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ANTIHYPERTENSIVE THERAPY EFFECTIVENESS DEPENDING ON ADHERENCE TO TREATMENT IN OUTPATIENT PRACTICE IN PATIENTS WITH STAGE 1-2 ARTERIAL HYPERTENSION

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The purpose of the study was to assess the influence of antihypertensive therapy used in outpatient practice in patients with grade 1–2 arterial hypertension on parameters of central hemodynamics and organ protection in conditions of low adherence to treatment. The prospective study included 93 outpatients with newly diagnosed hypertension of grades 1–2 without a history of cardiovascular complications, including 49 men and 44 women (mean age 52.3±3.8 years). Depending on the prescribed antihypertensive therapy, the patients were divided into 3 groups: 1st – 15 patients who were prescribed monotherapy, 2nd – 40 – free combination and 3rd – 38 – fixed combination of two antihypertensive drugs. It was established that the appointment of patients with stage 1–2 hypertension in outpatient practice with antihypertensive therapy (monotherapy, various two-component combinations of antihypertensive drugs) for 6 months allowed achieving target blood pressure levels, which contributed to the improvement of left ventricular systolic function, a decrease in the degree of left ventricular hypertrophy and a nephroprotective effect. With low adherence of patients with stage 1–2 hypertension to treatment, the effectiveness of antihypertensive therapy and its cardioprotective and nephroprotective properties were significantly reduced. This indicates the significant relevance of determining adherence to treatment in real clinical practice, which will allow taking these provisions into account when drawing up programs of preventive measures to prevent cardiovascular complications in this cohort of patients.

Key words: arterial hypertension, antihypertensive therapy, adherence to treatment, organ protection.

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ЕФЕКТИВНІСТЬ АНТИГІПЕРТЕНЗИВНОЇ ТЕРАПІЇ В ЗАЛЕЖНОСТІ ВІД ПРИХИЛЬНОСТІ ДО ЛІКУВАННЯ В АМБУЛАТОРНІЙ ПРАКТИЦІ У ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ 1–2 СТУПЕНЯ

Метою роботи було вивчити вплив антигіпертензивної терапії, що застосовується в амбулаторній практиці у пацієнтів з артеріальною гіпертензією 1–2 ступеня, на показники центральної гемодинаміки та органопротекції в умовах низької прихильності до лікування. У проспективне дослідження включено 93 амбулаторних пацієнти з вперше виявленою артеріальною гіпертензією 1–2 ступеня без серцево-судинних ускладнень в анамнезі, серед них 49 чоловіків та 44 жінки (середній вік 52,3±3,8 років). Залежно від призначеної антигіперпензивної терапії пацієнти були розділені на 3 групи: 1-а – 15 пацієнтів, яким була призначена монотерапія, 2-а – 40 – вільна комбінація і 3-я – 38 – фіксована комбінація двох антигіпертензивних препаратів. Встановлено, що призначення пацієнтам з артеріальною гіпертензією 1–2 ступеня в амбулаторній практиці антигіпертензивної терапії (монотерапія, різні двокомпонентні комбінації гіпотензивних лікарських засобів) протягом 6 місяців дозволяло досягти цільових рівнів артеріального тиску, що сприяло покращенню систолічної функції лівого шлуночка, зменшенню ступеню гіпертрофії лівого шлуночка та нефропротективному ефекту. При низькій прихильності пацієнтів з артеріальною гіпертензією 1–2 ступеня до лікування ефективність антигіпертензивної терапії та її кардіопротективні та нефропротективні властивості суттєво знижувались, що свідчить про значну актуальність прихильності до лікування у реальній клінічні практиці і дозволяє враховувати ці положення при складанні програм профілактичних заходів попередження серцево-судинних ускладнень у даній когорті пацієнтів.

Ключові слова: артеріальна гіпертензія, антигіпертензивна терапія, прихильність до лікування, органопротекція.

The work is a fragment of the research project "To determine the features of immunocytokine imbalance in comorbid patients with hypertension and type 2 diabetes and cardiovascular and renal complications", state registration No. 0123U101711.

Hypertension (HTN) is one of the leading causes of premature death worldwide and a major public health problem [4, 11]. According to a 2015 survey, 1.13 billion people worldwide suffer from hypertension, one in four women and one in five men [13].

Hypertension is a major risk modifier for kidney disease, stroke, heart failure, and cardiovascular disease [14]. It is present in 70–80 % of patients with chronic kidney disease, contributing to the progression of end-stage renal disease, and inadequate nocturnal blood pressure reduction is associated with accelerated loss of renal function [9]. In addition, hypertension and its complications are one of the leading causes (more than half of cases) of cardiovascular mortality [8].

