ABSTRACT

Background: In this connection, we put in our work the following aim: to define the potential of simvastatin and non-medication combined impact on regular blood elements’ aggregative features of patients with arterial hypertension and dyslipidemia.

Methods: In our investigation, we took 55 patients of middle age with arterial hypertension of 1-2 degree, risk 3 with dyslipidemia of IIb type. For dyslipidemia correction, all the patients were prescribed simvastatin, hypolipidemic diet and graduated exercise. Registration of clinical and laboratory indices was made before the start of treatment, in 6, 12, 18, 52 and 104 weeks of therapy. We applied biochemical, hematomal and statistical methods of investigation. Control group was composed of 26 healthy volunteers of the middle age examined once.

Results: Application to patients of simvastatin, hypolipidemic diet and graduated exercise during 104 weeks positively influenced lipid composition and level of lipid peroxidation in plasma and regular blood elements taking the given indices on the control level for 12 weeks. Fulfilled therapy normalized in patients with arterial hypertension and dyslipidemia erythrocytes’ aggregative abilities (aggregates’ quantity decreased by 47,1% during 6 weeks, and ability to platelets’ aggregation (aggregation inhibited with ADP on 74,1%, with collagen - on 47,1%) and neutrophils (aggregation weakened with lectin on 58,3%, with phytohemagglutinin - on 37,2% during 12 weeks.

Conclusion: Simvastatin reception on the background of non-medication by patients with arterial hypertension and dyslipidemia normalizes lipid composition and level of lipid peroxidation in plasma and regular blood elements for 12 weeks of investigation. These patients’ therapy lowers erythrocytes aggregative abilities for 6 weeks, and platelets’ and neutrophils’ - for 12 weeks of therapy.

Keywords: arterial hypertension, dyslipidemia, simvastatin, non-medication, aggregative activity, regular blood elements.

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INTRODUCTION

At present cardiovascular pathology among the population of all countries in the world is highly widespread with the increase of a part of arterial hypertension (AH) in it.\(^1\) The danger is represented more and more often by a combination of AH with metabolic abnormalities\(^2,3\) among which dyslipidemia occupies an important place.\(^4\) It was found out that combination of AH with dyslipidemia promotes accelerated formation in patients’ organisms of many negative phenomena significantly raise the risk of thrombosis formation what negatively influences the common prognosis.\(^5,6\)

It was noted that if a patient has AH and dyslipidemia simultaneously, it leads to significant functional-structural abnormalities of all the regular blood elements. It worsens microcirculation process\(^7,8\) in comparison with healthy persons\(^9\). Besides, it was noted that high concentration of atherogenic cholesterol in the blood is accompanied by depression of antioxidant organism’s protection and leads to activation of lipids peroxidation (LPO) in their organisms.\(^10,11\) Surplus quantity of LPO products destabilizes membrane-receptor and post-receptor mechanisms of regular blood elements negatively influencing their functional parameters.\(^12-14\)

Forming abnormalities inevitably strengthen aggregative features of all the blood cells what raises the risk of thrombosis of different localization.\(^15,16\)

It becomes clear that hypolipidemic diet plays a serious role in state correction of patients with AH and metabolic abnormalities including dyslipidemia, graduated exercise\(^17,18\) and pharmacological impact with the help of statins.\(^19,20\) In literature there is information about the impact that some statins\(^21,22\) and graduated exercise\(^22,23\) have on aggregative features of regular blood elements. High efficiency of correction of vessels’ haemostatic features of patients with arterial hypertension and metabolic syndrome\(^24-26\) was shown earlier. In this connection, we feel great practical interest to the potential estimation of an application to patients with AH and dyslipidemia of non-medication and
some statins aiming at the possibility of aggregative abilities’ weakening of regular blood elements.

The aim of this study was to define the potential of impact of simvastatin and non-medication on regular blood elements’ aggregative features of patients with AH and dyslipidemia.

METHODS

The fulfillment of investigation was approved by the ethic committee of Kursk Institute of Social Education (a branch of Russian State Social University) (record №5 from 12.05.2014). The study was fulfilled with the help of 55 patients of middle age with AH of 1-2 degree, risk 3 and dyslipidemia of IIb type. All the patients gave written informed volunteer agreement to take part in the investigation. The control group was composed of 26 healthy people of the same age who also gave informed agreement to take part in the investigation. Indicators of control group were considered as standard values for all considered parameters.

