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The Combined Impact Of Amlodipin And Regular Physical Exercises On Platelet And Inflammatory Markers In Patients With Arterial Hypertension.

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ABSTRACT

It is known that lasting existence of arterial hypertension is very dangerous in respect of stroke, myocardial infarction or sudden death coming and development of impaired cardial function. At the same time, the basic mass of cardio-vascular complications at arterial hypertension is connected with the development of arterial thromboses which develop, as a rule, against the background of atherosclerotic alterations in vessels. In the conducted research we estimated the potential of amlodipin therapy impact and its combination with regular physical exercises on risk markers of the development of thrombosis and inflammatory alterations in vascular wall of patients with arterial hypertension. There were examined 78 men with arterial hypertension of the 2nd degree and 28 clinically healthy persons of the second mature age. In our research we registered the aggregation of erythrocytes and platelets, leucocytes' activity, plasma concentration of von Willebrand's Factor and the quantity of adhesive molecules in plasma. One group of patients received amlodipin 10 mg/a day, the second group of patients received its combinations with physical exercises. The repeated examination of patients was conducted in 3 months. There were detected more evident positive alterations of all the accountable indices against the background of amlodipin therapy in the group having physical exercises. In this respect it can be considered that amlodipin intake by persons with arterial hypertension is more preferable against the background of dosed regular physical exercises as in this case it is possible to minimize the evidence of markers, high risk of thrombosis and active course of atherogenesis.

Keywords: arterial hypertension, platelets, erythrocytes, endothelial dysfunction, amlodipin, physical exercises.

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INTRODUCTION

High frequency of arterial hypertension (AH) occurrence among population of developed countries is very dangerous for society. It is connected with frequent coming of temporal disability episodes against its background and high frequency of its complications [1,2]. It is known that lasting AH existence is very dangerous in respect of stroke, myocardial infarction or sudden death coming and development of impaired cordial function [3,4]. At the same time, the basic mass of cardio-vascular AH complications is connected with the development of arterial thromboses which develop, as a rule, against the background of atherosclerotic alterations in vessels [5,6]. Thrombosis development is often preceded by rheology alterations of regular blood elements, its composition and continuity disturbance of vascular wall [7,8]. The formation of endothelial dysfunction [9] is also considered to be an important cause of thrombogenesis in patients with AH. Weakening of vasodilatation substances' synthesis in vessels against the background of endothelial cells' lack of capacity to inhibit regular blood elements' [10,11] adhesion to them nearly always lies in its basis. The rise of von Willebrand's Factor concentration and adhesive molecules' [12] level is often its marker at AH.

In previous researches it was shown that the width of artery walls often increased at AH. It is considered as not only hypertrophy manifestation of smooth muscle cells of vascular wall but also as its atherosclerosis manifestation [14,15]. Taking into account that vessels' atherosclerotic involvement has immune-inflammatory mechanism (in addition to some others), the development of inflammatory processes in vessels at AH is considered to be an unfavorable sign [16].

It is acknowledged that activation of calcium channels in vascular walls and regular elements plays a great pathogenetic role in the process of myocardium and vessels' remodeling and also in the course of atherosclerotic plaques' growth at AH. It is an important cause of persistent vascular spasm and hyperaggregation of erythrocytes and platelets [17]. In this respect the given category of patients should receive hypotensive drugs from the group of calcium antagonists. Amlodipin is one of their modern representatives. Its good hypotensive capacities were proved earlier [18]. However, its impact on regular blood elements' aggregation and inflammatory alterations in vessels needs clarification. In previous researches there was shown the possibility of strengthening of pharmacological therapy positive effects in cordial patients with the help of non-pharmacological treatment [19,20,21]. In this respect it seemed important to compare the effects of amlodipin therapy in patients with AH at regular physical exercises and without them.

Aim: to estimate the possibility of strengthening of amlodipin therapy effects with the help of adequate regular physical exercises in respect of pro-thrombotic and pro-inflammatory alterations in bodies of patients with arterial hypertension.

