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Weakening Of Platelet Activity In Patients With A High Degree Of Arterial Hypertension In The Metabolic Syndrome Who Received Complex Treatment.

Medvedev IN*.

Russian State Social University, st. V. Pika, 4, Moscow, Russia, 129226

ABSTRACT

According to the current views of patients with arterial hypertension with metabolic syndrome justified the use of complex treatment, consisting of safe antihypertensive drugs, hypoglycemic agents and non-drug therapy. Of great interest is the influence of this complex in patients with arterial hypertension with metabolic syndrome, increased platelet activity, which is an important factor in the formation of thrombophilia. The aim of this work is to assess the dynamics of platelet activity in patients with arterial hypertension 3 degrees in the metabolic syndrome on the background of complex treatment. The study included 24 patients with arterial hypertension 3 degrees, Mature age. The control group consisted of 25 clinically healthy people of similar age. Patients were prescribed amlodipine 10mg 1 time a day, valsartan 160 mg once daily, Metformin 500 mg 2 times a day. Non-pharmacological treatment included a reduced-calorie diet and adequate regular physical exercise. Applied biochemical, hematological and statistical methods of research. Among the examined patients there was increase of adhesive and aggregation activity of platelets with the weakening of their ability to disaggregate. This was largely caused by the presence in their blood of imbalance proaggregant and anti-aggregating substances. On the background of the applied complex therapy in the blood of patients noted a gradual decrease in the levels of lipids and acylhydrazines. The comprehensive therapy was accompanied by a patients gradual normalization in blood levels of metabolites of arachidonic acid and increase the content of nitric oxide. As a result of application of combination therapy in monitored patients, the severity of platelet aggregation in vitro have experienced the gradual weakening and normalized by 4 months of treatment. This was accompanied by patients in these terms persistent normalization of intravascular platelet activity, which significantly lowered the their risk of developing thrombosis. Conducted comprehensive therapy including amlodipine, valsartan, Metformin, hypocaloric diet and dosed physical load, was able to provide in patients with AH 3 degrees with MS after 4 months of persistent normalization of platelet activity, for maximizing the elimination of factors stimulating their functionality.

Keywords: arterial hypertension; metabolic syndrome; platelets; amlodipine; valsartan; Metformin; drug-free treatment.

Corresponding author

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INTRODUCTION

Currently, one of the leading places in the prevalence and level of deaths in the structure of common diseases belongs to cardiovascular pathology [1]. Arterial hypertension (AH) has a large proportion of it, significantly increasing the risk of thrombosis due to platelet activation [2]. In the case of adherence to hypertension of metabolic syndrome (MS), the risk of developing cardiovascular accidents increases even more [3]. The greatest risk in this regard are those with MS with hypertension of a high degree due to pronounced activation of their platelets [4].

It is believed that patients with hypertension with MS need complex treatment [5]. A combination of modern and safe antihypertensive drugs (including angiotensin receptor blockers and calcium antagonists), hypoglycemic drugs, and non-drug therapy are justified in this group of patients [6]. Of great interest is the effect of this complex on high platelet activity, which is an important factor in the formation of thrombophilia in grade 3 hypertension patients with MS.

Objective: to evaluate the dynamics of platelet activity in patients with hypertension of 3 degrees in MS on the background of complex treatment.

MATERIALS AND METHODS

The study was approved by the local ethics committee of the Russian State Social University on September 14, 2016 (protocol №19). The study was conducted on the basis of the Russian State Social University.

The study included 24 patients with AH grade 3, risk 4, including 10 men and 14 women of the second adult age (49.1 ± 1.9 years). All patients had a combination of hypertension with MS, which were diagnosed in strict accordance with generally accepted criteria [7,8]. The control group consisted of 25 clinically healthy people of similar age. Blood sampling in both groups was done after a 14-hour fast. The content of total cholesterol (cholesterol), high density lipoprotein cholesterol (HDL cholesterol) and triglycerides (TG) was determined by an enzymatic colorimetric method using Vital Diagnosticum (Russia). The level of cholesterol of low density lipoproteins (LDL cholesterol) was calculated according to W. Friedwald (1972). The activity of plasma lipid peroxidation (LPO) was detected by the content of acyl hydroperoxides (AHP) in it [9].

