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Study Designs in Clinical Research

Marlies Noordzij[a] Friedo W. Dekker[b] Carmine Zoccali[c] Kitty J. Jager[a]

[a]ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, University of Amsterdam, Amsterdam, and [b]Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands; [c]CNR-IBIM, Clinical Epidemiology and Pathophysiology of Renal Diseases and Hypertension, Renal and Transplantation Unit, Ospedali Riuniti, Reggio Calabria, Italy

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Abstract
In nephrology research, both observational studies and randomized controlled trials (RCTs) are commonly applied. Clinicians using the evidence from epidemiological studies should be aware of the specific qualities and limitations of each study design. The purpose of the article is therefore to provide a brief overview of the range of study designs and to comment on the most important strengths and weaknesses of these designs. In general, RCTs are the optimal study design to study the effects of therapy or other interventions and to establish causality, although their use is limited by ethical and practical concerns. Conversely, observational study designs, including case reports, case series, cross-sectional studies, case-control studies and cohort studies, are usually more useful than RCTs for non-therapeutic research questions. In conclusion, both observational studies and RCTs fulfill a complementary and valuable role in nephrology.

Introduction

Studies in clinical epidemiology often investigate whether an exposure, such as a medical treatment or an environmental factor, is related to an outcome such as a disease or death. To address these research questions, several study designs can be applied. Study designs that are commonly used in nephrology research are observational studies like cohort and case-control studies on the one hand, and randomized controlled trials (RCTs) on the other hand.

The purpose of this article is to provide a brief overview of the range of study designs and to comment on the most important strengths and weaknesses of these designs. This article can be considered as an introduction to later articles in this series, which will discuss the different study designs in more detail.

Observational Designs

Case Reports and Case Series

Case reports and case series provide detailed descriptions of cases without the use of a control group. The possible association between the observed outcome and a specific exposure is described based on clinical evalua-

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Marlies Noordzij, PhD
ERA-EDTA Registry, Department of Medical Informatics
Academic Medical Center, University of Amsterdam
PO Box 22700, NL–1100 DE Amsterdam (The Netherlands)
Tel. +31 20 566 78 73, Fax +31 20 691 98 40, E-Mail m.noordzij@amc.uva.nl

Table 1. Characteristics, strengths, and weaknesses of study designs used in clinical research

Study design	Characteristics	Strengths	Weaknesses
Case report and case series	One or a few subjects Detailed description of (a) case(s) without a control group	First form of publication Fast, inexpensive Hypothesis generating	Very limited potential to establish causal effects Selection bias*
Cross-sectional study	Exposure and outcome measured at same point in time Subjects with and without outcome are compared	Useful to describe the prevalence of disease Fast, inexpensive Hypothesis generating	Very limited potential to establish causal effects Selection bias* Survival bias*
Case-control study	Cases (those with the outcome of interest) are compared with controls (those without the outcome of interest) with respect to exposure	Efficient Suitable to study rare outcomes and multiple exposures Relatively inexpensive Hypothesis generating	Some potential to establish causal effects Can only study one outcome Choice of control group can be difficult Selection bias* Recall bias*
Cohort study	A cohort of subjects free of the outcome is followed and compared based on the exposure	Suitable to study multiple exposures, rare exposures, and multiple outcomes Hypothesis generating High generalizability	Some potential to establish causal effects Can take a long period Can be expensive Selection bias*
RCT	Randomization: allocation of subjects to experimental or control group by chance	Gold standard in establishing causal effects in studies on therapy Suitable to study more than one intervention	Very expensive Can take a long period Not suitable to study rare events Can be unethical Often low generalizability due to strict selection criteria

* Each study design may suffer from specific types of bias. These will be explained in the following papers of this series.

tions and histories of a single subject (case report) or a small group of subjects (case series).

These study designs may be the first in identifying a new disease or adverse health effect from an exposure. For instance, in 1985, the first case reports on acute phosphate nephropathy, a type of acute renal failure, after the use of oral sodium phosphate products for bowel cleansing before colonoscopy were described in the English-language literature [1, 2]. After these first reports, several other case reports and case series describing this rare but serious adverse event were published. Eventually, these reports led to recommendations from the United States Food and Drug Administration to avoid the use of oral sodium phosphate in patients with kidney disease, impaired renal function or perfusion, dehydration, or uncorrected electrolyte abnormalities [3].

This example clearly shows that case reports and case series play an important role in the progress of medical science. They permit the discovery of unexpected effects (adverse or beneficial) and new diseases, and play a role in the study of pathophysiological mechanisms and medical education [4]. The results of these fast and inexpensive studies are helpful in generating hypotheses that may later be studied with other study designs, but are rarely useful to establish causal effects. The main characteristics as well as the strengths and weaknesses of these and other study designs are summarized in table 1.

Cross-Sectional Studies

In a cross-sectional study, a certain outcome and an exposure status in a specified population are measured simultaneously. Cross-sectional studies can be thought of as providing a 'snapshot' of the frequency and characteristics of an outcome at a particular point in time. However, since exposure and outcome are measured at the same moment, it is usually not possible to distinguish whether the exposure preceded or followed the outcome, and thus cause and effect relationships are not certain.

