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POSSIBILITIES OF ANTIHYPERTENSIVE THERAPY IN CORRECTION OF COGNITIVE IMPAIRMENT IN HYPERTENSIVE PATIENTS

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Abstract

Data regarding possibilities of antihypertensive therapy to reduce a risk of the development of new cases of cognitive impairment are contradictory. So, **the purpose of the study** was to analyze the effect of antihypertensive therapy onto the dynamics of cognitive functions in hypertensive patients. We examined 90 patients with stage 1 and 2 hypertension, 2-3 degrees (middle age of patients was $49,66 \pm 8,74$ years). Clinical and anamnestic examination, laboratory and instrumental methods of examination were done to all patients. Neuropsychological tests, as GPCOG, MMSE, Schulte tables were used to study cognitive functions. Cognitive impairment were observed in 36 patients (40%). The combination of inhibitors of angiotensin-converting enzymes (iACE) or angiotensin II receptor blockers (ARB) + calcium channel blocker (CCB) was used as antihypertensive therapy. While using this therapy not only the decrease and normalization of blood pressure but also improvement of cognitive functions were noticed. Particularly, in 61,29% cases patients gained obviously more points in the retesting MMSE($p=0,003$) and GPCOG($p=0,01$) and almost all patients (96,77%) needed less time to fulfill tasks by Schulte tables ($p=0,0001$). The total sum of points by MMSE scale increased by 3,66% ($p=0,003$), the total score by GPCOG scale

increased by 22,24% ($p=0,01$), and in the control execution of Schulte test patients used less time by 14,39 % in comparison with initial results ($p=0,0001$).

Key words: hypertension; cognitive impairment; antihypertensive therapy

Introduction

The relationship between high blood pressure (BP) and disorders of cognitive function has been established in many epidemiological studies. Increase in systolic BP for every 10 mmHg increases the risk of moderate cognitive impairment (CI) by 7%, severe - by 9% [1].

Nowadays, there is also a sufficient evidence regarding the ability of antihypertensive treatment reduce the risk of development of new cases of cognitive impairment. Thus, according to a meta-analysis of 12 clinical trials where the effects of different classes of antihypertensive drugs on the development and progression of dementia were compared, the risk of occurrence of cognitive impairment is 9% lower in individuals receiving antihypertensive therapy, regardless of drug class [2].

Angiotensin II receptor blockers (ARB) have shown the best results in improving cognitive functions (including improved perception, memory, and concentration) compared to placebo and were more effective than β -adrenergic blockers, diuretics, and inhibitors of angiotensin-converting enzymes (ACE) [3, 5]. But there are contradictory data in the scientific literature. In particular, according to the results of a meta-analysis, in 15936 patients with hypertension without objectively diagnosed cerebrovascular diseases it was not found conclusive evidence that any decrease in blood pressure in the elderly reduces the likelihood of dementia or cognitive impairment [6]. Therefore, **the purpose of our study** was to analyze the effect of antihypertensive therapy on the dynamics of cognitive functions in hypertensive patients.

Materials and methods of investigation

We examined 90 patients with stage 1 and 2 hypertension, 2-3 degrees. Among the patients there were 53 males (58,89%) and 37 females (41,11%). The age of the patients was 27-60 years, the middle age of patients was $49,66 \pm 8,74$ years.

All patients underwent clinical and anamnestic examination during which blood pressure was measured and BMI (body mass index) was determined, laboratory tests (level of total cholesterol, low and high density lipoprotein cholesterol, triglycerides, glucose, creatinine calculating glomerular filtrate rate (CKD-EPI), electrolytes of blood) were done and instrumental methods of investigation (24-hour monitoring of blood pressure, electrocardiography, ultrasound examination of the heart) were used. 24-hour blood pressure

monitoring was done on the portative apparatus “ABPM 50” (“Heaco” Great Britain) before and after treatment.

Neuropsychological testing was used to objectify cognitive impairments: the General Practitioner assessment of Cognition (GPCOG), the Mini-Mental State Examination (MMSE). Stability of attention and sensomotor reactions rate were evaluated using Schulte tables.

All patients received antihypertensive pharmacotherapy according to the recommendations of the European Society of Cardiology (ESC) and European Society of Hypertension (ESH) of the year of 2018 as a combination of two drugs in one tablet. To study the effect of antihypertensive therapy on the parameters of cognitive functions in hypertensive patients, we selected 31 patients with stage 1 and 2 hypertension from the age of 46 to 60 years (middle age 55.19 ± 4.42). Among those surveyed were men, 19 (61.3%). All patients had moderate cognitive impairment detected by neuropsychological testing using the MMSE scale (24-26 points). The combination of iACE or ARB + calcium channel blocker (CCB) was used as antihypertensive therapy (Table 1), since according to data CCB showed a better effect on regression of cognitive impairment compared to diuretics [7, 8]. By simple method, patients were randomized to two clinical groups depending on the nature of pharmacotherapy. The first clinical group consisted of 17 patients receiving antihypertensive treatment for ARB (valsartan) at a daily dose of 80–160 mg/day and CCB (amlodipine) at a dose of 5–10 mg per day in a fixed combination. Patients randomized to the clinical group 2 (n = 14) were given medicine from iACE (perindopril) at a dose of 4–8 mg/day and amlodipine at a dose of 5–10 mg/day, also in a fixed combination.

