Study designs in thoracic surgery research

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Abstract: In this short review, we'll try to specify the differences between evaluation procedures of groups of data, as they present to researchers. The way and time data are gathered defines the type of study is going to shape. When we observe a cluster of data without deliberately interfering with the process we mean to evaluate, we perform an observational study. Observational studies are the main topic of this issue. Upon the contrary, experimental studies imply the direct action of the observer on the study population in order to define the role of a given exposure. The topic of experimental study design will be covered in another issue of this series.

Keywords: Case-control studies; cohort studies; observational statistics

Submitted Jul 16, 2016. Accepted for publication Jul 31, 2016.
doi: 10.21037/jtd.2016.09.06
View this article at: http://dx.doi.org/10.21037/jtd.2016.09.06

Introduction

In biomedical research, studies may be roughly grouped in two main categories (1). In the experimental setting, the researcher deliberately exposes the subjects to a given treatment (i.e., a new drug or procedure) and observes the outcomes. These outcomes may be compared to those obtained by a different treatment. The subjects should present homogeneous characteristics and should be allocated to different treatments only by chance (Randomization). In everyday clinical practice, experimental studies are difficult to conduct and bring to conclusion, and often are doomed to fail due to poor number of patients. An experimental trial that recently failed to provide a straightforward result was the Mesothelioma and Radical Surgery (MARS) Trial (2) which was conceived to define the role of extra pleural pneumonectomy (EPP) and pleurectomy decortication (PD). The study was suspended due to scarce accrual and high mortality of EPP. Often clinicians may only observe subjects which are already segregated in groups. The researchers are unable to deliver an exposure and implement allocation, they only can observe the outcomes (observational studies). This is the typical setting of the majority of clinical studies in surgical research. Observational studies may be further classified according to the presence of a comparison group. When a comparison group is given, the study is defined as *Analytical*, otherwise, depicting only unmatched data, it becomes a merely descriptive exercise. In this concise review we will concentrate mainly on observational studies.

Case series

Case series take into account a series of consecutive events, which should present some aspects of coherence and succession over time (e.g., all patients who underwent a given treatment in a given lapse of time). These studies usually aim to define:

- Mortality and morbidity;
- Failure percentage (or relapse) and time to failure/relapse;
- Analysis of the factors which probably affected the observed outcome.

The most important aspect is that the process involves firstly data gathering (the most different characteristics and variables are to be addressed) and then evaluate whether they eventually affected the outcome. Thus these studies are a posteriori observation. Easily they have some inherent vices, implied by their very nature of being conceived after the event they mean to analyze has already taken place.

Cohort studies

Cohort studies is a particular form of Longitudinal Observation Study, whose main feature is to track a given group (from latin *coorte*) from a point in time, assessing if a given treatment entails the expected result over time. In a cohort study the group may also be decided a posteriori (the starting point of the observation is in the past), then tracked in time. The observation may also start in the past and go on in the future: this kind of approach should be referred as bidirectional cohort study (3). Whatever the case, the direction in time is forward. It is more easily understood if we take the opposite example. We may observe a cohort of at-risk patients (example exposure to a toxic agent) and then observe who eventually get sick. To thoroughly fulfill the definition of cohort study, another group with known features should be employed (control group) (4). In the aforementioned example, the comparison or control group may be represented by person whose exposure to the toxic agent is not relevant. Given their temporal design, the time sequence between the exposure and the outcome is always clear. This kind of approach entails a high expense, but may be useful when reckoning the impact of various factors at the same time. Actually, assessment of the relationships with multiple factors may be abused by researchers. Wen testing the outcome against many possible causes, every ensuing outcome should be reported, acting otherwise would be misleading (3). To prevent this, the possible relationship to be addressed by the study analysis is to be defined at the beginning, and the researcher should stick to them.

