Clinical Trials Evaluating Drug Therapy: Types, Reliability of Results, Place in Modern Evidence-Based Medicine

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The article discusses the main methods of evidence in modern medicine. Special attention is paid to randomized controlled trials and observational studies. The advantages of randomized controlled trials over observational studies are considered. A comparison of the informative value of randomized controlled trials and observational studies in assessing the effect of therapeutic interventions is made. Attention is drawn to situations when conducting randomized controlled trials is not possible and when they become the main source of information. It is emphasized that in order to verify the results of randomized controlled trials in real clinical practice, it is necessary to conduct observational studies. The basic principles of conducting observational studies are considered.

Keywords: randomized controlled trials, observational studies, comparison of information content, principles of conducting observational studies.

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Introduction

The emergence of the results of large randomized controlled studies has dramatically changed the learning process in medicine. The results of these studies tend to take the main place in modern clinical guidelines, and the randomized controlled studies themselves have come to be considered the «gold standard» of evidence in medicine [1-3]. There are many questions in medicine to which randomized controlled studies either don't give an answer or give conflicting answers [3]. In addition, conducting randomized controlled studies is a process that requires a huge material investment, as well as a fairly large amount of time. Therefore, the question arises - can we do without randomized controlled studies and use other types of studies to study the effect of therapeutic interventions? Another question that constantly worries pharmacoepidemiologists is whether it's possible to transfer the results obtained in randomized controlled studies directly into real clinical practice. This publication is devoted to an attempt to provide answers to these questions.

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Different types of evidence in medicine

Before we begin to discuss the role of randomized controlled studies in the evidence hierarchy, we recall what evidence was dominant in medicine in the past. Traditionally, for centuries, the so-called clinical experience has served as the main type of evidence in medicine. This experience could be the experience of the doctor himself or his colleagues, especially those holding high positions in medical science. The classics of domestic therapy a little more than 50 years ago argued that their "experience has shown that prolonged resting (for 2-3 months) reduces mortality from myocardial infarction ..." [4]. This postulate was present in a textbook on cardiology and was a guide to action for students of the art of therapy.

When the sciences appeared that studied the pathogenesis of diseases and the mechanisms of action of drugs at different levels (normal and pathological physiology, pharmacology, etc.), the so-called pathophysiological method of proof appeared. In short, it was formed on the main mechanism of action of the drug. The effect of the drug on certain structures of the body (for example, certain types of receptors) or on the links of pathogenesis (for example, the process of occurrence of arrhythmias) explained its potential therapeutic efficacy. The pathophysiological method of proof often led to false conclusions not because of the flaw in the method, but because not all the mechanisms of the drug action have been fully studied [5].

A classic example of the failure of the pathophysiological method of evidence is the history of the use of antiarrhythmic drugs in patients with acute myocardial infarction. Previously, it was believed (but later it turned out that it was wrong) that ventricular arrhythmias always indicate a poor prognosis of the disease, and, accordingly, the use of antiarrhythmic drugs (which appeared at that time) will eliminate arrhythmias and prevent unfavorable outcomes of the disease. This practice has been used in the clinic for more than 10 years. However, the randomized controlled studies CAST (The Cardiac Arrhythmia Suppression Trial) completely negated the validity of the method of proof and existing clinical practice: it turned out that class Ic antiarrhythmics (flecainide, encainide, moricizine) effectively eliminated arrhythmias, but at the same time they significantly increased mortality rates [5].

Clinical studies

Clinical studies to prove the effects of drugs have been conducted since the mid-19th century. These studies had a wide variety of protocols that were constantly being improved.

Currently, there are two fundamentally different types of clinical studies – observational studies in which there is no active intervention, and randomized controlled studies [6]. As we said above, many consider the organization of randomized controlled studies as a breakthrough in the field of evidence-based medicine, and they call randomized controlled studies themselves its «gold standard».

What are randomized controlled studies?

Randomized controlled studies mean a type of experimental study performed in patients in compliance with the relevant ethical standards, with a predetermined goal (implemented in the analysis of the achievement of endpoints), clear inclusion and exclusion criteria, using randomization, which makes it possible to divide patients into two (or more) groups of patients (main and control) that are identical in terms of the main clinical signs, which differ only on the basis of whether the intervention of interest to the researcher is performed in these groups.

History of randomized controlled studies

Most experts in evidence-based medicine agree that the first prototype of randomized controlled studies was a study conducted by the English military doctor James Lind in 1747 to study the treatment of scurvy with orange juice in seafarers on long voyages [1]. It's believed that the basic principles of modern medical experimental research (which are randomized controlled studies) were formulated by Bernard in 1865 [1]. However, the first classical randomized controlled study was carried out much later: it happened in 1948 when studying streptomycin in patients with pulmonary tuberculosis [7].