All patients in the plasma was determined the levels of 6-keto-prostaglandin $F_{1\alpha}$ by enzyme immunoassay using kits company "Enzo Life Sciences" (USA). Blood observed individuals was determined the total content amount of nitric oxide metabolites [10]. Platelet aggregation was evaluated on two-channel laser analyzer of platelet aggregation ALAT2 - LA230-2 ("BIOLA", Russia) using as inductor ADP ($0,5\times10^{-4}$ M), collagen (dilution 1:2 primary suspension), ristomycin (0,8 mg/ml) ("Renam", Russia). Intravascular activity of platelets was determined with phase contrast.

Patients were prescribed a complex of drugs amlodipine 10 mg 1 time per day, valsartan at a dose of 160 mg once a day, metformin at a dose of 500 mg twice a day, non-drug therapy, which included an individually selected hypocaloric diet and feasible regular physical training [7, 8]. Evaluation of clinical and laboratory parameters was carried out at the beginning of treatment, after 2, 4, 12 and 36 months of therapy.

Statistical processing of the results was carried out by t-student criterion.

RESULTS AND DISCUSSION

Baseline blood pressure figures from patients under observation (systolic - 186.1±4.3 mm Hg, diastolic - 114.8±3.2 mm Hg) corresponded to grade 3 hypertension. After 2 weeks of therapy, the blood pressure in the observed patients stabilized at the level of: systolic - 135.0±2.1 mm Hg, diastolic - 85.3±1.3 mm Hg and remained at that level until the end of the observation.

In the blood of patients, an increased amount of total cholesterol was observed, prevailing over the control values 1.30 times (Table 1). At the same time, in the blood of the observed persons with hypertension of 3 degrees with MS, an increase in LDL cholesterol and TG by 1.52 and 1.67 times was found, respectively,

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with a decrease in HDL cholesterol by 1.32 times. Against this background, in patients with plasma, the level of AGP was increased 2.28 times.

Table 1. Dynamics of indicators in the examined patients

Consider indicators	Observed patients, n = 24, M±m					Control, n=25, M±m
	outcome	2 months of therapy	4 months of therapy	12 months of therapy	36 months of therapy	
Concentration of total cholesterol, mmol/l	6.25±0.07	5.79±0.06 $p_1<0.05$	4.83±0.06 $p_1<0.05$	4.88±0.03	5.18±0.04	4.79±0.02 $p<0.01$
Concentration HDL cholesterol, mmol/l	1.14±0.003	1.31±0.001 $p_1<0.05$	1.50±0.002 $p_1<0.05$	1.51±0.006	1.43±0.01	1.53±0.001 $p<0.01$
Concentration LDL cholesterol, mmol/l	3.92±0.06	3.42±0.05 $p_1<0.05$	2.60±0.08 $p_1<0.05$	2.62±0.04	2.87±0.03	2.56±0.03 $p<0.01$
Concentration of TG, mmol/l	2.63±0.02	2.34±0.008 $p_1<0.05$	1.61±0.006 $p_1<0.05$	1.65±0.01 $p_1<0.05$	1.93±0.02 $p_1<0.05$	1.56±0.01 $p<0.01$
Concentration of plasma AHP, D_{233}/1 ml	3.62±0.03	3.24±0.02 $p_1<0.05$	1.66±0.005 $p_1<0.01$	1.65±0.006	1.89±0.002 $p_1<0.05$	1.62±0.02 $p<0.01$
Thromboxane B_2, PG/ml	291.4±0.68	212.6±0.54 $p_1<0.01$	157.1±0.42 $p_1<0.01$	156.7±0.36	157.0±0.46	156.5±0.66 $p<0.01$
6-keto-prostaglandin $F_{1\alpha}$, PG/ml	70.2±0.42	74.9±0.35 $p_1<0.05$	81.9±0.46 $p_1<0.01$	82.3±0.29	82.2±0.38	82.4±0.49 $p<0.01$
Total metabolites of nitric oxide, µmol/l	26.3±0.52	29.6±0.45 $p_1<0.05$	33.7±0.40 $p_1<0.05$	33.9±0.48	33.7±0.37	33.6±0.35 $p<0.01$
Degree of platelet aggregation with collagen, relative units	10.1±0.25	9.4±0.32 $p_1<0.05$	8.0±0.27 $p_1<0.01$	8.1±0.25	7.9±0.29	8.0±0.32 $p<0.01$
Extent of platelet aggregation with ADP, relative units	9.3±0.34	8.3±0.30 $p_1<0.05$	7.2±0.22 $p_1<0.05$	7.1±0.25	7.0±0.27	7.1±0.24 $p<0.01$
Degree of platelet aggregation with ristomycin, relative units	9.4±0.22	8.5±0.29 $p_1<0.05$	7.3±0.28 $p_1<0.05$	7.4±0.18	7.3±0.23	7.4±0.15 $p<0.01$
Number of small units of 2-3 platelets per 100 free-lying platelets	18.2±0.09	14.4±0.04 $p_1<0.05$	3.1±0.02 $p_1<0.01$	3.3±0.02	3.7±0.05	2.9±0.06 $p<0.01$
Number of medium and large aggregates, 4 or more platelets per 100 free-lying platelets	5.7±0.03	2.5±0.01 $p_1<0.05$	0.28±0.004 $p_1<0.01$	0.25±0.002	0.29±0.003	0.2±0.06 $p<0.01$
Sum of active forms, %	50.6±0.15	40.5±0.05 $p_1<0.05$	19.3±0.03 $p_1<0.01$	20.2±0.10	22.5±0.30	17.9±0.09 $p<0.01$

