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Therapeutic Possibilities Of Rosuvastatin In The Medical Complex In Relation To Disaggregation Vascular Control Over Erythrocytes In Persons With Arterial Hypertension And Dyslipidemia.

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ABSTRACT

Serious progress in the therapy of dyslipidemia was the initiation of the use of statins in a wide clinical practice. Previously, the effect of individual statins, including rosuvastatin in combination with non-drug therapy, on the anti-aggregation properties of blood vessels against erythrocytes was not assessed. The aim is to evaluate the possibility of therapeutic effect of a combination of rosuvastatin, a Hypolipidemic diet and regular physical exertion on anti-aggregation control of blood vessels over erythrocytes in patients with arterial hypertension and dyslipidemia. In patients with arterial hypertension with dyslipidemia, there was a marked increase in erythrocyte aggregation and a decrease in the disaggregation of the vascular wall above them. As a result of the 6-week complex application of rosuvastatin and non-drug treatment in patients with arterial hypertension and dyslipidemia, the lipid composition and lipid peroxidation activity in the plasma was normalized and the anti-aggregation control of the vascular wall over erythrocytes was optimized. The result was preserved during the whole subsequent observation - 92 weeks. It was found out that 1.5 month application of rosuvastatin and non-drug therapy normalizes hypertension in patients with arterial hypertension with dyslipidemia, lipid composition of plasma and processes of lipid peroxidation in it. Continuation of treatment fixes the effect achieved and saves it while continuing treatment.

Keywords: arterial hypertension, dyslipidemia, vascular wall, erythrocytes, rosuvastatin, non-drug treatment.

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INTRODUCTION

Beginning often at a young age, arterial hypertension (AH) is one of the most common diseases in developed countries [1, 2]. It is rightly considered one of the major factors ensuring high rates of temporary disability, disability and mortality in persons of mature age [3, 4]. This is largely aggravated by the increase in the frequency of occurrence of various metabolic disturbances in hypertension [5, 6], a large prevalence, among which dyslipidemia (D) continues [7, 8, 9]. It was noted that even in the presence of isolated hypertension, the physiological properties of the vessels appear quite early, including the weakening of their disaggregation effects on the aggregation of blood elements. This significantly increases the risk of developing various vascular accidents [10, 11]. Given the great social and medical importance, the questions of AH and D have always been given great attention in experimental [12, 13] and clinical studies [14]. At the same time, the successes achieved in terms of treating these conditions separately and in combination [15] have so far not allowed to completely solve the problem of minimizing their manifestations and complications [16,17]. Serious progress in D therapy, especially in combination with AH, was the beginning of the use of statins in a wide clinical practice. Their long reception proved to be able to significantly reduce mortality from cardiovascular causes, improve the quality of life of patients and optimize their overall prognosis [1]. This was based not only on their Hypolipidemic properties, but also on the ability to positively influence the aggregation ability of blood elements [17, 18]. It was noted that the severity of their therapeutic effects increased significantly against the background of the use of lipid-lowering diets and feasible dose-related physical exertion [2, 19]. At the same time, this category of patients still does not evaluate the effect of the most active statins, incl. Rosuvastatin in combination with non-medicament us therapy, on the state of antiaggregatory properties of blood vessels in relation to the most numerous uniform elements of blood - erythrocytes. The aim of the work is to evaluate the possibility of therapeutic effect of a combination of rosuvastatin, lipid-lowering diet and regular physical exertion on anti-aggregation control of blood vessels over erythrocytes in patients with AH and D.

MATERIALS AND METHODS OF A RESEARCH

The study was approved by the local ethics committee of the Russian State Social University on September 14, 2016 (protocol No. 19). The study was conducted on the basis of the Russian State Social University. The study was performed on 61 patients with AH of 1 to 2 degrees, risk 3 with type D IIb, middle age. Before entering the study, all patients were repeatedly examined and well informed about the presence of arterial hypertension and dyslipidemia; however, they were not systematically treated for them. Patients occasionally took enalapril and perindopril, beta-blockers (nebivolol and bisoprolol), sometimes combining them with indapamide. They did not strictly observe the Hypolipidemic diet with episodes of its gross violation. Statins did not take any patient before entering the study. Before enrolling in the study, all patients abstained from taking antihypertensive drugs and did not comply with the Hypolipidemic diet for 3 weeks. The control group is represented by 26 healthy volunteers of similar age.

