Evidence for the future – Designing a clinical trial

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ABSTRACT

The quality of the evidence is a keystone in the understanding of Evidence Based Medicine. Randomized controlled trials (RCTs) rank first among the research designs providing clinical evidence. Knowing about the design of clinical trials is not only the cornerstone of clinical research, but also is a requirement for any clinician who wants to learn about new findings of clinical research in his/her field. Many clinicians have good understanding as well as some misunderstandings about the design of clinical trials. This article is going to provide some crucial comments to be considered in conducting RCTs in order to help in production of better evidence for future of urology research through RCTs

Key words: Evidence based medicine, randomized controlled trial, Research methodology

INTRODUCTION

A randomized controlled trial (RCT) is considered as most reliable research method for interventional study that seeks to lead the scientific ideals onto clinical experimentation.1 It is the only effective method known to control selection bias and controls confounding bias without adjustment. Also RCT facilitates effective blinding in some trials; theoretically it seems attractive and many statistical methods assume random assignment. Moreover, RCTs are widely accepted as best level of research to development and evaluation of a new intervention’s safety, efficacy, and cost-effectiveness in comparison with current standards of care. It is account as the cornerstone for most secondary databases like systematic reviews, evidence-based practice guidelines and health technology assessment in clinical practice. For this reason randomized controlled trials have been advocated. Currently less than 20% of current surgical interventions are based on RCTs. Therefore urologists not only need more evidence-based practice but also for increasing the quality and quantity of surgical RCTs. Consolidated standards of reporting trials (CONSORT) was initially recommended in 1996 and updated recently in 2010.2,3 CONSORT focused on sample size, randomization, allocation concealment, blinding, statistical methods, primary and secondary (adverse events) outcomes and overall generalizability of the evidence. Although after systematic reviews, RCTs stay on top of the evidence hierarchy pyramid, there is a big shortage of evidence. Assessing quality of reporting RCTs has gained more attention in literature than assessing quality of design and analysis of clinical trials.4

Only 4% of 4856 articles published in the four leading urology journals from 1996 to 2004 were designed as RCTs. From those only 1% were surgical RCTs.5 Having Recommended the CONSORT statement, the quality of RCT reporting improved, but still, many fundamental problems may threaten the gold standard position of RCTs.2,5 In addition, the strength of RCTs depends on the internal, external and social validity of the study. Most of the published evidences on critical appraisal of RCTs have shown that results of RCTs might be invalid. Randomization, allocation concealment, blinding, and clearly presented statistical methods such as intention to treat analysis and lost to follow–ups are underreported in most studies.5,6 The quality of the evidence is a keystone in the understanding of...
Evidence Based Medicine, and this article is going to provide some crucial comments to be considered in conducting RCTs in order to help in production of better evidence for future of urology research through RCTs.

**A clinical scenario**

A 55-year-old menopause woman comes to the urology clinic with severe stress urinary incontinence (SUI). Physical exam showed urethral hyper mobility with positive stress test without any pelvic organ prolapsed and SUI confirmed by urodynamic study. Pelvic muscle training did not improve her symptoms. She is asking for a minimally invasive method of treatment like trans obturator tape (TOT) surgical procedure. Therefore, you prefer to search for high-quality evidence available for the best intervention.

Burch bladder neck suspension is considered as gold standard surgical treatment for stress urinary incontinence. In our knowledge, gold standard means: An intervention or a test with highest effectiveness and reasonable cost which has been demonstrated in some valid and relevant RCTs. On the other hand an RCT is often considered as the best research design for casualty of an interventional research question. In the following sections we are going to explain what makes an RCT acceptable.

