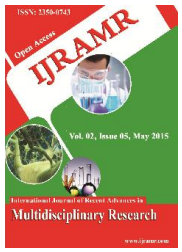

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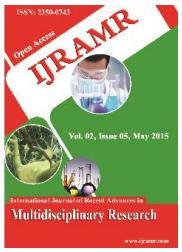

Research Article

GASTROINTESTINAL AND SURGICAL SPECIALTIES: CHALLENGES IN CLINICAL RESEARCH

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ABSTRACT

Background: The quality of a clinical research can be improved, and it´s results can become of a greater value, by exploring the advantages of the randomized controlled trial. This method has become widely explored in research trials given the concept that it is the only valid method that can ensure the results when comparing treatments. In some areas of knowledge, the use of only randomized controlled trial methods can present obstacles. Such studies must be approached with other tools to avoid doubtful bias and outcomes. To review the real advantages of randomized controlled trials in assessing surgical trials, to discuss the methodology challenges and conduct of these surgical studies, as well as to propose and orient possible solutions and options for these studies.
Discussion: In many instances, while planning a randomized controlled trial, ethical questions surrounding the trials are encountered. In most cases, the theoretic advantages of randomized controlled trials, when compared to other study designs, do not represent a visible superiority, in cases such as experimental studies that compare estimated side effects in certain treatments. In these cases, the randomized controlled trial superiority as a method should not be regarded in such an axiomatic form.
Summary: In our study, we show all the tools available methodologies for research, trying to teach and educate new researchers and assist those in usual researchers conducting studies in the area of surgery. This can bring greater reliability to studies in surgery.

INTRODUCTION

Background

The quality of a clinical research can be improved, and it´s results can become of a greater value, by exploring the advantages of the randomized controlled trial (RCT). This method has become widely explored in research trials given the concept that it is the only valid method that can ensure the results when comparing treatments. In some areas of knowledge, the sole use of RCT methods can present obstacles. Such studies must be approached with other tools to avoid doubtful bias and outcomes.

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In many areas the use of RCT can bump into ethical questions that surround these trials. In most cases, the theoretic advantages of RCT, when compared to other study designs, do not represent a visible superiority, in cases such as experimental studies that compare estimated side effects in certain treatments. In these cases, the RCT superiority as a method should not be regarded in such an axiomatic form. Ethical principles and codes of conduct in medical practice are millennial. The Code of Nuremberg has brought and consolidated ethics in modern medicine. It is composed of principles, laid down by lawyers, resulting from Nazi research methods throughout World War II, when great atrocities against human beings were committed. The Code brought to light important procedure questions to clinical research. Some of the guidelines include voluntary informed consent, properly formulated experiments, and prohibition of coercion, ethical approach principles and beneficence towards participants.

The Code of Nuremberg was ratified by the World Medical Association's Declaration of Helsinki in its last review. The objective of this article is to review the real advantages of RCT in assessing surgical trials, to discuss the methodology challenges and conduct of these surgical studies, as well as to propose and orient possible solutions and options for these studies. A good quality study design for a RCT must have a high internal validity and an acceptable external validity or generalizability. We should stress that the external validity will be useful provided that the internal validity of the trials is maintained. The ethical matter is an important point regarding every clinical trial and in many cases can constitute an obstacle for surgical trials (McDonald *et al*., 2010; Peter McCulloch *et al*., 2002 and Wolf and Buckwalter, 2006). The western biomedical ethic principles that also define ethical guidelines in research are guided by four key principles (McDonald *et al*., 2010):

1.Respect of autonomy; the capacity of every person or legal guardian, inherent to every human being, to have the right to choose and decide;

2.Nonmaleficence; "avoid causing harm or *primum non nocere*";

3.Beneficence; Ensure that the actions and benefits of the trials are for the well being of the patient, after checking for and weighing in eventual risks and harms;

4.Justice; The patient´s treatment must be based on the equilibrium of the risks and the costs;

Barriers in the development of randomized control trials in surgery are evident, such as commercial questions and the valorization of personal prestige. One example is found in abdominal's laparoscopic surgery, where the sales of new disposable surgical materials by the industries, which, sometimes, try to suggest use of there own materials. Other situation occur when surgeons not teaching there knowhow of new techniques and leading to an increase in damage in surgeries. However, only two randomized trials were conducted during this time. Other limiting factors are the technical difference and quality in multicenter studies, the need to alter the intra-operatory technique due to intra-operatory findings, emergency, etc. (McDonald *et al*., 2010). Another relevant issue in surgical trials is the patients' rejection to being drawn to a non surgical treatment group, leading to important dropout and bias. In some areas of knowledge, the use of only RCT methods can present obstacles. Such studies must be approached with other tools to avoid doubtful bias and outcomes.

