteria which are essential before a randomized, double-blind, placebo-controlled trial is done: (i) It should address an important research question that cannot be answered by a study with an alternative design, which poses a lower risk to the subjects. (ii) There must be preliminary but not conclusive evidence that the intervention is effective, and (iii) The treatment should be developed to the point where it is unlikely to become obsolete before the study has been completed. Supporting sham surgery controls, Albin[21] pointed out the problem in sham surgery is not tension between the highest standard of research design and the highest standard of ethics as proposed by the bioethicist, Ruth Macklin [22], "the problem is tension between obligations to individual research subjects/patients and obligations to the larger group of patients and the general public". An example is Beecher's[2] comments on sham surgery controlled trials of internal mammary artery ligation for treatment of angina, "a properly constructed study spared thousands the risks of unnecessary surgery". Macklin [22], however, rightly points out the inherent difficulties in assessing risk/benefit ratios and reliance on the doctrine of informed consent as a convenient escape from the ethical dilemmas raised by sham surgical controls. The informed consent process may be jeopardized by the so-called "therapeutic misconception" whereby desperate subjects have unrealistic expectations about benefits of research participation.

Five criteria for use of sham surgery controls have therefore been recommended[21]:

(i) All the general standards for ethical conduct of clinical trial as described by Emanuel et al[24] must be satisfied. These include value, scientific validity, fair subject selection, favourable risk-benefit ratio, independent review, informed consent and respect for potential and enrolled subjects. (ii) It should be well documented that there cannot be reasonable alternative research designs to exclude placebo effects of surgery or other forms of potential bias.(iii) The sham surgery should be constructed in the best way to minimize the risk-benefit ratio. (iv) Subjects enrolled should be the minimum necessary, with emphasis on careful biostatistical formulation of the trial with reliable estimates of power and sample size needs. (v) As required in any clinical trial, there should be an active, independent safety monitoring board which can stop the trial whenever necessary.

Surgical research requiring sham controls can be a possibility in Tanzania when surgery is being undertaken with a high degree of skill and all ethical requirements are met.

Conclusion

All efforts should be made to encourage surgical research in Tanzania and to ensure appropriate ethical standards are met. As surgical research gains momentum in Tanzania, a protocol on experimental surgery made available will guide surgeons on the scientific and ethical issues to evaluate new procedures. Partnership and honesty between surgeons and the participants in the research is essential to achieve scientific progress and help future patients. It is essential to design the study carefully including the statistical aspects and participants should be clearly told all the facts including risks involved and alternative procedures and then requested to give consent voluntarily. By doing this the ethical principles of beneficence and non-maleficence, autonomy and justice will be achieved. The lessons learnt in the US from the human radiation experiments and the Tuskegee syphilis studies prompted an advisory committee to propose 6 basic ethical principles[24] that should be adhered to: (i) one ought not to treat people as a mere means to the end of others, (ii) one ought not to deceive others, (iii) one ought not to inflict harm or risk of harm, (iv) one ought to promote welfare and prevent harm, (v) one ought to treat people fairly and with equal respect, and (vi) one ought to respect the self-determination of others. Scientists of the future must maintain a clear understanding of their duties to human subjects and the leaders of their fields value good ethics as much as they do good science.

Acknowledgement

I would like to sincerely thank Prof. Solly Benatar of Bioethics Center, University of Cape-Town, South Africa for his useful comments.

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