Interestingly, earlier randomized controlled studies were not required to prove the effect of streptomycin in another, more pronounced form of tuberculosis, tuberculous meningitis, since the effect of the drug was obvious without such a study (see below).

Is't possible to do without randomized controlled studies?

Until randomized controlled studies existed, this question, for obvious reasons, didn't arise. Until now, we widely use drugs and treatments that have proven their effect long before the advent of randomized controlled studies [6,8]. For example, this is the use of thyroxine for the treatment of myxedema (hypothyroidism), insulin for the treatment of diabetes mellitus, penicillin for the treatment of pneumococcal pneumonia, streptomycin for the treatment of tuberculous meningitis, electrical defibrillation for the relief of ventricular flutter, and many others. These therapies are united by the fact that they give a quick

and obvious effect, which doesn't require more rigorous evidence of drug efficacy [6]. It's noteworthy that there are examples when the effect of the drug was proven on a single patient: repeated injections of naloxone for a short time stopped methadone poisoning syndromes [9], and after this observation, naloxone began to be used to combat an overdose of narcotic analgesics.

The question of the possibility of proving the effect of the drug without conducting randomized controlled studies has not lost its relevance after the appearance of this type of studies. Is it always possible and necessary to conduct randomized controlled studies nowadays [6,10]? Obviously, it's impossible to do without randomized controlled studies to assess the effect of drugs intended for use in widespread diseases, often complicated by fatal and non-fatal complications (for example, in cardiovascular diseases), since there is no alternative to them [2]. On the other hand, it's believed that conducting randomized controlled studies is usually not justified for relatively rare diseases and/or diseases that rarely cause serious complications (for example, in rheumatic diseases, skin diseases, diseases of the gastrointestinal tract), since it will require inclusion a large number of patients, significant financial costs, etc. Then it's preferable to conduct observational studies, primarily of the case-control type [3,10,11], which was proved by conducting a number of comparative analyzes comparing the results of randomized controlled studies and carefully planned observational studies [11].

Interpretation of the results of randomized controlled studies

Not all clinicians really understand what the results of randomized controlled studies mean. There is a misconception that if a randomized controlled study is positive, then this result will affect the majority of study participants. In fact, this effect will not be felt by all patients, but only a small part of them, in most of the available randomized controlled studies with a positive result [12].

This reassessment of the relevance of randomized controlled studies benefits pharmaceutical companies, which typically sponsor such trials. There is a metric called NNT (Number Needed to Treat) that tells us how many patients need to be treated to prevent 1 adverse event (usually the primary endpoint). NNT is calculated as the reciprocal of the decrease in absolute risk under the influence of the studied drug. For example, in the well-known PARADIGM-HF study, the NNT was 21.2 for the new drug LVZ696 (angiotensin/neprilisin receptor inhibitor) [13]. This means that more than 21 patients need to be treated with this drug to prevent one cardiovascular event (cardiovascular death or hospitalization for worsening heart failure) compared to traditional treatment with enalapril.

The lower the NNT value, the more effective the new intervention is compared to the control (or placebo). NNT scores significantly higher in studies that are considered highly successful. For example, in the FOURIER study, the addition of evolocumab, a modern lipid-lowering drug, to therapy, reduced the absolute risk of developing a primary endpoint by only 1.5% compared to conventional treatment. NNT (=66.7) corresponded to such indicators of this study, while the results of the FOURIER study were presented as a breakthrough in modern lipid-lowering therapy [14].

All of the above tells us that a competent interpretation of the results of randomized controlled studies affects the judgment of its clinical significance, and that statistical and clinical significance are not the same thing. Accordingly, not all randomized controlled studies can be considered as studies of high clinical significance.

However, we note that obtaining a positive result is becoming more and more difficult in modern randomized controlled studies. The explanation is simple: the basic therapy, which is the control in such randomized controlled studies, is becoming more and more effective, therefore, fundamentally new drugs are required to get additional significant effect. On the other hand, the question arises, how much these fundamentally new drugs (if they give such a small increase in terms of effect, such as evolocumab) will be able to change the real practice of treating a specific disease?

Manipulating the results of randomized controlled studies

Sometimes the protocol of a specific randomized controlled study is planned in such a way as to de-

liberately place one drug (usually a comparison drug) in an unequal position compared to another drug (usually a new study drug): then the likelihood of a positive result for a new drug increases many times. A typical example of this approach is the already mentioned PARADIGM-HF study [13]. In this study, the comparison drug was the classic enalapril, which was undeniably shown to be effective in the treatment of chronic heart failure many years ago. But the dose of this drug in the PARADIGM-HF study was limited to 20 mg per day. Although it's known that the maximum dose of the drug (which about a quarter of patients received) was 2 times higher (40 mg per day) in the CONSENSUS study, which demonstrated an impressive effect of the drug on mortality rates [14]. If the maximum allowable dose of enalapril in the PARADIGM-HF study had been twice as high, there might not have been any differences with the comparison drug, and it would not be considered one of the most advanced in the treatment of chronic heart failure at present.