DISCUSSION

Defining the best surgical research

The medical advances in the last two decades, including surgical specialties, which have shown new techniques and surgical materials, led to an increasing need of RCT in surgery field (McDonald *et al*., 2010). This has very much contributed to what can be referred to as surgeon´s equipoise in RCTs. Differences in surgical practice increases the difficulty in assessing and obtaining research results, when subjected to the rigor of the Ethics Research Board (ERB) (McDonald *et al*., 2010 and Peter McCulloch *et al*., 2002). Authors recommend that every study that involves new technology should be researched with a RCT and subjected to (ERB) (McDonald *et al*., 2010; Bernstein and Bampoe, 2004 and Margo, 2001). Assessment of recent RCT surgery studies have shown that ethical criteria are valued in prospective studies (over 92% in ERB reviews), but rarely used in retrospective trials (28-30%) (Margo, 2001; Block *et al*., 2006 and Reitsma and Moreno, 2002). Perhaps, the best definition for a surgery study is a randomized prospective trial, based on ethical principles, should it involve human beings or animals, along with an observational study, an effective tool for surgical studies. Regarding retrospective studies, the best tool for the job might be a Survival Analysis for its use in objectifying outcomes and preventing bias. In many cases, the validation (clinic and statistic) of a new surgical procedure occurs after a retrospective study (McDonald *et al*., 2010; Wolf and Buckwalter, 2006; Reitsma *et al*., 2002).

Randomized trials in surgery: problems and obstacles

The history of the development of the field of surgery, taking in account how new surgical approaches were "discovered", many times in a tactical operatory chance, is extremely unfavorable to the validation of surgical trials by RCTs (Peter McCulloch *et al*., 2002 and Wolf and Buckwalter, 2006). In many cases, the advantages obtained with surgical treatment are so obvious that a randomized study with a placebo group could be understood as unethical. Historically, surgery researches are made unfeasible due to the qualitative and quantitative limitation of randomized studies in surgical techniques (Peter McCulloch *et al*., 2002; Wolf and Buckwalter, 2006).

Lack of infrastructure conditions

This can be one of the largest problems concerning the feasibility of a surgical trial. The lack of resources can generate many obstacles regarding the infrastructure that covers proper experienced personnel in data collection, the capacity of the clinical trial coordinator, and patient monitoring (McDonald *et al*., 2010; Peter McCulloch *et al*., 2002 and Mphil *et al*., 2010). Rare cases, urgent surgical cases and life-threatening cases: In literature review, studies of low incidence disorders and in those regarding new surgical approaches in comparison to previous treatments shows a number of challenges, such as the necessity for faraway experimental studies, large sample sizes, cost of new equipment and material, for instance, new surgical approaches with the use of a robotic instrument (McDonald *et al*., 2010; Mphil *et al*., 2010 and Wolf and Buckwalter, 2006). Emergency surgeries usually occur when the surgical staff and the surgeons involved in the trial are absent, which inevitably leads to the patients exclusion from the research. In many cases, when regarding emergencies, with the intention of preserving life and taking action in this sense, the technique used must be changed (McDonald *et al*., 2010 and Solomon and McLeod, 1995).

Learning curve

Many researchers orient that RCTs on new surgical techniques or technique enhancements should start off with the first

operated patient. However, surgery, in a broad sense, are complex procedures and a new technique or the enhancement of one, demand training, for the improvement of conditions in an procedure technique demands it. Therefore, during the period of the learning curve, errors and adverse outcomes are frequent. Aside from the already mentioned aspects, performing a randomized study with two groups of patients, where the matter at hand is the comparison of a consolidated technique and a new method in surgery, can permit bias (Bonenkamp *et al*., 1995 and Bonekamp *et al*., 1999).