MATERIALS AND METHODS

The research involved 78 men of the second mature age with AH of the 2nd degree (their average age – 47.8±2.3 years) with the duration of the disease – 8.2±3.0 years and normal body mass – the index of body mass – 25.2±0.19 kg/m^2. The examined patients included 37 (47.4%) patients with the smoking habit and 57 (73.1%) patients having burdened heredity in AH. Involved into the research patients had no clinically significant concomitant pathology. All the patients taken into the research knew about AH presence in themselves. However, they took no hypotensive drugs concerning it systematically. All the patients were prescribed amlodipin – 10mg in the morning. The titration of the dose was demanded in no cases as hypotensive effect was sufficient in all the cases. The patients were casually subdivided into two groups. The first group involving 36 patients was prescribed only amlodipin. In the second group amlodipin treatment was added by attendance an athletic section – an hour a day, 4 times a week. The observation lasted 3 months in both groups. After that all the patients were repeatedly examined. The control group was composed of 28 clinically healthy male-volunteers of the second mature age (their average age – 45.9±2.1 years) who were examined once.

In our research we estimated spontaneous erythrocytes' aggregation and spontaneous platelets' aggregation [22]. The quantity of leucocytes was registered in tests of whole venous blood with the help of automatic analyzer Sysmex, KX-21 (Kobe, Japan). Fractions of mononuclear leucocytes and neutrophils were received out of rich in leucocytes plasma by the method of differential centrifugation in density gradient – 1.077 (Histopaque, Sigma, USA). Adhesive properties of neutrophils were estimated with the help of man's

endothelial cellular line ECV304. The staining of preparations was conducted according to Mine-Grunwald-Romanovsky. Then we calculated the average number of neutrophils in $1mm^2$ of monolayer endothelium culture in 10 fields of view. The number of lymphocytes having early markers of activation (CD69+) and bM-subunits of the integrinal receptor Mac-1 (CDllb+), was registered by the method of flow cytometry (Becton Dickinson FACScan) while using the kits with monoclonal antibodies produced by the firm "CalTag" (USA): CD69-PE and CDllb-FITC. The level of ICAM-1 concentration in plasma was determined with the help of immune-enzyme analysis using the kit produced by the firm "Bender MedSystems" (Austria). The quantity of von Willebrand's Factor in plasma was determined with the help of immune-enzyme analysis using the kit :Asserachrom" (DiagnosticaStago, Roche).

Statistical processing of data was conducted using the package of applied statistical programs Statistica for Windows ver 6.0.The reliability of differences was estimated by the method of Mann-Witny. The differences were considered reliable at $p<0.05$.

RESULTS OF INVESTIGATION

Side effects of treatment were found in no cases. All the patients from both groups were observed to have persistent hypotensive effect which was a bit more evident at addition of dosed physical exercises. It manifested itself in downward trend of the levels of mid-morning, mid-day and mid-night values of systolic and diastolic arterial pressure.

The conduction of amlodipin hypotensive therapy was accompanied by spontaneous aggregation decrease of erythrocytes by 18.9% and platelets by 46.3%. The patients from the group receiving amlodipin hypotensive therapy together with regular physical exercises, reached more evident spontaneous aggregation decrease of erythrocytes (by 28.5%) and platelets (in 2.02 times) what brought them nearer to the control level (Table 1).

The increase of leucocytes' number by 28.8% in peripheric blood and the quantity of lymphocytes expressing early marker of their activation (CD69+) by 47.4% and adhesive molecules Mac-1 (CDllb+) by 20.2% was detected against the background of amlodipin therapy. The reached effect was more evident in case of regular physical exercises' addition to amlodipin intake. In this group we detected more significant decrease of leucocytes' number in peripheric blood (by 50.0%) and the quantity of lymphocytes expressing CD69+ (by 85.4%) and adhesive molecules CDllb+ (by 50.0%). It promoted approaching the values of the control group by these indices' levels. It was accompanied by the decrease of neutrophils' adhesive capacity to endothelium what was also more evident when the patients fulfilled regular physical exercises (75.0%) against 22.8% in those patients who received only amlodipin.