Table 1. Clinical characteristic and the structure of pharmacotherapy of hypertensive patients and moderate cognitive impairment

Index	Patients with moderate cognitive impairments (n=31)
Males, abs. / %	19 / 61,3
Age	$55,19 \pm 4,42$
MMSE, points	$25,74 \pm 0,44$
Schulte tables	$52,16 \pm 5,85$
GPCOG, points	$4,87 \pm 1,23$
iACE + CCB, abs. / %	14 / 45,16
ARB + CCB, abs. / %	17 / 54,84

Results

The main complaints among hypertensive patients were: headache (81.11%), dizziness (67.78%), tinnitus (64.44%), sleep disorders (57.61%), general weakness and increased fatigue (54.44%), impaired memory and attention (47.78%), rapid fatigue experiencing mental activity (45.56%). According to the results of neuropsychological testing of MMSE among the examined patients, cognitive impairment were detected in 36 patients (40%). Due to the fact that 5 patients with cognitive impairment did not pass retesting due to subjective reasons, data of 31 patients were used in the final analysis.

While using already administered antihypertensive therapy the level of systolic blood pressure and diastolic blood pressure decreased by 26.33% and 26.57%, respectively, and was characterized by stable normalization ($p = 0.0001$). This is evidenced by the results of the repeated 24-hour monitoring of blood pressure (Table 2).

Table 2. Dynamics of blood pressure in hypertensive patients with cognitive impairment before and after treatment (n = 31)

Data		Indices before treatment	Indices after treatment	Abs. change of index	% change of index	p
Median SBP, mm.Hg	M±SD	168,29±10,81	123,52±4,59	-44,78±11,36	-26,33±5,19	0,0001
	min. – max	150,8–186,5	114,6–129,9	-68,5– -26,7	-36,95– -17,71	
Median DBP, mm.Hg	M±SD	98,25±7,35	71,76±4,91	-26,49±8,82	-26,57±7,49	0,0001
	min. – max	84,60–112,30	62,00–79,90	-43,1– -10,1	-39,11 – -11,43	

Substantial improvement in subjective symptoms was observed under the influence of antihypertensive therapy. Most patients reported decreased in frequency and intensity of headache, dizziness, tinnitus, and improved sleep. Repeated neuropsychological testing conducted after three months of pharmacotherapy also revealed positive dynamics. Thus, in 61.29% of cases, patients obtained significantly more points while retesting MMSE ($p = 0.003$) and GPCOG ($p = 0.01$), and almost all patients (96.77%) required significantly less time to complete the tasks using Schulte tables ($p = 0.0001$). Improvement of all MMSE testing was observed, as shown in Table 3.

Orientation, memory, counting, and executive functions improved (although the difference between the indices was statistically insignificant ($p > 0.05$)) and the total sum of points increased by 3.66% ($p = 0.003$). The overall GPCOG point also increased by 22.24%

($p = 0.01$). In the control execution of Schulte test patients used less time by 14,39 % in comparison with initial results ($p=0,0001$) (Table 4).

Table 3. Effect of three-month antihypertensive treatment on the dynamics of cognitive function indices on the MMSE scale in hypertensive patients

Index	Before treatment	After treatment	p
Orientation (max- 10 points)	9,35 ± 0,49	9,58 ± 0,50	0,12
Counting (max- 5 points)	3,80 ± 0,79	4,03 ± 0,80	0,13
Memory (max- 6 points)	4,32 ± 0,60	4,52 ± 0,72	0,15
Gnosis and praxis (max- 9 points)	8,23 ± 0,62	8,48 ± 0,63	0,11
Total sum of points (max- 30 points)	25,74 ± 0,44	26,68 ± 0,79	0,003

Table 4. Indices of dynamics of neuropsychological test results in hypertensive patients (n = 31)

Indices		Index before treatment	Index after treatment	Abs. change of index	% change of index	p
MMSE, points	M±SD	25,74±0,44	26,68±0,79	0,94±0,85	3,66±3,34	0,003
	min – max	25 – 26	26 – 28	0 – 2	0 – 8	
GPCOG, points	M±SD	4,87±1,23	5,84±1,34	0,97±0,91	22,24±22,18	0,01
	min – max	3 – 8	3 – 8	0 – 3	0 – 66,67	
Schulte test, s	M±SD	52,16±5,85	44,24±4,3	-7,92±6,36	-14,39±10,45	0,0001
	min – max	43,22–62,49	34,53 – 50,25	-26,99 – 0,76	-43,87 – 1,67	