Systematic Error

Systematic error is an error that is not determined by chance but is introduced by an inaccuracy (as of observation or measurement) inherent in the method; it could lead to a false statement. A tangible example is a study that compares the survival rates of a surgery and the quality of life of patients. The results end up being completely different, what makes this estimate with bias and biased toward the null value. This occurs more frequent in surgical interventions that have a small to moderate sample size. In these cases, in order to minimize bias it is vital to take part from the very beginning in the trial´s planning. The use of randomization, the concealment of allocation, blinding study, complete follow up and the use of intention to treat principle can minimize systematic error. Therefore, the sample size calculation (check of power analysis) is important to minimize random error (Cadeddu *et al*., 2008; Devereaux *et al*., 2005; Devereaux *et al*., 2004 and Lilford *et al*., 2004).

Differences in Development and Research

Development of any long standing form of treatment, in most cases, corresponds to small modifications in medication or in surgical method. However, the RCTs in these areas represent a high cost and doesn´t justify a study in which these minor changes show little or no difference in treatment. Although RCT can be used in some of these cases, it is possible that the outcomes are not accepted for publishing. The RCTs are indicated and appropriately conducted when important technological or therapeutic goals have actual chances of being reached (Peter McCulloch *et al*., 2002; Tunevall, 1991 and Cadeddu *et al*., 2008). For other studies based purely on small alterations, even ethical questions can be motives for refusal.

Types of RCT in surgery

Type 1 trials: standard RCTs are based on the comparison of clinical treatments on surgical patients. They represent in average 70 - 75% of surgical trials.

Type 2 trials: are those which are aimed at comparing surgical techniques.

Type 3 trials: This trial is used to compare long standing surgical procedures to non surgical treatments (Cadeddu *et al*., 2008; Devereaux *et al*., 2005; Devereaux *et al*., 2004; Lilford *et al*., 2004 and Ramsay *et al*., 2001).

Options of statistic model to perform surgical trials

Conducting a RCT in surgery in most cases is impossible. The variables that involve patients oriented for surgical treatment, such as co morbidities or underlying diseases can bring serious complications, intra-operatory emergency, and scarring problems, influencing outcomes, through bias, as sampling bias of external validity or generalizability. Some study options are available with the intent to reduce such events.

First Option*: Using another outcome – quality of life – and a simpler analysis method (ANOVA or linear regression model)*

In some cases, the choice for a simpler analysis method can allow an easier interpretation. The Analysis of Variance (ANOVA) is a selection of statistic models used to assess differences between two distinct groups. It can be used in continuous and normal sampling, and if the study has more than two groups. The use of outcome – quality of life — can guarantee the study, using a quality life scale such as the SF-36. The Quality of Life Score can compare two distinct groups using the ANOVA model or a regression model in case the researcher needs to adjust covariates (Olschewski and Scheurlen, 1985 and Torgerson *et al*., 1996). In surgical trials, although the use of death (survival) as an outcome to try to improve the validity and avoid bias, sometimes a long term follow up is necessary and it makes the study unviable in a economic point of view due to an increase in dropout (Cox *et al*., 2000 and Box, 1954).

Second Option

Survival Analysis and Comparing two groups using nonparametric test (log rank test or Mantel-Cox test). In cases of asymmetric distributions, researchers try to use tests that don´t depend on the distribution of population groups, they are called nonparametric tests. When converting numbers to ranks or the differences in these numbers to positive or negative signs, the nonparametric tests become inferior to parametric tests when assessing population differences. Nevertheless, these tests are relatively simple in order to; for example, outline the outcome of a study where the rate of the event (for instance, death) has a similar tax rate. When there is a suspicion of Gaussian distribution, the nonparametric test is indicated. Among statistic nonparametric tests for ordinal data, we can mention: Wilcoxon Signed Rank Sum test, Mann-Whitney U test, Friedman test e Kruskal-Wallis test. As usual, we must maintain criteria from two or more groups and the use pairing, or not (Ulysses, 1999 and Box, 1954). When defining an outcome, for instance, the rate of death in a determined surgery, researchers can show the rate of survival using Kaplan Meier curves and then compare both sampling groups using the Longrank test method, which is a nonparametric test similar to the chi-square test (Fisher´s exact) (Jump up Harrington, David 2005 and Jump up Schoenfeld, 1981).

