 

ORIGINAL ARTICLE

# THERAPEUTIC APPROACHES TO THE CORRECTION OF COGNITIVE IMPAIRMENT IN PATIENTS WITH HYPERTENSION AND TYPE 2 DIABETES

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## ABSTRACT

**The aim:** Was to improve the effectiveness of the treatment of cognitive impairment in patients with hypertension and type 2 diabetes.

**Materials and methods:** 56 patients (11 women and 45 men, average age 61.7 ± 4.3 years) with hypertension II, 2 degree and type 2 diabetes (average severity, subcompensation stage) were examined. 40 patients had moderate CI and 16 had mild CI. After the examination, the patients were divided into two groups and treated accordingly. The control group consisted of 20 healthy individuals.

**Results:** Vascular brain lesions that cause hypertension and diabetes very often lead to impaired cognitive function whose therapeutic correction has received little attention, especially in the pre-operative stages. 56 patients have been examined to study the efficacy and safety a combination of Phenibut and Ipidacrine as an additional therapy to standard basic treatment (antihypertensive and hypoglycemic) for the correction of cognitive dysfunction in patients with comorbidity of hypertension and type 2 diabetes mellitus.

**Conclusions:** One month after the beginning of the treatment, an improvement in psycho-emotional state and psychometric parameters was identified, which was manifested by an increase in concentration of attention, memory, psychomotor functions, speech activity together with normalization of blood pressure and metabolic parameters.

**KEY WORDS:** hypertension, diabetes mellitus, cognitive impairment

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## INTRODUCTION

Arterial hypertension (AH) and diabetes mellitus (DM) of 2 types are among the three most common noncommunicable diseases and, also, are risk factors for cardiovascular complications, which are leading in the world as for the frequency of fatal cases [1]. Prolonged existing uncontrolled hypertension leads to the secondary damage to the heart and blood vessels and almost all vessels in the body from the aorta to the capillaries suffer from it. The lesion of the brain as a target organ of AH is manifested not only by strokes but also by impaired cognitive functions (memory, thinking, attention and so on). Vascular cognitive disorders are disorders of higher brain function caused by cerebrovascular pathology. This concept combines both vascular dementia and less severe cognitive impairment of vascular etiology [2]. Recently, the problem of cognitive disorders is becoming more and more of a medical and socio-economic importance, which is associated with an increase in the life expectancy of economically developed countries and the one in the prevalence of both moderate cognitive disorders and dementia [3].

Currently, in a large number of patients of working age with insufficiently controlled blood pressure (BP), even on the basis of antihypertensive therapy, cognitive functions have not been sufficiently studied [4,5]. Moreover, in the specified cohort of patients, asymptomatic lesions of cerebral vessels are more common among other target organ lesions [6]. Therefore, it is necessary to diagnose cognitive impairment as early as it is possible, i.e. before the onset of pronounced clinical signs, in order to optimize the tactics of managing such patients.

It is known that the treatment of hypertension in patients with type 2 diabetes is a complex problem, often with unsatisfactory results, which necessitates the search for new, effective ways of treating this pathology. In addition, when prescribing antihypertensive therapy to patients with hypertension and type 2 diabetes it is necessary to take into account their effect on the functional state of target organs, including cognitive function, as well as their effect on lipid and carbohydrate metabolism [7]. The use of a combination of an ACE inhibitor and a calcium antagonist amlodipine has shown to significantly affect the elastic properties of blood vessels in patients with hypertension and with type 2 diabetes mellitus [8], but the effect of this therapy on cognitive function in patients with hypertension type 2 diabetes with cognitive impairment remains unclear.

In our country, drugs with neurometabolic effects are used for treatment of mild and moderate cognitive impairments. The presence of the neuroprotective properties in a drug is fundamental, as it is also about the prevention of the growth of cognitive disorders and the development of dementia. In this regard, Phenibut, a representative of the

modern generation of nootropic agents with GABAergic activity gains lots of interest. Anxiolytic, nootropic, anti-stress and tranquilizing effects of Phenibut are realized due to the influence of GABA on the functional state of the nervous and cardiovascular systems [9]. It has been demonstrated under the influence of phenibut, that the drug stimulates learning and memory improvement, increases physical performance, eliminates psycho-emotional tension, anxiety, fear and improves sleep [10]. At the same time, unlike tranquilizers, indicators of higher nervous activity such as attention, memory, speed and accuracy of sensory-motor reactions are improved under the influence of Phenibut [10].