Most published cross-sectional studies describe the prevalence of a condition in a population or the treatment provided to specific patient groups. A good example of a cross-sectional study was published by Bello et al. [5]. As part of a population-based screening program, a type of cross-sectional study, they evaluated the prevalence of microalbuminuria in relatives of patients with chronic kidney disease (CKD) compared with the general popula-

tion. The investigators found that the prevalence of microalbuminuria was significantly greater in those with a family history of CKD than the prevalence in the age- and sex-matched control group. In contrast to many other cross-sectional studies, it is clear in this example that the exposure of having a family history of CKD preceded the outcome of microalbuminuria [5]. The results generate the hypothesis that, also beyond classical hereditary renal diseases, relatives of patients with CKD may have an increased risk of CKD. However, the prognostic value of microalbuminuria in this category of at-risk individuals remains to be determined in longitudinal studies.

Despite their important weaknesses, cross-sectional studies are frequently used, as they are fast and inexpensive.

Case-Control Studies

The case-control study aims to identify factors that may contribute to an outcome. In this type of study, subjects are selected based on the outcome variable; subjects who have the condition (cases) are compared with subjects who do not have the condition (controls). Looking back in time, the cases and controls are compared with regard to exposure.

Case-control studies are particularly efficient to investigate rare outcomes. An example of such a rare outcome is end-stage renal disease (ESRD). Ibanez et al. [6] studied whether the long-term use of aspirin and other analgesic and non-steroidal anti-inflammatory drugs (NSAIDs) was associated with the development of ESRD. As cases, they selected all patients entering the local dialysis program because of ESRD within a period of 2 years. Looking back in time, they recorded the use of the drugs. Subjects with the same age and sex distribution, admitted to the same hospital as where the cases arose, were selected as controls and the use of the drugs was also recorded in this group. When comparing both groups, the authors could not detect an association of non-aspirin analgesic drugs and NSAIDs with a risk of ESRD. However, the chronic use of aspirin appeared to be associated with an increased risk of ESRD when compared to the control group [6].

A case-control study requires a relatively small sample size, and is therefore an efficient design, particularly in case of rare outcomes. Moreover, these studies can be performed relatively fast and are inexpensive. However, case-control studies may also have some disadvantages, such as recall bias and surveyor bias, which will be discussed later on in this series in the paper on this study design.

Cohort Studies

In a cohort study, an investigator defines a study population (cohort) consisting of subjects who are free of the outcome of interest. This study design aims to determine which factors are associated with the development of this outcome. Depending on the exposure status at the start of the study, subjects are classified as exposed or unexposed (controls). Thereafter, subjects are followed over time to see who will develop the outcome and who will not.

A cohort study enables investigators to study multiple outcomes as well as multiple exposure variables. The Dialysis Outcomes and Practice Patterns Study (DOPPS) may serve as a good example of that. As part of this large international cohort study of hemodialysis patients, the effects of various risk factors on several outcomes were studied. For instance, Mapes et al. [7] assessed indicators of health-related quality of life at the start of the study and recorded death and hospitalizations during follow-up on dialysis. They were able to show that lower scores for health-related quality of life measures were associated with increased risks of death and hospitalizations among hemodialysis patients. This study apart, DOPPS answered a large number of related and unrelated research questions [8], perfectly illustrating how great the potential of well-designed observational studies for clinical research is.

Cohort studies can be inefficient because it may take a long time before an outcome occurs and, as a result, these studies can be rather expensive. An advantage is that cohort studies on the effects of therapies may generate hypotheses and provide an indication for the effect size, which is necessary for sample size calculations in RCTs. In this respect, RCTs largely depend on work from preceding observational studies [9].

RCTs

For the evaluation of a therapy or other intervention, the RCT is seen as a gold standard. The distinct advantage of RCTs over observational studies is that they can provide evidence for a causal relationship because they have the potential to avoid selection bias and selection by prognosis (also known as confounding by indication) [10, 11]. The key principle is randomization where patients are allocated to either the intervention under study (experimental group) or to the control group by a pure chance process. Randomization breaks the link between therapy prescription by the physician and the patients' prognosis.

Subsequently, the experimental and control groups are followed up for a specified period and then compared in terms of the outcome.

An example of an RCT in nephrology is the ADEMEX study [12]. In this RCT, 965 peritoneal dialysis patients from Mexico were randomly assigned to continuation of their preexisting peritoneal dialysis prescriptions (control group) or to a modified prescription to achieve a higher peritoneal creatinine clearance (experimental group). After randomization, the baseline characteristics of both groups were similar, with the exception of a few small differences between the groups, like a somewhat higher proportion of diabetics in the control group. However, this difference depended on chance and not on the choice of the investigators. Both groups were followed up for at least 2 years, and after comparing mortality rates between the groups, the investigators concluded that no clear survival advantage was obtained with increased peritoneal small-solute clearance.

Although RCTs are powerful tools, they also have some weaknesses [9]. First and foremost, they are much more expensive than observational studies, and because of the extremely large number of health care interventions it will not be possible to test all of them in an RCT. In addition, exposing patients to an intervention believed (but not yet proven) to be inferior to current treatment is often thought unethical. Finally, there are examples of cases where RCTs are possible but inappropriate, such as for the detection of adverse events that are rare or take years to develop. Further details on the design of an RCT will be provided in the next article in this series.

Summary and Conclusions

This paper outlined the different study designs. Clinicians using the evidence from epidemiological studies should be aware of the strengths and weaknesses of each of them.

Although the use of RCTs is limited by ethical and practical concerns, they remain the optimal study design to study the effects of therapy or other interventions, and to establish causality. For non-therapeutic research questions, observational studies are generally more useful than RCTs. The hierarchy of these designs will be discussed in one of the following articles. For this paper, we conclude that both observational studies and RCTs fulfill a complementary and valuable role in nephrology.

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