Third Option: Adjusting for covariates using survival and Cox proportional model

In many studies that involve surgical expertise, the surgical techniques employed don´t change, despite many other intra-operatory conditions (anesthesia equipment, anesthetics, quality of equipment and surgical materials), as well as post-operatory conditions represent covariates for the surgical study. In statistic analyses clinic researches, the covariate is a variable that can possibly predict the outcome. In these cases, the Cox Regression model (analysis) is useful to construct a predictive model to adjust the time-to-event data. This model can

replicate a survival function to predict the probability that the event of interest occurred in a specific *t* for those predictor variable values. The coefficient of regression for the predictors can be estimated from subject observation and be applied to new events in a study that have physicians to analyze the predictor variables (Everitt, 2002; Hosmer and Lemeshow, 2000 and Lin, 2000). For instance, in a study demonstrating the existence of different risks among smokers (both sexes) subject to the same lung cancer surgery. To build a Cox Regression model using the cigarettes (e.g. number of cigarettes smoked per day) and gender as covariance, the hypothesis related to the effects of smoking and age can be tested using the time-to-onset for lung cancer surgery. A very important confounding factor for surgery research is based on surgery indication. Many important variables can be spread out randomly among groups, which tend to be one of the main problems regarding observational studies. A confounding variable is a variable strange to the statistic model that has a positive or negative relation with the dependent or independent variable of the study (Hosmer *et al*., 2000; Lin, 2000 and Schulz and Grimes, 2006).

Propound Solutions

***Evidences in History*:** A good review of existing evidence on technical aspects on the surgery that is the object of the study must be done in order to learn the technical differences and advantages, or disadvantages, of the new surgery or the alternate treatment.

***Commercial competition and prestige*:** Commercial competition and prestige are factors that should least of all influence or obstruct the ongoing of a scientific research. A specific company as a research financer can be a great influence for bias.

***Lack of funding*:** In this topic, the different cultural situations of each region should be valued. It is also important emphasize the cooperation between the different study groups, universities and industries. In this sense, it is possible to attract more funds to finance trials and bring closer a larger and more involved group that culminates in an effective and thorough research. The greater the capacity to require and attain funding, the greater the infrastructure suitable for the study (Peter McCulloch *et al*., 2002; JAMA, 1995 and Vogelzang *et al*., 1995).

***Urgent and life threatening situations*:** In surgical trials, emergency surgeries end up being performed by medical doctors on duty in the ER, possibly casing external influences to the outcome due to a change in surgery technique during operation in case of emergency or complementary findings, with the intention of saving the patient´s life (Bonenkamp *et al*., 1995; JAMA 1995; Vogelzang *et al*., 1995 and Olschewski and Scheurlen, 1985).

***Rules to determine the intervention, model of pathological specimen*:** The type of surgery, it´s technique and intra-operatory tactics should be determined, if possible even drawn up and digitalized step by step, not only to serve as a model, but to be used as documentation in the paper resulting from the study. In order to pre-determine how the surgical specimen will be identified in parts, photographic and cataloging documentation make up an important factor to controlling the ongoing of the current research (Peter McCulloch *et al*., 2002; Mphil *et al*., 2010; Cadeddu *et al*., 2008; Devereaux *et al*., 2004 and Vogelzang *et al*., 1995).

***Recruitment*:** In surgical trials, the sample size predetermination is, in many cases, a complementary challenge. Firstly because we are dealing with a surgical approach, and secondly because most of the time the research involves new or rare scenarios in medical literature. Therefore, decades are needed to finalize sample size, for instance, in a study that compares advantages between laparoscopic and conventional surgery on children with Hirschsprung´s disease or in a study that compares surgical video laparoscopy with conventional surgery in cholecystoduodenal fistula (incidence of 1%). One of the best options to increase the recruitment of patients is to perform a multicenter trial. A multicenter trial of a rare disorder can raise the sample´s heterogeneity, which can contribute to the applicability and the generalizability of the surgical trial (Csimma and Swiontkowski, 2005 and Thoma, 2005).