The appointment of antihypertensive therapy involves taking into account not only the effect on blood pressure (BP) levels, but also organoprotective properties [2, 5]. Modern recommendations for the

management of patients with hypertension [10] state that therapy should be started with a combination of antihypertensive drugs, which allows for the implementation of synergism of their action and suppresses counterregulatory mechanisms of increasing BP. This approach contributes to achieving more pronounced stabilization of BP and improving the portability of therapy. [15]. At the same time, the appointment of fixed combinations of antihypertensive drugs leads to increased adherence to treatment compared to patients who took the same drugs separately [1]. Meta-analysis data [12] indicate that the most common reason for refusing treatment is the asymptomatic course of hypertension, which is not perceived by patients as a condition requiring regular treatment.

The purpose of the study was to assess the impact of antihypertensive therapy used in outpatient practice in patients with grade 1–2 arterial hypertension on indicators of central hemodynamics and organ protection in conditions of low adherence to treatment.

Materials and methods. The prospective study included 93 outpatients with newly diagnosed hypertension of 1–2 degrees without a history of cardiovascular complications. Among them, 49 were men and 44 were women (mean age 52.3±3.8 years). Depending on the prescribed antihypertensive therapy, the patients were divided into 3 groups: 1st – 15 patients who were prescribed monotherapy, 2nd – 40 – free combination and 3rd – 38 – fixed combination of two antihypertensive drugs (Table 1).

Table 1

Antihypertensive therapy in examined patients with hypertension

Groups	Therapy regimen		
	Lisinopril 10–20 mg/day	Lisinopril+amlodipine besylate 10–20/5–10 mg/day	Fixed combination Lisinopril+amlodipine besylate 10–20/5–10 mg/day
Group 1	15 (16.1 %)	-	-
Group 2	-	40 (43 %)	
Group 3	-	-	38 (40.9 %)

The control group consisted of 20 practically healthy individuals (mean age 51.5±3.8 years).

Informed consent was obtained from all subjects to participate in the study. All patients included in the study were examined in accordance with the recommendations of the European Society of Hypertension and the European Society of Cardiology (ESH / ESC, 2018).

All subjects underwent a general clinical examination, which included a questionnaire to identify risk factors for cardiovascular diseases, physical examination, anthropometric measurements, office BP measurement, calculation of glomerular filtration rate [eGFR] (CKD-EPI formula). Also, fasting serum glucose concentration (FG) and during a glucose tolerance test, lipid profile indicators, serum creatinine concentration,

All laboratory and instrumental examinations were performed at the State Institution "National Institute of Therapy named after L.T. Mala, NAMS of Ukraine".

All subjects underwent echocardiography using the diagnostic system "GE Medical Systems" (Germany) with a phased array sensor with a modulated frequency of 2.25–3 MHz in M- and B-modes in accordance with the recommendations of the American Society of Echocardiography (ASE, 2016) with determination of ejection fraction (EF) and myocardial mass index (MMI) of the left ventricle (LV). Analysis of the studied parameters was carried out retrospectively based on medical documentation.

According to the initial (primary) examination, patients were prescribed antihypertensive therapy. The duration of the study was 6 months.

After the treatment, the assessment of adherence to therapy was determined by means of a patient survey. The criteria for low adherence were the patient's self-correction of the antihypertensive therapy regimen (partial refusal) or complete non-compliance with medical recommendations (complete refusal).

Mathematical computer processing of the study results was carried out using the software package "Statistica 10.0" (StatSoft Inc, USA). The nature of the distribution of quantitative data was assessed using the Kolmogorov-Smirnov criterion. Quantitative data are presented in the form of arithmetic means (M) and standard deviations (SD). To compare related groups of patients by one or more characteristics, the distribution of which was subject to the law of normal distribution, a one-way analysis of variance with repeated measures (repeated measures ANOVA/ANOVARM) was used.

Results of the study and their discussion. After 6 months of treatment, according to the survey, low adherence to treatment was detected in 3 (20 %) patients in group 1, 11 (27.5 %) in group 2 and 8 (21.1 %) in group 3, which corresponded to the category of “partial refusal”.

