Experimental design and statistics in orthopaedic research

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Abstract

An understanding of the fundamentals of experimental design and statistical analysis is essential in the undertaking of any successful clinical research. There is no substitute for methodological quality but even well-designed studies can be let down by a poor examination of the data and incorrect application of statistical methods. The purpose of this article was to help provide an overview of the basic principles used in the design of clinical research. It covers both observational and experimental studies including case control studies, cohort studies and the gold standard randomized control trials (RCTs). It highlights the importance of sample power, type I and type II error, study randomization and blinding, and the effects of bias on outcome measures. The article uses examples from the published orthopaedic literature to stress the importance of these variables and the need for caution when interpreting the results. As a reader the most important thing is to maintain a critical eye with particular focus on the experimental design and study power and any interpretation of the data must be coupled with an awareness of the potential pitfalls.

Keywords case control study; cohort study; orthopaedic research; RCT; statistics; study design

Introduction

The undertaking of a research project is a process. Although the statistical analysis of data is a fundamental part it is important to remember the other essential elements involved in successful clinical research. An appropriate question must be formulated and the study designed to effectively answer this. There also needs to be the implementation of an efficient and effective way of collecting and assimilating the data. No statistical algorithm or technique will make up for a poorly designed study.

The application of statistical methods to the analysis of biological and medical data seems to be an area which may be poorly understood by clinical researchers. This is in most part due to a lack of awareness in the application of the appropriate methods and analyses rather than mistakes in the techniques used.[1] This allows well-designed studies to be let down by a poor examination of the data and the incorrect application of statistical methods. If ineffectively applied to clinical and medical research this can have significant healthcare and cost implications. The demands generated by the ever increasing development of new technologies and implants cannot be met by finite healthcare resources alone. Statistical science will always remain an essential step in the appropriate utilization of resources alongside improvement in patient care.[2] The analysis therefore should be carefully performed and clearly described with the authors presenting enough information to allow the readers to evaluate the validity of the study results.[3,4]

It is crucial that the statistical analysis is considered at an early stage in the design of a study as it can help avoid potential problems once the data have been collected. It is very useful to enlist the expertise of a statistician from the outset but it must be remembered that this should not be a substitute for a basic grounding in statistical methods. The purpose of this article is to help provide a brief overview of the basic principles of study design and statistical analysis used in orthopaedic research.

Statistics in biological systems

Qureshi et al., used Heisenberg's uncertainty principle as an example to help explain dependent and independent variables. The theory proposed that an electrons spatial location was best understood as existing within a cloud of probability where a precise location was 'uncertain'. This uncertainty arises from an understanding that countless factors exert a varying magnitude of influence on the behaviour of the electron. In the same way it is important to understand that when biological systems are subjected to observation the one intended true measure of a variable is rarely observed due to variation in the phenomenon of interest as a result of complex interplay of competing influences.[2]

Dependent and independent variables

The dependent variable which represents the output or outcome whose variation is being studied will be affected by independent variables which represent inputs or causes and potential reasons for variations. For example, is it possible to quantify the observed variation in the survival of a particular orthopaedic implant and which independent variables (e.g. age, co-morbidity, infection) have the greatest effect on survivorship. By knowing the potential effect of these independent variables is it then possible to predict the length of survivorship of the implant in a given cohort of patients. Statistics attempts to address such questions, which in turn helps guide clinical decision-making.

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Study design

The purpose of a study is to address a scientific hypothesis while minimizing bias. Studies can be broadly divided into either observational or experimental. In observational studies the independent variable is not under the control of the researcher and the outcomes of interest are observed along with the factors which contribute to them. If an attempt is made to assess a relationship between the two, the study is termed epidemiological. In contrast in the design of experimental studies the investigator intervenes in some way to affect the outcome. Such studies are longitudinal and prospective with the investigator applying an intervention and observing the outcome at a future time point.[1] Bias refers to the tendency of a measurement process to over- or underestimate the value of a population parameter. Bias can be minimized by using a control group or/and prospective enrolment or/and randomization of patient or/and blinding.[5]

Observational studies

There are different types of observational study.