Ipidacrine exhibits the following pharmacological effects: restores and stimulates neuromuscular transmission; restores the impulses in the central and peripheral nervous systems; enhances contractility of smooth muscle organs under the influence of all antagonists except potassium chloride; improves memory and learning abilities; inhibits the progressive development of dementia; specifically stimulates the CNS; exhibits analgesic effect; exhibits antiarrhythmic effect [11]. The combination of Phenibut and ipidacrine properties causes an increase of the cognitive functions of the brain due to the influence on the GABAergic, cholinergic and dopaminergic brain systems.

Anti-stress drugs have not yet been used in the comorbidity of hypertension and type 2 diabetes in widespread clinical practice. The effect of neuroprotective therapy on the state of the stress system in patients with hypertension and type 2 diabetes has not been sufficiently studied. The research based on a systematic approach methodology will allow to develop a strategy for optimizing the activity of a multilevel stress system taking into account the individual characteristics of patients with cognitive impairment. This research seems promising and justified for patients with hypertension in combination with type 2 diabetes

## THE AIM

The purpose of the study was to improve the effectiveness of the treatment of cognitive impairment in patients with hypertension and type 2 diabetes.

## MATERIALS AND METHODS

56 patients (11 women and 45 men, average age 61.7 ± 4.3 years) with hypertension II, 2 degree and type 2 diabetes (average severity, subcompensation stage) were examined. 40 patients had moderate CI and 16 had mild CI. The diagnosis of hypertension was established in accordance with the recommendations of the European Society of hypertension and the European Society of Cardiologists (ESH / ESC, 2013) [12]. The diagnosis of type 2 diabetes was established according to the general recommendations of the European Association for the Study of Diabetes (EASD, 2013) [13].

The diagnosis of moderate cognitive impairment (MCI) was established according to the criteria of R.S. Petersen et al. [14]. The diagnosis of mild CI was established in accordance with the criteria of N.N. Yahno et al. [15]. All patients were diagnosed with at least one of the following complaints: noise, tinnitus, decreased performance, headache, dizziness, instability in walking, emotional lability as well as sleep disorders.

All patients underwent general clinical examination, physical examination, measured office blood pressure, heart rate (HR), total blood and urine analysis, biochemical blood test with determining of fasting serum glucose (GCN) levels, glycosylated hemoglobin (HbA1c) levels in whole blood, of insulin and lipid profile; insulin resistance was evaluated by the NOMA-IR index.

Daily blood pressure monitoring (DMBP) was performed using an «ABPM-02» device (Meditech, Hungary). The following indicators were determined: daytime, nighttime, average daily (24 hours) SBP and DBP as well as heart rate [16].

Expanded neuropsychological research, which included a set of quantitative tests for attention, memory, psychomotor functions, intellectual abilities, language activity, etc. were performed by a neurologist. The study of cognitive functions was performed according to the method of A.R. Luria [17], the short scale of the study of mental status (MMSE) [18] and the Montreal scale of assessment of cognitive functions (MoCa) [19].

After registration of baseline data, 28 patients of the main group (group 1) were prescribed basic therapy for hypertension (lisinopril 10-20 mg / day, amlodipine 10-20 mg / day) and a fixed combination of Phenibut 300 mg and Ipidacrine hydrochloride 5 mg («Kognifen», « Olainpharm", Latvia) 1 capsule 3 times a day for 4 weeks. 28 people who were in the comparison group (group 2) were prescribed basic AH therapy. Patients in both groups also received antihypertensive therapy (metformin + gliclazide), statins, antiplatelet therapy. These patient groups were compared according to the age and gender. The control group consisted of 20 healthy individuals (4 women and 16 men, average age 60.8 ± 2.9 years).

All patients successfully completed the study according to the protocol. The second study was performed after 4 weeks of treatment. Side effects and undesirable effects during this period have not been reported.

The mathematical computer processing of the study results was carried out using the software package «Statistica 8.0» (StatSoft Inc, USA). Mean value (M), variance, standard deviation, median (m), probability and significance leveli (p) have been calculated. Differences were considered significant at the level of statistical significance $p < 0.05$. The method of correlation analysis with the calculation of the Pearson correlation coefficients (with normal distribution) and Spirman (with a distribution different from normal) were used in order to evaluate the relationship between the indicators.