The level of lipid peroxidation (LPO) in the liquid part of the blood was determined by the content of thiobarbituric acid (TBA) -active products in it with the help of the "Agat-Med" (Russia) kit and the number of acyl hydroperoxides (AHP). The antioxidant activity of plasma was recorded [20].

The concentration of total cholesterol (CH) and triglycerides (TG) in the plasma of the examinees was determined by the enzymatic colorimetric method using the kit of the company Vital Diagnosticum (Russia).

The amount of high-density lipoprotein (HDL) cholesterol in the liquid part of the blood was elucidated by an enzymatic colorimetric method, using the OlvexDiagnosticum (Russia) kit. A quantitative assessment of the total lipid (TL) in the blood was carried out using the Erba Russ kit (Russia).

The concentration of low-density lipoprotein (LDL) cholesterol was determined by calculation using the Firewall formula. The level of high-density lipoprotein cholesterol (VLDL) was calculated by dividing TG by 2.2.

Disaggregation properties of the vascular wall in relation to erythrocytes were elucidated during the evaluation of the weakening of their aggregation in a sample with temporal venous occlusion. Aggregation of erythrocytes was clarified before and after temporary ischemia of the vessel wall by light microscope as a

result of counting the number of erythrocyte aggregates in the Goriaev chamber, their number in the aggregated and non-aggregated state [21].

All patients were prescribed rosuvastatin 5 mg per night and enalapril 10 mg 2 times a day, lipid-lowering diet and feasible regular exercise [19]. Assessment of clinical and laboratory indicators was performed before the start of treatment, after 6, 12, 18, 52 and 104 weeks of therapy. The results are presented in the form M±m. The results were processed by Student's criterion (t). Statistical processing of received information was made with the help of a program package "Statistics for Windows v. 6.0", "Microsoft Excel". Differences in data were considered reliable in case of $p<0.05$.

RESULTS AND DISCUSSION

During 104 weeks of follow-up, none of the patients showed any side effects of the treatment. In the patients enrolled in the study, the blood levels of TL and total cholesterol in the blood were increased in comparison with the controls by 1.7 and 1.3 times, respectively (Table).

Table: Dynamics of biochemical and hematological parameters of patients on the background of complex treatment

Registered parameters	Complex treatment, n=61, M±m						Control, n=26, M±m
	initial state	6 weeks	12 weeks	18 weeks	52 weeks	104 weeks	
total cholesterol, mmol/l	6.5±0.08**	4.3±0.07	4.2±0.04	4.2±0.05	4.1±0.07	4.1±0.04	4.8±0.05
HDL cholesterol, mmol / l	1.09±0.005**	1.72±0.006	1.73±0.008	1.74±0.003	1.74±0.007	1.75±0.006	1.60±0.006
LDL cholesterol, mmol/l	4.13±0.008**	1.83±0.007	1.72±0.008	1.71±0.009	1.62±0.006	1.61±0.004	2.43±0.004
VLDL, mmol/l	1.28±0.006**	0.75±0.009	0.75±0.006	0.75±0.005	0.74±0.006	0.74±0.008	0.77±0.005
triglycerides, mmol/l	2.82±0.004**	1.66±0.003	1.65±0.006	1.64±0.009	1.63±0.007	1.62±0.006	1.70±0.002
total lipid, g/l	9.6±0.05**	5.5±0.07	5.5±0.06	5.4±0.06	5.3±0.08	5.1±0.05	5.6±0.03
acylhydroperoxides of plasma, D_{233}/l ml	3.19±0.008**	1.42±0.005	1.42±0.006	1.41±0.007	1.41±0.005	1.40±0.007	1.42±0.009
thiobarbituric acid-products of plasma, umol/l	5.16±0.005**	3.56±0.005	3.55±0.007	3.55±0.009	3.54±0.006	3.54±0.008	3.56±0.07
antioxidant activity of plasma, %	22.6±0.18**	32.9±0.05	32.9±0.09	33.0±0.05	33.0±0.07	33.1±0.10	32.9±0.12
sum of all erythrocytes in the unit against a background of venous occlusion	57.7±0.10**	44.8±0.12**	32.5±0.07	32.5±0.10	32.4±0.05	32.7±0.12	32.6±0.14
number of aggregates against a background of venous occlusion	10.5±0.08**	8.5±0.04*	7.0±0.05	6.9±0.04	6.9±0.08	6.8±0.04	7.0±0.07
number of free erythrocytes in the background	182.8±0.35**	248.3±0.28**	305.4±0.42	305.4±0.38	308.5±0.29	304.5±0.35	305.3±0.18

