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The self-controlled studies in clinical homeopathic research

Introduction

In the past decade, the medical and biological sciences have experienced a new way of operating their practice: the use of clinical trials' outcomes for making medical decisions and interventions. However, the current methods of statistical inference are not 'evidence-based', but 'error-based'. The misperception that randomized clinical trials, preferably double-blinded and placebo-controlled, give us objective and scientific results is so widespread, with no questioning, that has profoundly transformed how we think about the process of science and the nature of scientific arguments. The dissemination of the 'P value fallacy' (Goodman, 1999) converted a method with its limitations into a panacea that almost eliminated our ability to distinguish between statistical results and scientific conclusions.

The weaknesses of the conventional research methods, as well as their limitations to find expression to reality in a binary logic ($p<0,05$ means that my association is true, for example), have led to the development of various alternative methodologies, yielding new concepts, from the definition of probability to the meaning of epidemiologic designs (Struchiner, 2004). In this study, we discuss the use of controls in homeopathy and propose the use of the subjects as their own controls, presenting some aspects of three designs that already use this approach, examining their potential for homeopathic clinical research and reviewing proposals of statistical inference and analysis.

The use of subjects as their own controls

The causal inference basic problem is the impossibility of comparing the effect of the exposure and the nonexposure, simultaneously, at the same individual. In other words, we cannot determine, at the same time, what is the effect of a drug or a placebo, at the same person, since it is impossible to administer the two interventions. Hence, there are two options: examining several individuals at the same time, with analyses of the exposure and the nonexposure in different individuals (cases and controls); or evaluating the same individual at two or more points in time. The analysis of cases and controls at the same moment is the predominant situation in clinical and epidemiologic conventional research. We analysed three alternative models, which follow the case-base paradigm: the case-crossover and case-time-control studies, and the self-controlled clinical trials. In these designs, each case is its own control, analyzed at different points in time.

Epidemiologic researches begin with examinations of cases. The case series often show the queries and base future studies (Greenland, 1999). The use of subjects as their own controls has been present in scientific investigations since the beginning of clinical studies. Recently, the analysis of the same individuals at different points in time has been rescued by MacLure (1991) and Suissa (1995). MacLure has introduced an innovative epidemiological design (case-crossover), a variation of the classical case-control strategy, for the analysis of transient effects on the risk of acute illness events. Suissa has proposed the case-time-control design for the study of chronic exposures. In homeopathy, each subject is considered unique, with peculiar responses and dynamics. The selection of other people as controls substantially biases the analyses, once the variables used for matching are insufficient to express the supposed similarity among individuals. Gender, age, smoking and physical inactivity, for example, do not correspond to the measures used for the prescription of homeopathic medicines. The actual variables, characteristic and individual, make the cases to be so distinct from potential controls that the search for an appropriate control would be formidable, if not impossible. This way, we have the confounding by indication, in which the condition that determined that therapeutics is so peculiar that it is, by itself, an important predictor of the effect under study. This makes practically unfeasible the use of other individuals as controls. At the brink of a new paradigm, the designs described here intend to coexist with other alternate methodologies and to be a suitable model for clinical homeopathic research.

The use of cases as their own controls removes confounding from many unchangeable characteristics, that means, uncontrollable and intrinsic properties of each person, such as intelligence, genetics, susceptibility. Moreover, the self-matching designs are more powerful from a statistical perspective and offer savings in the sample size. The case-crossover design was introduced in 1991 for examining the transient effects of a brief exposure on the onset of an acute outcome. Such analyses can be completed with minimal ethical worries, at low cost and are usually quick. Common and rare outcomes can be tested, and the clinical and statistical significance determined. They are appropriate to rapidly fluctuating processes, such as activity, emotion or pain (Redelmeier & Tibshirani, 1997). Each case corresponds to a stratum, and contributes one case window and one or more control windows. The case window is defined as the period just preceding or during the event under study. The control windows are periods of the same length as, and not overlapping with, the case window, and provide an estimate of the expected frequency of exposure for each case. The case window and the control window derive from the same person at different times (MacLure, 1991; Hernandéz-Dias et al.,

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2003). In 1995, the case-time-control design was proposed, very similar to the case-crossover, used, however, to the study of chronic exposures. The time trends in exposure are limitations to the results of self-matching studies. Thus, the case-time-control design includes an adjustment for time trend from the controls.