Cross-sectional study: it may be cross-sectional in which all observations are made at a single point in time showing the incidence or prevalence of an event in a specified population, or more often longitudinal where individuals are followed over a period of time, either prospectively or retrospectively.[1]

Case-control study: a case-control study is an example of a retrospective observational study in which a control group is added. As the number of patients is increased there is a reduction in the chance of observing a random result and therefore is less prone to bias than a study without such a control group.[5] In examining the occurrence of disease or complications after surgery, the investigators do not have the luxury of randomization. For example, patients cannot be randomly assigned to have a dislocation following a total hip replacement (THR) or develop a deep infection. Instead the study is designed to look at those patients with a given complication and compare them to those without the complication, looking for risk factors. Causal relationships are much more difficult to tease out from case-control studies than from randomized control trials (RCTs). The things to look for in case-control studies are the inclusion and exclusion criteria, whether the groups were matched to account for any extraneous variables, and the overall population from which the sample was taken.[6] Did the dislocation group consist overwhelmingly of patients with a high body mass index?

Cohort study: in a cohort study information is collected on individuals and comparisons made to determine whether a particular factor (risk factor) occurs more or less frequently in those who develop a given condition or complication. The studies can be either prospective or retrospective.[6] A longitudinal cohort study is a prospective study in which a group of patients is followed longitudinally while the baseline parameters and their evolution are recorded. The measurement tools are chosen before the patients are included in the study. For example, one could study the quality of life and range of movement in shoulder patients prior to and after arthroscopic rotator cuff repair. However, in this prospective design, there is still a potential selection bias: investigators can choose which patients to enrol unless all patients with a given diagnosis are included (i.e. a consecutive series). Even if all patients are included, there can still be other forms of bias, such as referral bias which happens frequently when cases are selected in a hospital whose activity is linked to the studied exposure or diagnostic bias in which specific criteria are required for diagnosis but potentially exclude other patients.[5]

It is also possible to carry out retrospective cohort studies relying on databases and hospital records. The studies can be limited by the quality of the records and often it is difficult to have retrospective access to longitudinal data sets. The exception would be large databases in countries with centralized healthcare systems and as patients are followed up over time, associations between risk factors and outcomes can, with caution, be interpreted as causative.[6]

In such settings, there is always the possibility that data for particular patients are not complete. Often the data missing are random, but sometimes patterns of missing data vary within the data set itself. In these situations it is important to consider how the data is analysed. In some cases the patients with data missing are removed in their entirety leaving a single homogenous population for the rest of the analysis. This is referred to as complete case analysis. Another option would be to only remove patients from consideration for those variables for which they are missing data. This option is referred to as available case analysis and is relatively simple to do. It does however leave different subpopulations for each analysis undertaken and can introduce bias, particularly if the missing data within the population are not random. A third option is conditional or unconditional mean imputation where the missing values are replaced with a mean of the remaining non-missing values. This is either an actual mean or an estimate derived from a regression with some random variation added to the estimate.[13] Whatever method is used care must always be taken when using missing data sets to ensure that the validity of the study is maintained.

The relative risk, which manages the magnitude of an association between an exposed group and a non-exposed group, is commonly used to assess the effect of a risk factor in a cohort study.[1] If the relative risk is 1, then the risk is the same in the exposed group and non-exposed group. If in our hip example the relative risk is 3, then the individual is three times more likely to develop a hip dislocation postoperatively if the factor is present. The relative risk must not be considered in isolation but in relation to the absolute risk. If the absolute risk is very low then even if the relative risk is high the overall risk is still very small. In cohort studies it is impossible to estimate the relative risk directly as some individuals will have the condition at the outset and so their risk of developing it cannot be evaluated. In this case the odds ratio is used which is a measure of the association between an exposure and an outcome. The odds of developing a condition in those exposed to the risk factor divided by the odds in those not exposed.

Experimental studies including clinical trials

A clinical trial should be comparative. In statistical terminology if it is comparative it is controlled. If for example you are investigating the effect of a new implant and have nothing to compare it

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