of venous occlusion							

Legend: reliability of differences in the parameters of the observation group and the values of control * – p<0, 05, **– p<0, 01.

Atherogenic fractions of cholesterol in their blood - LDL cholesterol and LDLP cholesterol were significantly increased in them with an increase in TG in 1.7 times and a decrease in HDL cholesterol by 46.8%. This was accompanied in patients with AH and D by significant activation of LPO in plasma. The AHP content in it was increased by 2.2 times, and the level of TBA-active products was 1.4 times higher than the control. At the same time, the value of the antioxidant plasma activity in patients was 1.4 times lower than the control (Table).

In the initial state, the observed patients in the sample with temporal venous occlusion showed an increase in the total number of erythrocytes in aggregates and in the number of aggregates themselves when the free red blood cells decreased, by 76.9%, by 50.0% and by 67.6%, respectively.

After 6 weeks of complex therapy, normalization of lipid composition of plasma was achieved in patients (Table). Target values of LDL cholesterol were achieved after 6 weeks of complex therapy in all persons taken in the study. By 6 weeks, the value of this indicator was 1.83 ± 0.007 mmol / l in the patients. Subsequently, with the continuation of therapy, the LDL cholesterol level reached a tendency to decrease. After 6 weeks of therapy, the level of antioxidant activity of plasma was also normalized (32.9 ± 0.05%). This ensured the normalization of the amount of lipid peroxidation products in plasma.

As a result of the therapy, a gradual decrease in the total number of erythrocytes in the aggregate and in the number of these aggregates with the increase in the number of freely lying red blood cells against the background of temporary ischemia of the venous wall was achieved. So, by the 12th week of observation in the sample with a temporary overlap on the cuff, the normalization of the sum of all erythrocytes in aggregates was revealed, the resultant decrease was 76.9%, the number of aggregates decreased by 50.0%, and the number of free red blood cells increased by 67, 6% (Table). During the continuation of treatment, the maintenance of the achieved normal level of the counted indicators until the end of the observation was noted.

According to modern views, the vessels are not only a blood channel, but also powerful regulators of blood flow. This is achieved through the allocation of various biologically active substances that affect the state of the blood elements [22, 23]. Due to this, the vascular endothelium regulates the aggregation of platelets, erythrocytes and leukocytes, which plays an important role in hemorheology [24].

One of the most potent vascular inhibitors of the aggregation of blood cells and vasodilators is prostacyclin [25]. It is synthesized in the vascular wall from the endopersides of arachidonic acid, formed locally in the endothelium or released from platelets [26]. Its synthesis occurs under the action of the prostacyclin synthetase enzyme, which is very sensitive to LPO activity and can be significantly inhibited by fatty acid hydroperoxides. Norepinephrine, acetylcholine, angiotensin II, bradykinin stimulate this enzyme, increasing the release of prostacyclin from the endothelium [27, 28].

In conditions of blood flow, the expression of erythrocyte aggregation largely depends on the ratio of the influence of thromboxane-prostacyclin mechanism on them, which is based on the balance of synthesis of thromboxane and prostacyclin [29, 30].

Another important regulator of the process of aggregation of erythrocytes, produced in the endothelium, is nitric oxide (NO) [31]. NO is formed from L-argentine with the participation of NO synthase [32]. With cardiovascular pathology, depression of NO synthesis can be developed due to the weakening of NO synthase. A serious and common reason for lowering the concentration of NO in the blood of patients is the acceleration of NO degradation and a decrease in the content of L-argentine in the body. This leads to a weakening of the vasodilatation, increased hypoxia, the development of lumpy aggregation of erythrocytes and the formation of a tendency to thrombosis [33].