## RESULTS

The results of numerous clinical studies [20-24] indicate that hypertension increases the risk of cognitive impair-

**Table I.** Indicators of blood pressure according to the office measurement and DMBP of patients with hypertension

| Indicators | 1st group (n=28) | | 2nd group (n=28) | |
|---|---|---|---|---|
| | before therapy | after therapy | before therapy | after therapy |
| Sphygmomanometry: | | | | |
| SBP, mmHg | 164,3±6,3 | 132,5±3,5*** | 165,1 ± 6,4 | 135,8 ± 3,5*** |
| DBP, mmHg | 93,8 ± 4,5 | 80,3 ± 3,6* | 94,1 ± 4,6 | 82,2 ± 3,8* |
| DMBP | | | | |
| SBP24, mmHg | 151,6± 4,6 | 128,5 ± 4,3*** | 151,9 ± 4,5 | 129,3 ± 4,1*** |
| DBP24,mmHg | 91,7 ± 4,2 | 78,3 ± 3,5** | 91,6 ± 4,3 | 79,1 ± 3,3** |
| PBP, мм рт.ст. | 57,9 ±2,3 | 50,1 ± 2,3* | 57,7 ±2,5 | 50,8 ± 2,1* |
| TI SBPday, % | 61,5 ± 7,3 | 35,1 ± 7,1** | 62,1 ± 7,4 | 36,3 ± 7,1** |
| TI SBPnight, % | 65,1 ± 5,3 | 49,7 ± 4,1* | 66,3 ± 5,1 | 49,5 ± 4,3* |
| TI DBPnight, % | 43,3 ± 5,1 | 20,9 ± 4,3*** | 43,2 ± 5,3 | 21,3 ± 4,1*** |

Notes:
1. * - reliability of differences compared to the original data;
2. * - p <0.05;
3. ** - p <0.01;
4. *** - p <0.001.

**Table II.** Indicators of blood pressure (office and according to DMBP) patients with hypertension and type 2 diabetes.

| Indicators | 1st group (n=28) | | 2nd group (n=28) | |
|---|---|---|---|---|
| | before therapy | after therapy | | before therapy |
| TC, mmol / l | 6,31 ± 0,35 | 5,23 ± 0,28* | 6,35 ± 0,32 | 5,29 ± 0,25* |
| LDL-C, mmol / l | 2,56 ± 0,12 | 2,15 ± 0,10* | 2,57 ± 0,11 | 2,17 ± 0,10* |
| HDL-C, mmol / l | 0,98 ± 0,06 | 1,13 ± 0,02 | 0,95 ± 0,05 | 1,15 ± 0,03 |
| Tg, mmol / l | 2,28 ± 0,07 | 1,89 ± 0,06 | 2,35 ± 0,07 | 1,98 ± 0,05 |
| FBG, mmol / l | 7,30 ± 0,35 | 6,28 ± 0,31* | 7,31 ± 0,36 | 6,29 ± 0,30* |
| HbA1c, % | 7,19 ± 0,42 | 6,13 ± 0,40* | 7,21 ± 0,42 | 6,36 ± 0,31* |
| Insulin, uU / ml | 22,17 ± 0,49 | 19,09 ± 0,45 | 22,21 ± 0,46 | 19,08 ± 0,45 |
| HOMA-IR | 7,21 ± 0,56 | 5,42 ± 0,52* | 7,23 ± 0,59 | 5,46 ± 0,47* |

Notes:
1. * - reliability of differences compared to the original data;
2. * - p <0.05.

ment. It has been shown that the frequency of cognitive dysfunction increases with type 2 of diabetes mellitus [25, 26]. The exact mechanisms forming the basis of the association between type 2 diabetes and dementia are not clear. However, the effect of type 2 diabetes on cognitive function is probably realized through a whole set of mechanisms, reflecting the metabolic complexity of this disease. At the same time, studies on the characteristics of cognitive impairment in comorbidity and type 2 diabetes mellitus as well as methods for their correction are insufficient.