Both groups of observation were noted to have level lowering of von Willebrand's Factor and circulating adhesive molecules ICAM-1 in blood plasma (Table 1). Reached effect was more evident in the second group (lowering – by 30.5% and 26.2%, respectively) what let accountable indices approach the values of the control group.

Table 1: The dynamics of registered indices in the examined patients

Indicators	Treatment with amlodipine, M±m, n=36		Treatment with amlodipine against the background of exercise, M±m, n=42		Control, M±m, n=28
	Beginning of observation	End of observation	Beginning of observation	End of observation	
mid-term systolic blood pressure, mmHg	163.6±0.57 p<0.01	130.1±0.62 p_1<0.01	164.3±0.73 p<0.01	121.9±0.56 p_1<0.01	118.4±0.37
mid-day diastolic blood pressure, mmHg	106.2±0.62 p<0.01	80.4±0.67 p_1<0.01	105.0±0.51 p<0.01	80.2±0.53 p_1<0.01	78.3±0.40
average daily systolic blood pressure, mmHg	169.7±0.73 p<0.01	134.2±0.82 p_1<0.01	171.3±0.68 p<0.01	126.7±0.73 p_1<0.01	126.7±0.50

average daily diastolic blood pressure, mmHg	107.8±0.62 p<0.01	89.0±0.70 p_1<0.01	108.2±0.65 p<0.01	84.2±0.64 p_1<0.01	82.2±0.39
mean systolic blood pressure, mmHg	141.7±0.58 p<0.01	116.2±0.43 p_1<0.01	143.4±0.52 p<0.01	112.3±0.38 p_1<0.01	110.6±0.46
mean diastolic blood pressure, mmHg	92.6±0.41 p<0.01	75.6±0.39 p_1<0.05	93.4±0.43 p<0.01	71.7±0.43 p_1<0.01	70.2±0.32
Aggregation of erythrocytes,%	88.2±0.32 p<0.05	74.2±0.40	87.8±0.29 p<0.05	68.3±0.34 p_1<0.05	67.2±0.36
Aggregation of platelets,%	18.0±0.14 p<0.01	12.3±0.21 p_1<0.05	18.2±0.20 p<0.01	9.0±0.17 p_1<0.01 p_2<0.05	8.6±0.15
Leukocytes, x 10^9/l	7.6±0.29 p<0.01	5.9±0.33 p_1<0.05	7.5±0.25 p<0.01	5.0±0.34 p_1<0.01 p_2<0.05	4.7±0.25
Lymphocytes CD69+, %	11.2±0.42 p<0.01	7.6±0.38 p_1<0.05	11.5±0.32 p<0.01	6.2±0.42 p_1<0.01 p_2<0.05	5.0±0.48
Lymphocytes CD11b+, %	32.1±0.51 p<0.01	26.7±0.33 p_1<0.01	33.0±0.44 p<0.01	22.0±0.26 p_1<0.01 p_2<0.05	21.7±0.31
Severity of adhesion of neutrophils to ECV304, kl/mm^2	15.6±0.27 p<0.01	12.7±0.39	15.4±0.30 p<0.01	8.8±0.34 p_1<0.01 p_2<0.01	8.3±0.28
Concentration of von Willebrand factor, %	88.1±0.58 p<0.01	73.8±0.63 p_1<0.05	86.4±0.62 p<0.01	66.2±0.52 p_1<0.01 p_2<0.05	65.2±0.45
Concentration sICAM-1, ng/ml	419.2±1.12 p<0.01	353.4±0.75 p_1<0.05	415.5±1.07 p<0.01	329.2±0.62 p_1<0.01 p_2<0.05	324.1±0.91

Conventional signs: p – reliability of differences of initial indices and the control; p_1 – reliability of indices' dynamics in the course of treatment; p_2 – differences' signification of treatment results between the groups.