**The disease, the patients**

Usually the researcher is quite confident in choosing a disease or medical condition of interest for conducting a clinical trial. However, it is necessary to have a clear-cut definition especially in case of diseases, disorders, and conditions with controversial or variant definitions. For example if you want to investigate a therapeutic or diagnostic modality on depression among dialysis patients, you need to provide a valid, widely used, and clear-cut definition for depression. Secondly, one should decide on who will be eligible for enrolment. Suppose you want to study the effect of a life style improvement protocol on progression of nephrolithiasis. Nephrolithiasis is a condition that can easily be defined using imaging criteria. But the decision has to be made whether everyone with detectable nephrolithiasis will be eligible for enrollment, or otherwise, some particular eligibility criteria will be applied. The researcher may be interested to limit the study to the symptomatic patients, to patients with previous treatment history, to patients with a given severity of disease, to patients with given educational level, or to patients referred to a particular clinic. The decision depends on several factors. For instance, the investigational intervention may be supposed to affect mild cases better than severe cases or vice versa. This can be referred to as, efficacy factor, which is critical not only in defining the eligibility criteria, but also in selecting the intervention or defining the primary outcome of the study. Many other factors may affect the eligibility criteria; the most popular ones being convenience, budget, and ethics.

In designing a clinical trial the generalizability is usually of lower priority compared to internal validity of the study. Therefore, most clinical trials use a convenient sample rather than a random sample. Obtaining valid results instead, is of higher importance to be ensured in designing a clinical trial. Recruiting consecutive patients visiting a urology outpatient clinic is considered as a convenient sampling method.

**The intervention, the outcome**

The intervention and possible outcomes to be studied should clearly be defined. The efficacy factor as discussed above has a major role also in determining the intervention, its variants, as well as the primary outcome of the study. Although there may be many factors important in deciding which outcome to choose as primary among several possible ones, three most reasonable criteria are; 1-clinical importance 2-objectiveness 3- efficacy. Based on the context and disease of interest, the objectiveness of the primary outcome can be cared for controversially. Regardless of selecting an outcome as the primary outcome, both subjective and objective outcomes are recommended to be mentioned in a clinical trial. Recent studies show that in most interventional studies patient-oriented and reported endpoints are more important than some independent objective testing.

In deciding about the interventions ethical issues have also a major role. In our scenario we are looking for minimally invasive intervention with minimal side effects that improve patient reported outcome and urodynamic parameters in SUI. As the last point in this paragraph, it should be mentioned that, although some researchers have considered slightly different applications of the two terms “outcome” and “endpoint”, generally these can be considered as synonymous. We prefer to say primary endpoint is a measure of primary outcome which is measured to help in gaining primary objective of a clinical trial.

**Controlled study or before-after study**

Assessing the effect of an intervention through a before-after design is also called a clinical trial. This type of study design, especially when only two measurements of outcome are done, may not be strong enough to attribute the change in outcome measure to the intervention. This is because the role of intervention i.e. treatment cannot be separated from natural pattern of disease or from the role of other factors potentially capable of affecting the outcome over the study period.

Adding control subjects who won’t receive the test intervention would be helpful in this regard. So a controlled clinical trial seems to yield more valid results than a before-after study. Yet, due to the role of confounders, a controlled design is not considered as gold standard unless the randomization is done.
Randomization
In a large enough randomized clinical trial (RCT); random assignment of participants to the study or control group, produces comparable groups at the end of the study and ensures that the mere difference between the groups is due to the intervention. It means that each group is a random sample of eligible study subjects, so both are representative of that population. Control of unknown confounders is the valuable but not the sole advantage of randomization.\(^7\)

Method of randomization is dependent on sample size, endpoints, confounding and prognostic factors.\(^8\) Irrespective of the different types and details of the randomization, most researchers prefer to have equal number of subjects in each trial arm. This can be achieved using block randomization method. Block randomization is a commonly used technique to reduce bias and achieve balance in the allocation of participants to treatment arms.\(^9\) Block randomization guarantees the equal number of subjects at the beginning of and frequently throughout the study. It will also ensure low imbalance in number of subjects, at the end of the study or preterm abortion of a controlled clinical trial.