It has been proven that a significant reduction of the risk of developing ischemic and especially hemorrhagic strokes can be achieved in the treatment of hypertension [27]. Moreover, lowering blood pressure has been shown to help improve the performance of screening tests for dementia and memory, which indicates the beneficial effect of antihypertensive therapy on cerebrovascular morbidity. At

**Table III.** Dynamics of indicators of neuropsychological testing of patients with hypertension and type 2 diabetes.

| Tests | Period of study | 1st group (n=28) | 2nd group (n=28) | Control group |
|---|---|---|---|---|
| MMSE scale, | before therapy | 26,6±0,3 | 26,5±0,5 | 30±0,3 |
| score | after therapy | 29,1±0,2*** | 27,3±0,3 | |
| 10-word memorization test (word count) | before therapy | 6,0±1,1 | 6,1±1,7 | 8,7±0,2 |
| | after therapy | 8,5±0,2* | 7,0±1,5 | |
| MoCa, score | before therapy | 23,1±0,2 | 23,6±0,3 | 29,3±0,2 |
| | after therapy | 29,2±0,3*** | 24,1±0,3 | |

Notes:
1. * - reliability of differences compared to the original data;
2. * - $p < 0.05$;
3. *** - $p < 0.001$.

the same time, some of the cognitive functions (perception process, learning ability) may not improve against the background of a decrease in blood pressure, which indicates an uneven effect of a decrease in blood pressure on different cognitive functions [28,29].

In our study there was a significant decrease in blood pressure according to the office measurement of blood pressure and DMBP after a course of treatment the patients with comorbidity of hypertension and type 2 diabetes (table.1. Indicators of blood pressure according to the office measurement and DMBP of patients with hypertension). However, differences in the dynamics of BP between the groups were not observed.

To date, type 2 diabetes pharmacotherapy is highly effective in reaching targeted glycemic levels as well as additional positive effects, significantly reducing the risk of complications, possibly including cognitive impairment.

There was an improvement in carbohydrate metabolism, a decrease in the insulin resistance index of HOMA and a lipidogram in patients in both groups after the treatment.

## DISCUSSION

Drugs with neurometabolic effects are used in the treatment of mild and moderate cognitive impairment in Ukraine. The presence of the neuroprotective properties in a drug is fundamental, as it is also about the prevention of the growth of cognitive disorders and the development of dementia. In this regard, Phenibut, a representative of the modern generation of nootropic agents with GABA-ergic action is of a great interest. Due to the influence of GABA on the functional state of the nervous and cardiovascular systems, anxiolytic, nootropic, antistress, and tranquilizing effects of Phenibut are realized [30]. The drug has been demonstrated to improve memory and learning, increases physical performance, eliminates psycho-emotional tension, anxiety, fear and improves sleep [31]. However, unlike tranquilizers, indicators of higher nervous activity such as attention, memory, speed and accuracy of sensory-motor reactions are improved under the influence of Phenibut [32].

We have found in our study that with the same decrease in blood pressure and positive dynamics of glucometabolic indicators the additional appointment of a fixed combination of Phenibut and Ipidacrine hydrochloride in the complex therapy of patients with hypertension and type 2 diabetes led to a more significant subjective improvement ($p < 0.05$) according to the dynamics of complaints (from 17.5 [16.2; 19.0] at baseline to 8.6 [6.3; 9.1] after the treatment ($p < 0.05$) versus 17.5 [16, 3; 19.1] to 12.5 [10.9; 14.6] in the comparison group ($p > 0.05$).

Changes in neuropsychological testing during treatment are presented in table 3. According to the MMSE scale, after 4 weeks of drug therapy, statistically significant positive dynamics were found, which differed significantly in the group receiving an additional fixed combination of Phenibut and Ipidacrine hydrochloride. The same tendency was found in the 10-word memorization test. The MoCa scores make it possible to evaluate cognitive functions more accurately. Improved cognitive function after 4 weeks of therapy was observed, It occured more pronounced in group 1 which indicates an improvement in brain functionality under the influence of treatment with the addition of a fixed combination of Phenibut and Ipidacrine hydrochloride.

## CONCLUSIONS

Thus, the addition of a fixed combination of Phenibut and Ipidacrine hydrochloride to basic antihypertensive therapy increases the effectiveness of cognitive function and, mareover, along with good safety, manifests itself in improving the psychometric parameters of patients with hypertension and diabetes mellitus type 2.

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**Conflict of interest:**

*The Authors declare no conflict of interest.*


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