

**PROFESSIONAL EXPERIENCE OF CLINICAL STUDIES
ON PATIENTS WITH DISEASES REPRESENTING PUBLIC
HEALTH PROBLEMS (DIABETES MELLITUS AND
HYPERTENSION)**

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ABSTRACT: *Diabetes mellitus and hypertension represent major health care problems worldwide. Most diabetic patients present associated pathology, especially cardiovascular complications. Enrollment of them for clinical studies is crucial, providing useful new information for investigation and treatment. Purpose: This work focused on attitude of patients selected for trials and the knowledge of them and their physicians regarding medical ethics. Materials, methods: Information regarding the patients were obtained*

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during presentation of the study protocol and discussing about their consent. Data regarding the physicians were collected directly during an interview by the main investigator. Results: Studies were carried out between October 2013 - July 2016, the average age of patients was over 60 years. Patients from urban areas requested more detailed information about the study compared to rural subjects. The rejection rate for enrollment was low. Doctors having previous experience with trials were aware of medical laws and ethical standards, other physicians were not so well informed, but didn't disagree with our studies. All of them requested for the laboratory results of their enrolled patients. Conclusions: Subjects had generally positive attitude for enrollment to trials, all physicians appreciated our effort and were willing to use the results for the benefit of their patients.

KEYWORDS: *diabetes mellitus, hypertension, clinical study, medical legislation, ethical standards*

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1. INTRODUCTION

Diabetes mellitus is a metabolic disease with growing incidence in the last decade. Hypertension is approximately twice as frequent in diabetic patients compared to non-diabetic individuals. Cardiovascular complications represent the major cause of mortality in diabetic patients, and many factors, such as hypertension, contribute to these conditions (Ciocan, 2015), (Sowers, 2001). Management of hypertension is critically important in preventing heart attacks and strokes. Proper investigation of these patients has a major role in achievement of individualized treatment plan.

Several studies has been carried out on different type of diabetics and subjects with hypertension, some of them being multicentric trials involving large patient numbers, but still there are some controversial aspects regarding cardiovascular risk factors, side-effects of different treatments, etc. (Nathan, 2014), (Hsu, 2013), (Ikramuddin, 2013).

The protocol of a clinical trial plays a key role in planning and conducting the study, interpretation of the data, and it is also crucial for the external review by detailing the plans from ethical approval to dissemination of the results obtained (Chan, 2013).

Another critical aspect is the proper formulation of the informed consent document, for the patients to fully understand the purpose of the study and the majority of the selected patients to agree to participate. The approval of the ethical committee is necessary for all forms of medical research trials involving human subjects before a study is initiated (Happo, 2016).

Besides the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, the Ministry of Health stated in 2004 in Romania the basic rules which should be respected, the responsibilities of those involved and the list of documents to be prepared in case of organizing any kind of clinical trials involving human subject¹.

¹ Order nr. 1.236/2004 of the Romanian Ministry of Health, published in Romanian Official Gazette (Monitorul Oficial al Romaniei), part I, nr. 1.132/30.XI.2004

Purpose:

The aim of this work is to reveal the differences between the attitude of distinct patient groups to be enrolled in clinical studies and the knowledge of the subjects and their physicians regarding healthcare legislation and ethical aspects.

Materials, methods

Our research group obtained information about the patients' medical data and attitude during the preselection period when the subjects were informed about the study and they were asked to provide personal data for the informed consent document. The knowledge of their physicians on healthcare laws and ethics regarding clinical studies was evaluated by an interview performed by the main investigator during the study period.

Results

Average age of diabetic patients involved in the preselection of our last clinical study during May-September 2015 was 65.61 years \pm 9.70 (SD), and for those with hypertension 63.2 years \pm 11.5 (SD). The studies on hypertensive patients took place between October 2013 - February 2014, April – June 2015 and a new preselection on this kind of patients was carried out between March-July 2016.

Diabetic patients from urban environment requested significantly more detailed information regarding the study compared to subjects from rural areas, only 3% of the subjects asked for written documents regarding the details of the clinical research (all of these patients being from urban areas), and the rejection rate for participation to the study for diabetic subjects was 2% (all of those deciding not to participate were from urban areas). This first step of the study was only about laboratory analyses performed from serum sample, blood for the special tests was collected in the same occasion with sampling for regular routine parameters.

The response rate was much lower when recruiting subjects for the second clinical phase of the study, performing complex ophthalmologic investigations on diabetic patients. 53 subjects from the previous study group were asked about their willingness to participate, 43 had positive response, and only 30 showed up in the scheduled day (56.6% of the invited subjects). The most frequent arguments for rejecting the enrollment to the second phase of the study were: difficulties to walk (due to old age, handicap and/or complications of the diabetes causing pain at the level of the feet), recent participation to a less complex ophthalmologic check-up, desire to avoid busy personal schedule.