Observational studies

Observational studies are characterized by a lack of active intervention; in a classic observational study, the investigator only assesses what happens in normal clinical practice. There are different types of observational studies – studies with historical control, prospective cohort studies, studies of the «before-after» type, studies of the "Case-control" type, as well as clinical observations (both for a group of patients and for an individual patient) [6]. A description of the features of each of these stages of observational studies is beyond the scope of this article. We note that modern medical registries (as opposed to large databases) are also a type of observational studies.

It's very important that different observational studies have different quality and, accordingly, different degrees of persuasiveness and reliability of the results obtained. That is why most authors note, when comparing the value of randomized controlled studies and observational studies for evidence-based medicine, that a prerequisite for such a comparison is high quality of both [6].

The role of observational studies in modern evidence-based medicine

The debate about whether observational studies are inferior to randomized controlled studies in terms of informativeness in assessing the effectiveness of drugs has been going on for several decades. We have already noted that the conducted comparisons of the results of randomized controlled studies and observational studies when studying the same drugs didn't always reveal the advantages of randomized studies [12]. It should be noted that these comparisons were made at the end of the 20th century. Since then, the methodological level of randomized controlled studies has significantly improved [15,16,17]. Also, the approaches to observational studies have changed: the emergence of big databases and special statistical methods that allow inside such databases to simulate the conduct of randomized controlled studies (in particular, various pseudo-randomization methods – "propensityscore") again raised the question of the possibility of replacing randomized controlled studies with results, obtained in observational studies, in particular, analyzes of big databases [18]. The main conclusion of the discussion is that these methods, for various reasons, can't make up for the lack of true randomization in observational studies. These reasons include, first of all, the inability to take into account the so-called interfering factors, and the propensity score method doesn't allow to compensate for this deficiency. Accordingly, no observational studies can be considered as a viable alternative to randomized controlled studies in proving the effectiveness of a particular drug for a particular disease.

One of the most famous specialists in the field of biostatistics S. Pocock believes that at present the role of observational studies in modern evidence-based medicine should be limited to clarifying the results of randomized controlled studies: first of all, it is the study of the effectiveness of the drug in wider groups of patients, especially those who were not recruited into randomized controlled studies, including other ethnic groups. In addition, according to this researcher, the analysis of the results of observational studies helps to formulate various hypotheses (but not conclusions) for the organization and conduct of new randomized controlled studies [2].

We will also add that observational studies need to be carried out in several more cases: first, when randomized controlled studies can't be carried out for ethical or any other reasons; secondly, in order to verify the results of randomized controlled trials, that is, to assess the agreement with the results of randomized controlled trials in real clinical practice.

Are the results of randomized controlled studies always reproduced in real clinical practice?

Extrapolating the results of randomized controlled studies into real clinical practice is not always easy and unambiguous for many reasons. It's well known that randomized controlled studies are conducted, as a rule, by the most qualified physicians, in conditions far from routine practice, and at the same time adherence to physician prescriptions for the investigational drug is carefully monitored [7,16]. Therefore, the question arises whether the results obtained in randomized controlled trials for an intervention will be reproduced in real clinical practice. In other words, randomized controlled studies give us an idea of the effect of a drug under ideal conditions, and real practice, as a rule, is very far from such conditions. That is why recently the concept of "effectiveness" has been introduced into pharmacoepidemiologists, meaning the effect of a drug in a routine clinical setting. The effect of a drug registered in randomized controlled studies is called "efficacy" [19]. Later in this article, the same terminology will be observed.

The foregoing dictates the need to verify the results obtained in randomized controlled studies with the help of real clinical practice studies, that is, effectiveness studies. Such studies can be just observational studies of effectiveness, which were mentioned above.

How to conduct effectiveness studies

We note that there are currently no strict requirements for conducting observational studies of effectiveness (as opposed to requirements for conducting randomized controlled studies) [19,20]. Therefore, the National Society for Evidence-Based Pharmacotherapy has considerable experience in conducting studies of this kind [21-23]. The basic principles for conducting these studies are presented below.

Observational studies of effectiveness are observational. However, we interpret them somewhat broader than just observational studies. From our point of view, their main difference from randomized controlled studies is the absence of an experimental component, that is, the study should not go beyond what is permitted (but not always performed) in routine clinical practice. Therefore, this doesn't preclude the presence of a specific study protocol – fixed dates for a patient's visit to a doctor and the implementation of recommendations for the use of any specific drugs (strictly in accordance with the official instructions).