Comparing the effect of treatment with different combinations of drugs at the level of blood pressure, no significant differences between the indicators of the two groups were found. As shown in Table 5, systolic BP and diastolic BP in groups of the patient did not differ significantly at the beginning of treatment. Positive clinical dynamics and normalization of blood pressure were observed in both groups of patients within three months of treatment, which was observed in the indicators of the repeated 24-hour blood pressure monitoring. The antihypertensive efficacy of valsartan in combination with amlodipine was confirmed by decrease in average daily systolic BP and average daily diastolic BP by 44.64 ± 10.31 mmHg

and 25.12 ± 9.73 mmHg respectively. Pharmacotherapy with perindopril and amlodipine resulted in decrease in average daily systolic BP and diastolic BP by 44.95 ± 12.92 mm Hg. and 28.16 ± 7.58 mmHg. respectively. However, no significant difference in the reduction of blood pressure between the groups was found ($p = 0.95$ for CAT and $p = 0.38$ for DAT), both combinations showed good results.

Table 5. Comparison of dynamics of indicators in groups 1 and 2 during three-month treatment, $M \pm SD$

Data	Group 1 (n=17)			Group 2 (n=14)			t (p)
	before treatment	after treatment	% changes of index	before treatment	after treatment	% changes of index	
average daily systolic BP, mm. Hg	168,54± 10,09	123,9± 5,0	-26,27± 4,74	168± 12,01	123,05± 4,18	-26,4± 5,87	0,07 (0,95)
average daily diastolic BP, mm. Hg	96,49± 7,75	71,37± 4,45	-25,5± 8,32	100,4± 6,46	72,24± 5,55	-27,85± 6,39	0,89 (0,38)
GPCOG, points	4,65± 1,11	5,35± 1,22	17,06± 20,23	5,14± 1,35	6,43± 1,28	28,52± 23,53	1,44 (0,16)
MMSE, points	25,76± 0,44	26,71± 0,77	3,68± 3,53	25,71± 0,47	26,64± 0,84	3,63± 3,22	0,05 (0,96)
Schulte test, s	51,84± 5,61	44,68± 3,89	-12,98± 10,91	52,54± 6,33	43,7± 4,84	-16,11± 9,99	0,83 (0,41)

Note. t - Student's t-test between two groups after treatment; at $p < 0.01$ - the difference between the indicators is significant

Obtained findings also indicate an improvement in cognitive functions on the top of already administered antihypertensive therapy in both groups of patients: an increase in total MMSE and GPCOG points and a decrease in the average time of Schulte test fulfillment, but no significant difference between retest rates in the groups was also found (Table 5)

The results of neuropsychological testing of the patients in clinical group 1 showed a significant increase in MMSE by 3.68% after treatment compared with initial indices, 26.71 ± 0.77 points against 25.76 ± 0.44 points ($p = 0.003$). It should be noted that among the patients of group 1, the best dynamics of indices was noted in the domains of memory and counting. A similar pattern was observed for the GPCOG test, an increase in total points by 17.06% ($p = 0.01$). Also, while fulfilling a control Schulte test the patients in group 1 spent less time by 12.98% ($p = 0.0001$).

The analysis of the neuropsychological examination of the patients in clinical group 2 showed a significant improvement in MMSE results, in particular the total sum of points increased by 3.63%, 26.64 ± 0.84 points compared to 25.71 ± 0.47 points at the beginning of the study ($p = 0.003$). The patients in group 2 showed better results in the domains of orientation and executive functions. The total sum of points of the GPCOG test increased by 28.52% ($p = 0.01$), and the time of tasks fulfillment by Schulte tables decreased by 16.11% ($p = 0.0001$).

Recent studies have highlighted the important role of the renin-angiotensin-aldosterone system (RAAS) in both brain aging [9] and progression of dementia [10]. This relationship can be explained by the effect of angiotensin II on vascular and metabolic homeostasis and on metabolism of amyloid. Blood angiotensin is also known to affect the neuroendocrine system and the brain through the circumventricular organs [11]. It is likely that the suppression of the negative effects of RAAS may be related to the positive results of ARB and iACE therapy in the combination of CCB in our study.

Conclusions

1. Therefore, obtained results of the clinical study indicate an undeniably positive dynamics of cognitive functions in hypertensive patients with cognitive impairment while using antihypertensive therapy, which is characterized by a significant improvement in the results of MMSE and GPCOG testing, as well as an increase in the reaction rate while fulfilling tasks by Schulte tables.

2. We did not find significant therapeutic benefits in the correction of cognitive impairments between the admitted iACE or ARB + CCB combinations; the difference in the dynamics of neuropsychological testing between the two groups was statistically insignificant. Therefore, RAAS blockers (in particular ARB valsartan and iACE perindopril) in combination with CCB may be recommended in clinical practice for the treatment of hypertensive patients diagnosed with cognitive impairments.

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