The self-controlled designs have some limitations. The use of subjects as their own controls already adjusts for fixed factors, but it does not account for the variations over time. The adjustment for time trends in the case-time-control studies is limited to the measured variables, in frequentist analyses. This adjustment may be imprecise for time trends that vary over immeasurable variables. There is a tendency to overstate the exposures in the current period and to underestimate in the reference periods. The model is based on the assumptions that the exposures are independent and that there is no carryover effect from one period to the other. There is, also, the selection and the information bias, as in any case-control study. The use of the subjects as their own controls has been limited in clinical trials, for many reasons. One of them is the ethical worry of allowing patients with placebo, only, during the reference period (control window). This is not possible in lots of situations under study (Louis et al., 1984; Suissa, 1998; Greenland, 1996; Greenland, 1999; MacLure & Mittleman, 2000). This way, the bidirectional studies may be an option to this limitation.

Statistical approaches

In order to make the self-controlled clinical trials widespread, there is the urgent need for the development of effect estimates that are free from bias caused by time trends. MacLure (1991) proposes the Mantel-Haenszel estimator of the rate ratio, with confidence intervals for sparse data. Since that, other choices have been used, like maximum likelihood (Marshall & Jackson, 1993) and logistic regression (Suissa, 1995). Recently, Navidi & Weinhandl (2002) have compared four sampling schemes for case-crossover designs, to evaluate which one would better control for confounders that vary predictably with time. The best scheme, according to this study, was the semi-symmetric bi-directional. Other new methods for achieving control of unmeasured confounding have been studied, from more elaborate extensions of Poisson regression to hierarchical modeling. It is also fundamental the development of methods that can handle exposures which occur concurrently and non-independently.

It is also possible to use less orthodox statistical approaches. The increasing power of computers is bringing Bayesian methods to the fore. It allows handling unknown heterogeneity sources or, at least, not attributable to any specific variable (Struchiner, 2004), dealing with the uncertainty. The proposal of the self-controlled studies also allows the review of the variables, going beyond the simple dichotomies, searching for a deep understanding of the patient as human being, once he will be compared only to himself. The fuzzy logic handles this imprecision at the analysis and the variables construction. It works the concept of partial truth, where the transition between sets is gradual, and not abrupt (Shaw & Simões, 1999). The fuzzy sets theory is an important tool for homeopathy, since it allows a more realistic expression of events, exploring linguistic variables and representing thoughts more similar to the human ones. Ortega says (2004): "...we can group the uncertainties in two groups: the variability, that comes from the population heterogeneity or from the stocacity; and the partial ignorance, from systematic measurement errors (imprecision) or because we do not know part of the considered process (subjectivity)." So, uncertainty due to the future occurrence of some event is treated by conventional probability. Imprecision occurring because we do not have enough knowledge about the internal structure of our object of study is dealt with diffuse treatment (Oliveira Jr., 1999).

Conclusion

Researches in clinical homeopathy are often criticized for the quality of their analyses (Jonas et al., 2001), or for the use of clearly incompatible models. All method involves some diminution of the reality under study. For some situations, probably the people who are best representative of the population base that produced the cases are the cases themselves. The proposal of the self-controlled studies in clinical homeopathic research seams feasible from the theoretical point of view, in order to use these models or to produce new ones from this pattern. It allows the use of frequentist and Bayesian statistical analysis. However, only the use can prove its viability. Today, we need a clinical epidemiology that moves beyond dichotomies. And it is not only a matter of homeopathic needs. The reason is scientific: our object of study demands it. There is a requirement for searching strategies and methodologies that may express the homeopathic paradigm, and this will raise challenging questions, from the way of approaching the patient to the methods for statistical inference. It is also essential to acknowledge and conceive of other possibilities rather than the randomized clinical trials with frequentist statistical analysis. Thereby, homeopathy and the case-base paradigm are occasion to debates and investigations, through approaches that elicit homeopathy's foundations, in search for its own episteme.