Using stratification with blocked treatment assignments, can also be considered as an alternative to adjusted analyses in order to ensure that the treatment groups are balanced with respect to influential prognostic variables.\(^10\) For instance, equalization of the numbers in the main groups may not be the sole goal in our scenario. Stratifying the allocations according to the severity of incontinence helps to control the treatment effect for the severity of incontinence without conducting an adjusted analysis. However, the rational for widely using stratification in randomized clinical trials has been debated in literature.\(^10\)

As part of the randomization technique, allocation concealment is defined as a method used to implement the random allocation sequence, clarifying whether the sequence was concealed until interventions were assigned.\(^3,10\) After an appropriate randomization, we need to separate the person who generates allocation list from those who access eligibility. In other words, allocation should be concealed by using third-party schemes like: Pharmacy randomization, telephone randomization service, web-based service, and use of sealed and opaque envelopes. This point needs special attention because some people confuse allocation concealment with blinding.

A good RCT have at least two arms; one for intervention and another for comparison, often referred to as control arm. The control arm subjects may be allocated to receive a standard and current therapy, placebo or a sham procedure. If Burch bladder neck suspension is gold standard procedure, you should find some articles confirming the effectiveness of Burch bladder neck suspension compared to the sham surgery. In such a design, a patient who clinically needs a surgery may be put on medication or sham surgery (if ethically permissible). Recently, JAMA published a review of surprisingly equal results of some gold standard surgeries in comparison with sham. Therefore a sham surgery as a control arm of surgical trials will be best method if all ethical issues are followed well.

Blinding
Blinding, or better to say masking, is generally defined as hiding the knowledge of a particular treatment. Application of blinding is after allocation and in procedural phase. So for reducing the emotional effects of the studies, patients have to be blinded about their interventions. However, blinding of surgical techniques in most surgical trials is impossible.

In such situations the outcome assessor should be a separate person and blinded to the therapy.

Ethical issues
Careful attention is needed to be paid on ethical issues in design, conduct and reporting of clinical trials. For example, using placebo as a control for therapeutic intervention may expose some patients to the risks of an ineffective treatment. So it is stated that in case of mild and self-limited diseases or when no treatment is the standard of practice, then a placebo might be appropriate.\(^10\) Another example is to conduct an underpowered clinical trial. This may expose the patients to possible risks of a new treatment as potential efficacy of it cannot be defended due to low statistical power. Moreover, conducting a clinical trial larger in size than necessary, such as in earlier phases of clinical trials, will also be unethical. Planning a monitoring body in clinical trial projects may be another instance for the importance of ethical issues in clinical trials. Aside from what we know about medical ethics, specific principals have also been presented regarding the ethics in clinical trials. These principals include: Collaborative partnership, Scientific value, Scientific validity, Fairness of subject selection, Favorable risk-benefit, Independent review, Informed consent, and Respect for enrolled subjects. We refer the reader to further details as presented by Emanuel et al.\(^11\)

Analysis of clinical trials
There are also some specific points in analysis of clinical trials. Some points carrying higher importance in clinical trials compared to other types of studies are as follows: a priori knowledge and having a preregistered analysis plan and hypotheses, handling of missing data, handling of non-coherence, violations of randomization and use of intent to treat analysis, blinding, strength of association balanced with randomness of association, clinical importance and clinical versus statistical significance, necessity for effectiveness statistics and so on. These topics are out of
the scope of this review and we may discuss them in detail elsewhere.

**Surgical interventions**

Other aspect of surgical trials is learning curve of new techniques which can influence the result of the study. On the other hand, a very late interventional study may lead to an unethical clinical decision. Minimally invasive techniques for SUI are a good example in this subject. Also follow-up time should be long enough in all RCTs. Unfortunately, there is no ideal definition.

For that reason, if during an RCT, researchers find statistically meaningful benefit of intervention, they may stop the study earlier. But recent studies have demonstrated that early stopping of study may super-estimate the results. On the other hand all subjects in both groups should be followed until the end of the study. So the follow-up time has to be long enough and complete.

**CONCLUSION**

To provide and use better evidence in urology practice, there are some crucial points to be considered in designing, conducting and reporting RCTs. Controlled investigation, randomization, blinding, following ethical standards, proper reporting, and selecting appropriate outcomes and statistical methods are the cornerstones in this regard. International standards such as in CONSORT and ICH guidelines are recommended to be followed carefully.

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