Legend: p - reliability of differences in indicators between the group of patients and the control, p_1 - reliability of the dynamics of the indicators taken into account against the background of correction. In the following table, the notation is similar.

As a result of the use of complex therapy in the blood of patients, there was a gradual decrease in the level of total cholesterol, reaching control values after 4 months (Table 1). In the observed patients, this was accompanied by a decrease in plasma concentrations of LDL cholesterol, VLDL and TG cholesterol, and an increase in HDL cholesterol to the control figures after 4 months, keeping them at the achieved level until the end of the observation. In the blood of patients at the same time, stable normalization of the level of AHP was observed (1.66 ± 0.005 D_{233}/1 ml). Further treatment retained the optimum lipid composition and activity of POL in the plasma of patients.

The outcome in individuals who formed the observation group, blood was found an imbalance of metabolites of arachidonic acid – thromboxane B_2 was increased by 84,8% and the derivative of its functional antagonist is 6-keto-prostaglandin $F_{1\alpha}$ was reduced by 17.9% (table.1). This was accompanied by the surveyed patients a decrease in plasma by 28.7% of the total metabolites of nitric oxide.

When conducting complex therapy in patients, a gradual normalization of plasma concentrations of arachidonic acid metabolites was noted. After 4 months of treatment, a reduction of tromboxane B_2 by 85.5%, and an increase in 6-keto-prostaglandin $F_{1\alpha}$ by 14.3% (Table 1). In the examined patients, this was accompanied by an increase in the number of total metabolites of nitric oxide (by 21.9%). The continuation of treatment ensured the preservation of the result.

At the end, platelet aggregation in patients was significantly enhanced (Table 1). Their platelets most actively reacted to collagen (the degree of aggregation with it exceeded control by 25.0%). Patients' platelets were slightly weaker with aggregation to ristomycin (the degree of aggregation with it was higher than control by 25.7%). Patients' platelets were even less actively aggregating in response to the addition of ADP - the degree of ADP aggregation in patients exceeded control by 25.7%.

As a result of 4 months of use of complex therapy, aggregation in observed patients showed normalization of collagen aggregation due to a decrease in its degree by 26.2%. This was accompanied by optimization of the degree of aggregation with ristomycin (decreased by 28.8%) and with ADP (decreased by 29.2%). The continuation of therapy allowed AT to be fixed at the achieved level until the end of the observation.