DISCUSSION

It is determined genetically that in the norm vessels' endothelium provides functionally necessary vasodilatation, represses adhesion and platelets' aggregation, erythrocyte aggregate-formation and weakens inflammatory processes connected with leucocytes' activation and adhesion [23,24]. In conditions of AH these capacities of vascular endothelium weaken very often what leads to the increase of blood viscosity, hemostasis activation, pressure fall in capillaries, increase of tissue hypoxia, weakening of nitric oxide synthesis and strengthening of anti-inflammatory alterations [25,26]. All this significantly disturbs blood stream in vessels of microcirculatory course and decreases the number of functioning capillaries [27]. At the same time, aggregation strengthening of erythrocytes and platelets increases blood viscosity and aggravates microcirculatory disturbances mostly in the result of strengthening of vasoconstrictive substances' emission out of them. Surplus erythrocytes' aggregation leads to microcirculation disturbance in vazavazorum, aggravating endothelium dystrophy. Developing in these conditions continuity disturbance of endothelial layer forms additional conditions for further aggravation of blood rheological properties and development of thrombophilia [28].

Rise of plasma concentration of von Willebrand's Factor and worsening of rheological properties of regular blood elements in patients with AH are mostly caused by persistently high level of arterial pressure [29]. Detected in the research strong positive impact of amlodipin against the background of physical exercises

in respect of regular blood elements' aggregation should be connected with the blockade of calcium channels in their membrane, weakening of thromboxane A_2proaggregant action, and also – with the increase of nitric oxide production providing antiadhesive impact [30]. Therapy effect from calcium antagonist application was more evident in case of regular physical exercises because of their known positive impact on the endothelial function and minimization of metabolism disturbances in vascular walls against their background [31,32].

It is known that endothelium is always a participant of an inflammatory process. Its active course at AH is pointed by concentration rise of adhesive molecules ICAM-1 in plasma, strengthening of neutrophils' adhesive properties, quantity rise of lymphocytes having markers of their activation (CD69+) on membranes and integrin receptors (CDllb+). Besides, strengthened expression of adhesion molecules on leucocytes points indirectly at production rise of anti-inflammatory cytokines by these cells [25,33]. In this respect, monocytes and neutrophilsbecome at AH a serious cause of endothelium damage in the result of surplus production of superoxide anions and proteolytic enzymes by them in the process of their adhesion to endothelium.

Treatment of patients with AH with the help of amlodipin was accompanied by quantity decrease of lymphocytes expressing early markers of activation (CD69+) and adhesive molecules (CDllb+), and also – lowering of neutrophils' adhesive capacity. It was maximally evident against the background of physical exercises. Given fact pointed at their evident potentiating impact on amlodipin effects, including – in respect of leucocyte markers of inflammation [34].

Aggregation weakening of erythrocytes and platelets and activity decrease of leucocytes which were more evident against the background of amlodipin and physical exercises combination, were mostly provided by concentration decrease of von Willebrand's Factor and freely circulating adhesive molecules ICAM-1 in blood [35,36]. It pointed at significant restoration of endothelium antiadhesive properties in the observed patients with AH. Reached optimization of functional properties of regular blood elements and endothelium was, evidently, caused by not only antihypertensive effect of the pharmacological preparation and physical exercises but also by suppression of thromboxane A_2 synthesis, production rise of nitric oxide and prostacyclin against their background [37].

CONCLUSION

In the conducted research there were estimated impact capacities of amlodipin therapy against the background of regular physical exercises on risk markers of thromboses' development and the course of inflammatory process in vascular wall of patients with arterial hypertension. There were examined 78 men with AH of the 2^{nd} degree and 28 clinically healthy persons of the second mature age. In the research we registered aggregation of erythrocytes and platelets, leucocytes' activity, plasma concentration of von Willebrand's Factor and quantity of adhesive molecules in plasma. The patients received amlodipin – 10mg/a day, or its combination with physical exercises. In 3 months of treatment more evident positive results were detected in the group with physical exercises. It allowed considering that regular physical exercises potentiate the impact of amlodipin therapy in patients with AH providing approach the indices' control levels of erythrocytes, platelets, leucocytes and antiadhesive properties of endothelium. In this respect we can consider that amlodipin intake by persons with arterial hypertension is more preferable against the background of dosed regular physical exercises as in this case it is possible to reach maximally evident positive alterations of markers, thrombosis risk and accelerated course of atherogenesis.

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