***Surgeon and Patient Preferences*:** The surgeon's personal preference for a specific surgical procedure or for a specific operatory tactic can influence in a negative way the trials validity by increasing dropout and risk of bias, so can a patient´s preference for a specific treatment approach (mac Dermid *et al*., 2006). The surgeon´s or patient´s preference for a surgical procedure, for instance, and it´s very common nowadays, laparoscopic or conventional surgery, has caused a 45% drop out of all eligible patients in Australia Laparoscopic Colorectal Cancer Groups study (Mphil *et al*., 2010 and Abraham *et al*., 2006). Conducting a pilot study is an important for surgeon and researcher training; it can also demonstrate the possibility of the same surgical result among different techniques to the patient and bring forth acceptable degrees of pain and esthetic results, provided there is surgical access accuracy and analgesia support. Therefore, by using these resources, factors that affect feasibility such as recruitment issues, follow-up, surgeon and patient preferences can be attenuated, and collateral events and eventual anticipated designs or surgical problems can be clarified. What must remain clear is that a pilot study can´t be used to answer the research question, but it should be used to help demonstrate or to refine previous hypothesis (Becker, 2008).

Minimizing Threats to Validity in Surgical Trials

To achieve a good trial, the research designs should minimize alternate plausible explanation to the hypothesized cause-effect relationship (remember the three conditions that must be identified: co variation, temporal precedence and no plausible alternate explanations). However, different forms of hypothesis can be prepared, excluding or reducing the differences in design. Here are three steps to minimize validity threats: (Trochim and Land, 1982)

DISCUSSION

If a potential threat to validity is appointed, the first step is to ensure that it doesn´t threat the study at hand. Such discussion can take place at the beginning or at the end of the research,

but the decisions made beforehand are effective and acceptable. For instance, stating that the surgical instrumentation can influence the ongoing and the results of the surgery. In this case, the staff handling instrumentation should have previous training for the study or the pilot. One argument could be to demonstrate that in past surgical studies this did not represent an invalidation factor nor did it alter the result. However, there is one argument that must be avoided in trial discussions, making use of the following methods (Jurs and Glass, 1971; Trochim and Land, 1982 and Trochim, 1982).

Observation period: In most cases, surgical trials are complex due to the surgery itself, the post-operatory observation period for result evaluation, as well as eventual sample loss due to already mentioned motives. Complex designs should permit a longer observation period as well as proper training to those involved in the team, and retraining if necessary (Schulz and Grimes, 2006; Lin, 2000 and Trochim and Land, 1982).

Observation or Measurement: Surgery studies face great difficulty due to the impact of low frequency rates of events in research. A light must be shined on the apparent difficulties in sample-size calculation. The use of real-life clinical scenarios methodology, altering baseline event rate and reducing relatively the event rates (Bonenkamp *et al*., 1995).
There are three kinds of observational studies:

• Prevalence Survey or Cross-Sectional Study
• Case Control Study
• Prospective or Retrospective Cohort Study

Summary

In our study, we show all the tools available methodologies for research, trying to teach and educate new researchers and assist those in usual researchers conducting studies in the area of surgery. This can bring greater reliability to studies in surgery. Trials in surgical areas are a constant challenge to researchers. A great trial obstacle has been the constant need for a large sample group. Another obstacle is sample randomization, for most patients, as well as their families, become reluctant learning that the chance of falling into a clinical treatment group and not a surgery group relies only on a lottery draw. This leads to patient dropout during the surgery trials. Surgery researchers should defend and ensure trials based on a concrete objective, in a prospective fashion, with a large sample size, and preferably based on clinical data derived from multicenter studies.

List of Abbreviations

Research's designes

RCT	Randomized Controlled Trial
ERB	Ethics Research Board
ANOVA	Analysis of Variance
ER	Emergency Room

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

EHP participated in the conception and design and drafted the manuscript. ALGS participated in the design and drafted the manuscript. FJCP participated in the design and drafted the manuscript. FPGR participated in the design and drafted the manuscript. FF participated in the design and drafted the manuscript. All authors read and approved the final manuscript.

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Endnotes

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