As a rule, such studies are carried out by ordinary doctors who can undergo special training in compliance with modern clinical guidelines for participation in the study. An example of such a study is the PRIORITY study, which studied: the possibility of implementing in real clinical practice clinical guidelines for statin treatment in patients with high and very high cardiovascular risk, the features and main problems of this therapy. The results of the study revealed treatment shortcomings – doctors' erroneous assessment of cardiovascular risk values and, as a result, target lipid profile values, clinical inertness of doctors in titrating statin doses and achieving target values, but the results also showed that there are effective opportunities to eliminate these problems and improving the quality of lipid-lowering therapy. These include conducting educational trainings for practicing physicians on the main provisions of modern clinical guidelines, the use of affordable, effective and safe generic drugs [22].

Recruitment and inclusion of patients in observational studies

As a rule, patients are included in observational studies of effectiveness on the principle of registering, that is, each patient who meets the specified inclusion criteria is sequentially included. Obviously, these criteria are not as stringent as in randomized controlled studies. This allows a much wider range of patients to be included in observational studies compared to patients who participated in randomized controlled studies. A consistent way of including patients will make it possible to achieve the formation of fairly representative groups of patients, which is of great

importance for further interpretation of the results obtained.

After being included in observational studies, patients receive information from a doctor about participation in such a project and sign an informed consent to participate in observational studies and consent to the processing of personal data, approved by the institution's ethical committee.

Interference (prescribing drugs) in observational studies

As we have said, intervention as such is absent in classical observational studies. In observational studies of effectiveness, intervention is possible, but only within the limits of clinical practice, which corresponds to the basic rules of patient management according to current clinical guidelines.

There are fundamental differences between randomized controlled studies and observational studies of effectiveness in relation to the source of the study drug that is given to the patient. It's very important that in randomized controlled studies, a drug is almost always *issued* to a patient and is subject to special registration. In observational studies of effectiveness, the attending physician *recommends* that the patient take the drug, and the patient should get/purchase it from the pharmacy network (but he doesn't always do this). This dictates the need to monitor the actual intake of the drug by patients, that is, to assess the patient's adherence to taking the drug. For this purpose, special questionnaires are being created, without which observational studies of effectiveness actually lose their meaning. One such questionnaire is the original validated questionnaire approved for use in this type of studies by the National Society for Evidence-Based Pharmacotherapy. This questionnaire allows us to determine various types of adherence (potential and actual, primary and secondary, full and partial, general adherence and adherence to certain combination therapy drugs), as well as to identify the most significant factors of non-adherence [23,25].

Evaluation of the efficacy in observational studies

It's known that not all patients adhere to the treatment prescribed by the doctor, even in the framework of randomized controlled studies [26]. In observational studies of effectiveness, the proportion of patients not adhering to treatment is even higher. Therefore, patients are usually divided into three subgroups (not necessarily equal to each other). These subgroups are formed of patients who are fully adherent to treatment, partially adherent to treatment and non-adherent to treatment. The presence of such subgroups makes it possible to form comparison groups in observational studies of effectiveness by analogy with the groups of active treatment and placebo control in randomized controlled studies, and further evaluate the effect of the studied drug. Of course, this approach is very far from the approach used in randomized controlled studies. However, the results of the effectiveness of nicorandil in the NIKEA study according to the principle described above were very similar to the results of the IONA RCT, which examined the effect of nicorandil. The components of the combined primary endpoint in the observational studies of the NIKEA were identical to the cardiovascular events assessed in the IONA randomized controlled studies. Both randomized controlled studies investigating the effect of nicorandil (IONA) and observational studies of the effectiveness of this drug (NIKEYA) showed that patients taking nicorandil were significantly less likely to have a combined endpoint and components of a combined endpoint [24].

Legal differences

Don't forget that in our country the conduct of randomized controlled studies is clearly regulated by Federal legislation [27]. Any trial that goes beyond the real clinical practice, without fail, requires obtaining permission from the Ministry of Health of the Russian Federation and the Ethics Council under the Ministry of Health of the Russian Federation. We also note that all patients participating in randomized controlled studies are subject to compulsory insurance: the contract of compulsory life insurance, health insurance of patients participating in a clinical trial of a drug for medical use is one of the mandatory documents when considering the issue of granting permission to conduct a clinical trial. [27]. All studies of this type are registered on a special website of the Ministry of Health of the Russian Federation. Since observational studies are within the scope of normal

clinical practice, they don't require the above registration and insurance procedures.

Conclusion

We will summarize and note that there is currently no alternative to well-planned, well-organized and correctly interpreted randomized controlled studies in the field of evaluating the effect of new drugs. However, there are situations where randomized controlled studies can't be carried out, or there is no need to conduct them. Then well-designed observational studies can serve as a substitute for randomized controlled studies. In turn, observational studies are also the main way to confirm the effect of a drug in real clinical practice, proven in randomized controlled studies.

Relationships and Activities: none.

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