A very famous example of cohort study is the Framingham study, which has been following a cohort (the dwellers of the small city of Framingham, Massachusetts), in order to define the cardiovascular risks correlated with some everyday habits. In Thoracic surgery research we have many examples of retrospective cohort analysis. A good example is the evaluation of the role of surgery in clinical stage IIIa. Surgical researchers usually have a prospectively collected database of their patients, so that they can extrapolate different cohorts (such as patients who were clinically staged as IIIa), and analyze the factors affecting the results of the treatment (5). Unfortunately, often a control group is not selected, dampening the statistical power of the study. To date, the main difficulty in sorting out a properly defined cohort study is to select a control group whose features are identical to the cohort in study, except for the exposure. Furthermore, the risk of selection bias is "built into" cohort selection (4). For instance, if the researchers want to investigate the role of surgery in mesothelioma, it is likely that patients undergoing surgery are fitter (i.e., have a better performance) that those patients not undergoing surgery. It may be difficult to decide whether a prolonged survival is due to the procedure, or to the characteristics of the patients.

Case control studies

Case control studies represent an easier approach to research as they require less time and effort, although being more prone to biases. They are based on the fact that the subjects are defined by outcome, and not by exposure (on the opposite to cohort study) (6). For instance, when evaluating the possible link between smoking and lung cancer, in a cohort study the group to be addressed are the smokers (definition by exposure) then observed over time looking for the development of cancer (outcome). In case control, we observe the cases of lung cancer (definition by outcome), and analyze retrospectively any possible difference with people not suffering the disease. Once defined the group of study, used to provide a control group, subject with similar features (except the outcome) are matched. The "direction" of the study in time is thus retrospective. This enables a quick analysis, especially in incidence is high. They are more practical when dealing with long latency of an outcome (for instance relapse after lung resection). It is important to clearly define the inclusion criteria, and rely most in incident data than prevalent data (new ones instead of old + new ones). When dealing with biomedical research definition criteria for disease change over time, therefore selection should limit its reach in time to ensure more homogeneity of the patients (for instance, in thoracic surgical research, long retrospective series may inevitably bring about skewed results, due to different definitions and techniques coming in succession over time, and this should be taken into account by the reader).

The scientific literature is thronged by observational designed studies, and this is particularly true for surgical research, where an experimental design is often difficult to set up and conclude. Usually, a technique is analyzed retrospectively, to define its outcomes. This kind of approach, loses analytical power by definition, as clearly stated by its level of evidence.

Whenever possible, it should be the investigator to manage the distribution of a given treatment. This kind of approach is defined experimental. Given the fact that the allocation to treatment is managed by the investigator, a

series of inclusion criteria are generally defined a priori. A stronger analytical power therefore ensues from this approach, being the selection of the characteristics of the patients defined before they are allocated to a given treatment. Usually these studies encompass a control group, which undergo a different, or more established, treatment. The patients should be randomly allocated to either of these two groups. This kind of prospective randomized trial ideally should reduce the selection bias. When neither the patient nor the caregiver is aware of the treatment (double blinding) also the so called "performance bias" is reduced. The issue of experimental studies will be addressed elsewhere in this series.

Cross-sectional studies

These studies are meant to assess both the exposure and the outcome of a given treatment, at the same time. They are very useful to describe the frequency of a given condition (prevalence) in a selected group of patients. The main risk of this approach is that it sometimes may be difficult to define the cause and effect relationship, since both are observed at the same time. Cross-sectional study fits well a wide population, but it is seldom employed for surgical cohorts. A typical example of cross sectional studies is screening studies, which try to detect a condition (lung cancer) in a well definite subset of population (active smokers) in a short period of time (7).

Conclusions

To sum up, whenever possible a prospective randomized trial may warrant the best results in terms of limitation of bias, even if those studies are difficult to carry out outside an academic setting, whither a greater deal of human and financial resources may be employed. Another major burden of prospective trials is the scarce accrual, thus we have been witnessing many studies being closed before stated time without providing any reliable result. Analytical studies may offer a good alternative whenever a control group is provided (limiting bias) and the end-point is clearly stated from the beginning, sharpening the analytical power of the study.

Cite this article as: Viti A, Terzi A, Bertolaccini L. Study designs in thoracic surgery research. J Thorac Dis 2016;8(9):E932-E934. doi: 10.21037/jtd.2016.09.06

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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