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Should randomized trials be the definitive clinical reference?

L'essai randomisé est-il la référence clinique absolue ?

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Article following an invited paper at the French Society of Phlebology Congress in December 2019.

Introduction

If by randomized trial one means the prospective, multicenter, double-blind, randomized controlled trial, then yes, the randomized trial tends to be the gold standard.

All authorities place meta-analyses of randomized controlled trials (RCT) at Level 1 evidence of efficacy, Grade A recommendation, i.e., as the optimal means of establishing evidence of superiority or non-inferiority of a treatment or strategy; they are the foundation, the backbone of recommendations and evidence-based medicine (EBM) [1].

However, each word has its importance, and a good understanding of these words, the care taken to avoid bias, the quality of the definitions, and the relevance of the evaluation criteria will determine the true value of a randomized trial.

We will successively consider the genesis of clinical trials, the different types of trials, the randomized controlled trial, the possible drifts and gimmicks, and the application to article reading.

Genesis of clinical trials, interest and limitations

The concept of a clinical trial probably dates back to Avicenna (980-1037) who already pointed out the need for a control group.

The history of controlled clinical trials begins in 1747 when Scottish naval surgeon James Lind (1716-1794) compared six remedies then used to treat scurvy, which killed many sailors on long voyages.

He demonstrated on 12 patients (2 patients per remedy) at similar stages of the condition, placed in the same part of the ship, receiving the same diet and care, that oranges and lemons, which we know today contain vitamin C, were the effective remedy for scurvy.

The Admiralty subsequently ordered that lemon juice be provided on all ships, which led to the disappearance of scurvy in the Royal Navy before the end of the 18th century[3].

Two centuries later, in 1948, the BMJ [2] published the first blinded randomized controlled trial demonstrating on 107 patients the benefit of Streptomycin in advanced pulmonary tuberculosis with a clear improvement in chest X-ray (51% vs *8%) and a significant reduction in mortality (7%* vs *27%).*

The rationale for the trial and the details of the procedure are remarkably well described, everything was said or almost said:

- problem well exposed (serious disease, product tested effective in vitro and on animals, some human tests not conclusive),
- low probability of spontaneous regression, need for a control group and ethics of control discussed (here streptomycin + bed rest 6 months *vs.* bed rest),
- randomization resulting in two groups differing only on the tested treatment, patients unaware of their participation in a therapeutic trial (informed consent is now required),

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3. The story goes that this is one of the reasons for the defeat of the Franco-Spaniards in Trafalgar, despite their numerical superiority, the Franco-Spaniards had remained deficient in vitamin C and were less brave.

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– utmost discretion about the trial (only the direct treating physician who received the envelope knowing the treatment).

A few years later (1955-1995), genius iconoclasts (T.C. Chalmers, A. Cochrane, D.L. Sackett, G. Guyat) were to move Medicine from empiricism, from dictates, from rote learning without discussion, to a practice based on solid validated data that would become Evidence-Based Medicine, EBM [3].

It was not without tensions and sometimes fierce criticism, but in 2020 EBM could be considered to have proved its worth and to have become a major key to medical reasoning. The media outbursts over hydroxychloroquine during the Covid-19 crisis have shown us that this is not yet the rule.

One could thus read "*The idea of returning to the '70s medicine, before the randomized double-blind placebo-controlled clinical trials is attractive",* and even *"one does not treat with statistics but with one's guts"* [4].

One can understand some criticism and a certain mistrust, or even rejection, of an overly dogmatic vision of EBM (it is not a question of replacing one dictatorship with another). There is no need for randomized trials for everything and not all situations have been evaluated by RCT, many commonplace situations are simply managed based on common sense and symptomatic treatment.

In emergency situations, especially when faced with the unexpected, one often manages with experience, pragmatism, and a few rules ... which does not prevent from validating this treatment, this attitude, afterwards as soon as possible.

For the rest, basing one's practice on well-conducted comparative trials is not at all incompatible with great medicine, quite the contrary.

– First of all, this does not exempt from listening and examining one's patient correctly and establishing the clinical probability a priori as low, intermediate or high [5].
– Then taking into account the placebo effect or the nocebo effect means taking into account the possible spontaneous favorable evolution of the clinical situation in question, the incidence of the doctor-patient relationship, the possible doubt/systematic rejection of the patient or the doctor.
– Concern for iatrogenic risk and the benefit-risk ratio means applying a key principle of medical ethics (*Primum non nocere*).
  Iatrogenic risk concerns not only therapeutics (whether drugs or invasive procedures) but also diagnosis (including cascading acts following non-justified procedures or the discovery of "incidentalomas").

It should also be taken into account:

– that a given drug may be effective in research laboratory and without clinical benefit,
– that the effect varies according to the dosage,
– that the improvement of an image or a physiological parameter does not ipso facto improve the patient,
– that a product may be effective in prevention and not in therapy, in secondary prevention but not in primary prevention,
– that what is effective in early stage of a disease is not necessarily effective in advanced stage (or vice versa), etc.

In order to assess the benefit-risk ratio, the cost-effectiveness ratio, to evaluate a new treatment, a new technique, a new strategy, it is necessary to have studies that address perfectly the given issue.

But first of all, a distinction must be made between retrospective and prospective studies, observational studies and randomized controlled studies.

Retrospective studies, whatever they are, even when paired, have intrinsic biases (we only deal with the content of the available records); they are useful for testing a hypothesis and often need to be verified by prospective studies.

Prospective studies are not free of bias, but they are the best way to proceed when evaluating a new treatment or strategy:

– either in a randomized cross-over trial (with the patient as its own control) if the study makes it possible,
– or in a randomized controlled trial against a reference treatment or technique or against placebo or abstention, making sur statistical power is optimal.

The purpose of randomization is to ensure that the groups are different only in the treatment or strategy tested; double-blind is intended to achieve maximum objectivity.

There are two types of RCT, explanatory trials and pragmatic trials.

– The first ones are conducted in expert centers and the question is "Is the intervention effective?".
– The second ones are conducted in any center treating patients responding to the given issue at hand and the question is "Is the intervention effective in everyday practice?".
  - *In explanatory trials* there is a strong pre-selection with numerous exclusion criteria in order to obtain a group with maximal expected effect and minimal adverse effects.
  - *In pragmatic trials*, on the contrary, pre-selection is weak as soon as the indication for the intervention is well respected.
  - *In explanatory trials*, the follow-up is strict and often rather heavy, the analysis can be done according to different modes, and the results are not always easily extrapolated in daily practice.