The activity of erythrocyte aggregation is provided by many processes in the body. It affects the theology of blood in vessels of any diameter [34]. In the presence of D, arisen against the background of the existing AH, the antioxidant activity of the plasma inevitably decreases, which ensures the growth of the amount of products of lipid peroxidation in it. This situation, very often accompanies the aging process, contributing to the pronounced alteration of erythrocyte membranes [6, 8, 9]. There is a point of view that with AH and D, accelerated aging of the vessels develops. This leads to inhibition of their control over the aggregation of blood elements and is accompanied by an increase in the expression of adhesion molecules on the blood elements and the walls of the vessels [35].

Evaluation of the expression of erythrocyte aggregation in plasma, obtained against the background of venous occlusion, in patients with AH and D revealed in them a low ability of blood vessels to synthesize disaggregating compounds (prostacyclin, nitric oxide, prostaglandin D_2). This was manifested in patients in the form of a marked increase in the aggregation activity of erythrocytes, recorded in a sample with a temporary venous occlusion. Obviously, an increase in erythrocyte aggregation in patients with AH and D is largely due to a weakening of the ejection from the vascular wall of disaggregating substances while simultaneously affecting the electro-oscil- lance of their outer membrane by reducing the amount of negatively charged proteins on it [5]. The weakening of the control of the vascular wall over the aggregation of erythrocytes apparently is based on a decrease in the amount of prostacyclin and NO in the blood, as well as an imbalance in the red blood cells of adenylatecyclase and phosphodiesterase activity, which leads to a decrease in the cytoplasm of the amount of cyclic adenosine monophosphate and Ca^{2+} increase [9].

Reduction of vascular wall control over erythrocyte aggregation in hypertension with D required treatment [36]. It seemed reasonable to evaluate the dynamics of antiaggregatory properties of the vascular wall in relation to erythrocytes against the background of rosuvastatin in combination with a Hypolipidemic diet and regular exercise.

The results obtained allowed us to agree with the opinion in the literature that non-pharmacological action enhances the effect of statin [37]. The treatment resulted in a rapid improvement in the lipid composition of the plasma and stimulated the level of its antioxidant defense, normalizing the lipid peroxidation in it. At the same time, a reduction was achieved to the values of the comparison group for the aggregation capacity of erythrocytes in a plasma taken without temporal venous occlusion and against its background. This greatly facilitated the optimization of the rheological properties of blood in patients in general. Evidently, the exit to the level of control of spontaneous aggregation of erythrocytes in patients after 6 weeks of complex therapy was due to the elimination of a violation of one of the leading mechanisms of their aggregation - the optimal level of electro negativity of erythrocytes as a result of increasing the amount of proteins on their membrane with negative charge. In addition, a pronounced weakening on the background of the treatment of generation of active forms of oxygen minimizes oxidative damage to electronegative proteins of the membrane and globular plasma proteins that play the role of "bridges" between erythrocytes in the process of aggregation. Under these conditions, the forces of adhesion of erythrocytes in already formed aggregates are weakened. Accumulation of prostacyclin and NO in these conditions in the vascular wall stimulates the activity of adenylatecyclase in erythrocytes, causing a rise in the cytoplasm of the level of cyclic adenosine monophosphate, a weakening of the entry into their Ca^{2+} cytoplasm, and a decrease in the activity of the phosphodiesterase enzyme.

CONCLUSION

For patients with hypertension A is associated with increased aggregation of erythrocytes, which is largely due to a reduction in the disaggregation capacity of the vascular wall against the background of disturbances in the lipid metabolism and activation of the peroxide oxidation of plasma lipids. As a result of the 6-week complex treatment used in patients with AH with D, the lipid composition and the plasma lipid peroxidation processes in the plasma are optimized with complete normalization of the anti-aggregation capacity of the vascular wall after 12 weeks of exposure while maintaining the achieved level of the counted values until the end of the observation. In this regard, use rosuvastatin in patients with AH and D is justified in combination with non-drug therapy, as it potentiates its therapeutic effects.

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