The hypertensive patients were all patients of the cardiology compartment of the Procardia medical unit where our laboratory is located, the preselection was performed by the clinicians before the patients presented for sample collection, so rejection of the participation to the study was not an issue in this case. During the last ongoing preselection on hypertensive patients, cardiologists currently use a short mental test to differentiate between hypertensive subjects with and without mental dysfunction due to microvasculopathy. The patients were very positive about the possibility of participation, especially because of the special investigations (including magnetic resonance imaging and some pricey laboratory investigations) available for free for the subject of the trial.

Those physicians who formerly participated to similar clinical studies (elderly, experienced specialists being also university teachers, and younger clinicians being also doctoral students) were aware of the medical laws and ethical standards. Their colleagues who work only at the hospital and/or in other medical units were not well informed about the current legislation, but didn't disagree with the study. All the physicians

(diabetologists, internal medicine specialists and general practitioners) requested the chief investigator to provide them the laboratory test results for their patients involved in the clinical study to use the information for clinical purposes.

Discussion

Diabetic patients are usually very cooperative, the majority of them heard about our study from their diabetologist, and they specifically addressed to our laboratory to have the chance to participate to our trial. This preselection made by the clinicians (most of them working outside our medical unit) explains the very low rejection rate for enrollment to our study. In case of the studies on hypertensive subjects, the clinicians selecting the patients worked inside our medical unit, which was even better from the point of view of the compliance. Direct access to the medical records of these patients in the computer system of the Procardia medical unit made processing of the data easier. Chronic diseases make the patients somehow dependent on their physicians who prescribe their medication and follow their state of health, a good collaboration between clinicians and laboratory personnel is essential for the proper management of clinical trials.

The competence of the medical staff also counts very much. The quality of sampling, a clear list of the selection criteria, a proped protocol, the capacity of the investigators to explain in a few words the essence of the proposed study to the patients before they actually read the Informed consent document are all important factors for the success of a clinical trial.

The confidence of the patients in the physician is crucial from the point of view of the compliance for the clinical study. Interventional studies (including administration of pharmacologic substances) are more difficult to be carried out because the physicians or the investigators should provide detailed information for the patients to understand the potential benefits of the substances intended to be used and the potential hazards of being enrolled to the trial. These studies are also usually on long term, and require several visits to the medical unit. The patients have to be strongly motivated to participate to all the phases of the protocol, the compliance of the patients is critical for the proper outcome of the study. Scoring systems might be used to evaluate the compliance of the patients enrolled in clinical studies (Abraham-Fuchs, 2015).

Protection of personal data is the responsibility of the medical team involved in clinical trials. None of the diabetic or hypertensive patients commented or raised difficulties on providing personal information for the laboratory analyses or for the enrollment to the trial, not even filling in the special questionnaire about lifestyle habits, medication, body weight and diet. Among the subject of another study recently carried out by our research group a young male patient having urinary stones (who works in an institution of national security) showed difficulties in providing personal data to be registered in the laboratory database for analyses. This was a singular case, probably related to the patients' profession.

Because of the time delay between applying for the ethical approval and receiving the document (which could last for several months), it's advisable to submit the request as early as possible. In case of long term studies it's comfortable to select more cases than strictly necessary, because some of the subjects is very likely to withdraw from the trial after a certain period, and the risk to have few data for statistics should be prevented this way.

A real challenge is the proper recording of data regarding the participants of the study, and the measures to be taken to prevent losing data (Wieseler, 2012). One of the methods implemented by our research group was double sampling, and regular updating of the database, making safety copies of it. Besides routine tests special parameters were also determined for the subjects of the studies mentioned before, processing the entire database for statistical evaluation, and providing complete information regarding their patients for the clinicians are two distinct aspects of the outcome of the study. The results were sent to the clinicians by email and handed personally to the patients.

Ethical aspects should be strictly respected, the selection should not exclude subject of certain race, religion, nationality, gender, social status, education (Tomic-Petrovic, 2016). Patients have the right to refuse or give up participation to the trial, they need to be assured that the rejection won't have any negative consequence on their medical management provided by the clinicians and laboratory personnel responsible for the preselection of the subjects.

2. CONCLUSIONS

Diabetic patients, with very few exceptions, had positive attitude for participation to clinical studies, especially subjects from urban areas requested detailed information regarding the research plan and investigations performed. Hypertensive patients were very compliant with our studies, confidence of them in their physicians and a good collaboration between the members of the medical team are essential for the success of clinical trials.

Regardless their level of knowledge concerning medical legislation and ethical standards, physicians having different specialities, age and experience agreed with our research and were willing to use the results for the benefit of their patients.

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