Among the examined patients, there were no individuals who would correspond to the category of “complete refusal”. During the observation period, no side effects of drug therapy or cardiovascular

complications were registered in the examined patients. Target blood pressure levels were achieved in 12 (80 %) patients in group 1, 33 (82.5 %) in group 2 and 30 (78.9 %) in group 3. Office blood pressure data in the examined patients in the dynamics of treatment are presented in Table 2.

Table 2

BP dynamics under the influence of antihypertensive therapy (M±SD)

Parameters	Examination period	Group 1	Group 1	Group 1
SBP, mm Hg	Before treatment	155.6±3.1	156.9±3.3	157.3±3.5
	6 months	137.5± 4.5**	135.8±4.2**	135.3±4.3**
DBP, mm Hg	Before treatment	92.3±2.6	92.8±2.5	93.1±2.5
	6 months	83.7±3.1*	82.8±3.1*	83.3±3.3*
LVEF, %	Before treatment	63.3±2.5	62.4±1.7	62.1±2.7
	6 months	65.6±2.3*	65.4±1.8*	65.7±2.3*
LVMMI, g/m²	Before treatment	123.2±1.8	121.9±1.3	123.4±1.7
	6 months	118.2±1.5	118.3±1.1	118.1±1.5

Notes: 1. * – significant differences compared to the original data; 2. * – $p < 0.05$; 3. ** – $p < 0.001$.

As can be seen from the data presented, after 6 months of treatment, office systolic blood pressure decreased by 11.6 %, 13.4 %, and 13.9 % in groups 1, 2, and 3, respectively ($p<0.001$) compared to baseline. Office diastolic blood pressure decreased by 9.3 %, 10.7 %, and 10.5 % in groups 1, 2, and 3, respectively (all $p<0.05$).

After treatment, LVEF increased on average by 3.6–4.8–5.7 % in all examined groups of patients with hypertension. At the same time, LVMMI decreased by 2.9–4.2 % (all $p<0.05$).

The analysis of treatment results showed that low adherence to antihypertensive therapy was noted in 22 patients, and there were 71 individuals with high compliance. It was found that patients with high adherence to antihypertensive treatment had a more pronounced decrease in office systolic and diastolic blood pressure (Fig. 1, 2).

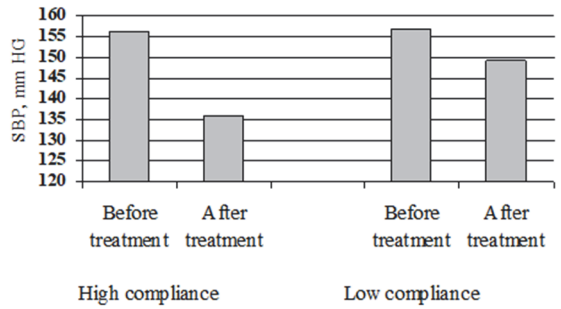

Fig. 1. Dynamics of office SBP in hypertensive patients with high and low compliance to treatment.

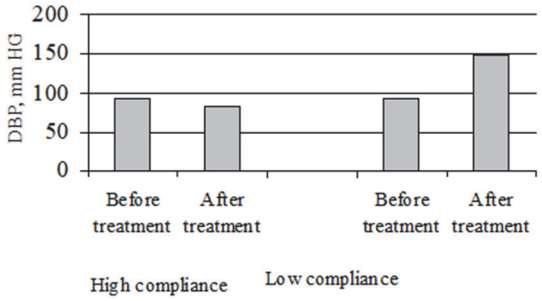

Fig. 2. Dynamics of office DBP in hypertensive patients with high and low compliance with antihypertensive therapy.

In addition, patients with high compliance to treatment had a greater increase in LVEF by 4.5 % ($p<0.05$) compared to individuals with low adherence to antihypertensive therapy (Δ0.9 %, $p>0.05$)) (Fig. 3).

In patients with hypertension with low adherence, after 6 months of therapy, an increase in LVMMI by 0.9 % was noted, while with high adherence, a tendency to a decrease in this indicator by 4.3 % was observed (Fig. 4).

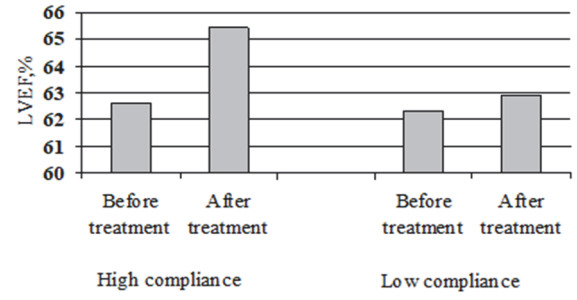

Fig. 3. Changes in LVEF in hypertensive patients with high and low compliance to therapy.