When assessing the intravascular activity of platelets (Table 1) in patients with hypertension of 3 degrees with MS, taking in the study revealed an increase in the amount of active forms of platelets by 2.8 times. Small and large aggregates in their blood contained 18.6±0.08 and 5.4±0.04, against control - 2.9±0.06 and 0.2±0.06 per 100 free-lying platelets, respectively.

The combined therapy provided the observed patients with a rapid weakening of the intravascular platelet activity, which allowed in 4 months to achieve normalization of the level of the total number of active platelet forms (19.3±0.03%). Also in the blood of persons of the observation group to 4 months. therapy, the number of small and large aggregates reached the control level (13.1±0.02 and 0.28±0.004 per 100 free-lying platelets, respectively). Further treatment ensured the stability of normal intravascular platelet activity in all patients until the end of the observation.

A marked increase in arterial pressure had a very negative effect on the vascular wall in the observed individuals, causing damage to the endothelium and exposing the subendothelial fibers capable of contact-activating platelets [11,12]. Patients' dyslipidemia also had a strong activating effect on platelets [13,14]. Under folding conditions, synthesis of prostacyclin and NO decreased in the vascular wall, limiting platelet aggregation [15,16]. At the same time, the observed patients in platelets found an intensification of the formation of thromboxane, which causes an increase in their aggregation.

Detected in the examined patients the initial high sensitivity of platelets to the inductors aggregation, were provided through the activation of a number of mechanisms [17]. So, on the surface of platelets in examined patients has been a significant increase in the density of glycoproteins that are receptors for inducers of aggregation [18,19]. Intensification of platelet aggregation in response to ADP and collagen is associated with excessive expression of the platelet receptors [20]. Amplification of platelet aggregation with ristomycin pointed to the increase in density on them receptors for von Willebrand factor [21,22].

High intravascular activity of platelets was talking about the excessive availability for platelets to collagen in the vascular wall due to damaged endothelium excessive concentrations of lipids and LPO products [23,24]. Elevated levels in the blood of patients freely moving aggregates of different sizes have caused mechanical damage to the endothelial cells [25]. This significantly weakened the activity of vascular hemostasis and increased risk of thrombosis [26,27].

Already after 4 months, a comprehensive correction stabilized the level of blood pressure, eliminated dyslipidemia in patients, which, combined with a decrease in their plasma AHP concentration, reduced their risk of atherosclerosis progression [28].

Early relief of dyslipidemia activated disaggregants synthesis in the vascular wall, resulting in patients after 4 months of complex therapy to restore to the level of control the balance of thromboxane and prostacyclin [29]. These positive changes were intensified due to an increase in the production of NO in the vessels, probably as a result of the activation of endothelial NO synthase against the background of the normalization of POL and the elimination of dyslipidemia [30,31].

Combined therapy provided in patients with grade 3 hypertension with MS a decrease on the platelet surface the number of fixation sites for ADP, collagen, von Willebrand factor and fibrinogen. This was an important mechanism for inhibiting platelet aggregation in them [32].

The inhibition of the intravascular activity of platelets against the background of the treatment shows the optimization of accessibility to the blood plates of the collagen of the vascular wall with a decrease in the blood of patients with dissolved aggregation inducers, lipids and POL products [33]. Stable normalization of blood pressure eliminated mechanical microtraumas of the vascular walls and intravascular activation of platelets in the examined patients [34]. The effects achieved as a result of the treatment provided a significant decrease in platelet activity, which should be regarded as an important basis for reducing the risk of the onset of thrombosis of any localization in these patients.

CONCLUSION

Excess platelet activity in patients with hypertension of grade 3 in MS is largely due to dyslipidemia, activation of POL in plasma, as well as an imbalance in it of biologically active substances that can affect blood platelets. The combined therapy, including amlodipine, valsartan, metformin, a low-calorie diet and dosed exercise, was able to provide in patients with hypertension of 3 degrees with MS already after 4 months stable normalization of initially high platelet activity due to the maximum elimination of factors stimulating their functionality.

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