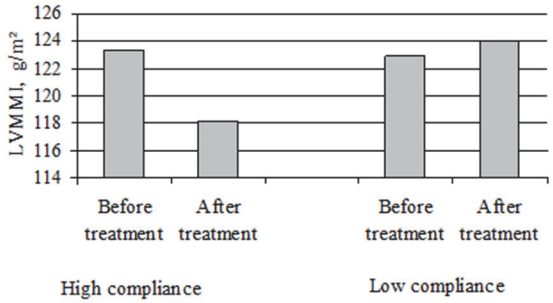

Fig. 4. Dynamics of LVMMI in patients with hypertension with high and low compliance with therapy.

It was noted that the estimated glomerular filtration rate increased against the background of treatment in patients with hypertension, but in patients with high adherence the increase was 13 %, while in patients with low adherence it was only 6.3 % ($p<0.05$).

The European Guidelines on Hypertension recognize that poor patient adherence to medication therapy is a major factor contributing to inadequate blood pressure control in patients with hypertension, along with physician inertia and deficiencies in health systems [9].

According to a systematic review [8], the prevalence of non-adherence to antihypertensive medication in Asia was 48 % (95 % CI: 41–54, p=0.001). Higher rates of non-adherence were observed in low- and lower-middle-income countries, 50 % (95 % CI: 47–54, p=0.220), compared with upper-middle-income and high-income countries, 37 % (95 % CI: 25–49, p=0.001) and 44 % (95 % CI: 29–59, p=0.001), respectively.

According to a meta-analysis [7], the global prevalence of non-adherence to antihypertensive medication was between 27 % and 40 %. Patients with non-adherence to antihypertensive medication had suboptimal blood pressure control, hypertension-related complications, all-cause hospitalization, and all-cause mortality. Non-adherence to treatment was more common in low-income countries than in high-income countries.

Another systematic review [12] showed that in low- and middle-income countries, adherence interventions for people with cardiovascular disease that included a combination of patient education, reminders, fixed-dose combination therapy, and a team approach to care were generally more effective than single interventions. Among patients with cardiovascular disease, adherence interventions were moderately effective.

Gardezi SKM et al. [6] conducted a study that assessed the impact of adherence to antihypertensive therapy in a database of patients from the Centers for Disease Control and Prevention (CDC) on total cardiovascular deaths. They found that for every 1% increase in nonadherence, total cardiovascular deaths increased by 7.13 deaths per 100 000 adults (95% CI: 6.34-7.92). This pattern persisted even after controlling for the percentage of residents with access to insurance, the percentage of residents eligible for Medicaid, the percentage of residents without a college education, median home value, income inequality, and poverty rate ($p<0.001$).

Another study [3] assessed the perceptions, motivations and barriers to adherence to antihypertensive therapy in patients according to emotional factors, lifestyle, medical risk profiles and risk of non-adherence. It was shown that ideal adherence was 59.8% of participants. The rate of reporting episodes of non-adherence to doctors was low at 13%. Participants with a high risk score for non-adherence had a higher number of comorbidities (obesity, sleep disorders, depression and cardiac complications), a higher burden of treatment on daily life, higher levels of stress and a higher number of antihypertensive tablets per day ($p<0.001$ for all). The authors concluded that emotions, family difficulties and stress certainly influence the risk of non-adherence, but non-adherence remains largely unrecognised.

According to our study, in patients with grade 1–2 hypertension, low adherence to antihypertensive therapy was observed in 22.9 % of the examined patients and did not significantly differ from taking antihypertensive drugs in a fixed or non-fixed combination, which was possibly due to the small number of patients and the insufficient observation period.

Conclusions

1. It has been established that the appointment of antihypertensive therapy (monotherapy, various two-component combinations of antihypertensive drugs) for 6 months to patients with stage 1–2 hypertension in outpatient practice allowed achieving target blood pressure levels, which contributed to the improvement of left ventricular systolic function, a decrease in the degree of left ventricular hypertrophy, and a nephroprotective effect.

2. With low adherence of patients with stage 1–2 hypertension to treatment, the effectiveness of antihypertensive therapy and its cardioprotective and nephroprotective properties were significantly reduced, which indicated the significant relevance of adherence to treatment in real clinical practice. Taking these provisions into account will increase the effectiveness of developing programs of preventive measures to prevent cardiovascular complications in this cohort of patients.

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