Concentrations of common cholesterol and triglycerides (TG) were estimated by an enzymatic colorimetric method with the help of a set “Vital Diagnosticum” (Russia). Cholesterol of high-density lipoproteins (HDL) was registered with the help of a set “Olvex Diagnosticum” (Russia). The level of common blood lipids was estimated with the help of a set “Erba Rus” (Czech Republic). The following formula found cholesterol quantity of low-density lipoproteins (LDL): cholesterol LDL = total cholesterol – cholesterol HDL – triglycerides / 2.2. A cholesterol level of very low-density lipoproteins (VLDL) was defined according to the formula: triglycerides / 2.2. The atherogenic index was estimated according to the formula: cholesterol LDLP / cholesterol HDLP. We took as norm values lower than 3.

The level of LPO processes in plasma was estimated according to the quantity in it of thiobarbituric acid-active products with the help of a set “Agat-Med” (Russia) and acyl-hydroperoxides. Antioxidant protection of blood liquid part was characterized by the value of its antioxidant activity.

The evidence of LPO processes taking place in regular blood elements was defined according to the quantity of malonic dialdehyde in washed and resuspended cells in the reduction reaction of a thiobarbituric acid and to the content of acyl-hydroperoxides. In washed and resuspended blood cells we also quantitatively estimated cholesterol levels by an enzymatic colorimetric method with the help of a set “Vital Diagnosticum” (Russia). Functional ability of intracellular antioxidant enzymes was found for catalase and superoxide dismutase.

The state of spontaneous erythrocytes’ aggregation was estimated on light microscope by calculation in Gorjaev’s box of erythrocytes’ aggregates’ quantity, number of aggregated and disaggregated erythrocytes.

Activity of platelets’ aggregation (PA) was examined by visual micromethod with the application, as inducers, of ADP (0.5 × 10⁻⁴ M), collagen (dilution 1:2 of the basic suspension), thrombin (0.125 un/ml), rhystomicin (0.8 mg/ml) and adrenalin (5.0 × 10⁻⁴ M) in plasma with standardized platelets’ quantity 200 × 10⁹ tr. The degree of intravascular platelets’ aggregate formation was found out with the help of phase-contrast microscope.

Neutrophils’ aggregative features were defined on photoelectrocolorimeter in their suspension received after washing and resuspending with lectin of wheat curcule 32 mkg/ml, concanavalin A 32 mkg/ml and phytohemagglutinin - 32 mkg/ml.

For dyslipidemia correction, all the patients were prescribed hypolipidemic diet, graduated exercise and simvastatin 20 mg before sleep. Hypotension therapy was fulfilled with the help of enalapril 10 mg twice a day. Examination of clinical and laboratory indices was made before the beginning of treatment, in 6, 12, 18, 52 and 104 weeks of therapy. Statistical processing of received results was fulfilled by Student’s t-criterion (p < 0.05).

RESULTS

Side effects didn’t accompany application of prescribed treatment during 104 weeks. In patients taken into the investigation, the quantity of total lipids and total cholesterol in blood were higher in comparison with control group nearly in 1.6 and 1.3 times, respectively (Table 1). Atherogenic cholesterol fractions (CS LDLP and cholesterol VLDP) in examined patients in comparison with a group of control were reliably higher in 1.7 and 1.7 times, respectively, with the increase of triglycerides’ level in blood in 1.7 times at lowering cholesterol HDLP by 50.9% and the increase of plasma atherogenic index in 2.5 times.

In liquid part of the blood of investigated persons with AH and dyslipidemia, we noticed quantity predominance of acylhydrperoxides and thiobarbituric acid-active products nearly in 2.3 and 1.4 times over the values of healthy people, composing control group, because of the weakening of their plasma antioxidant potential in 1.4 times (Table 1).

Patients under investigation were noted to have significant cholesterol increase in regular blood elements’ membranes. At the same time in all the registered regular blood elements of patients with
AH and dyslipidemia, we found LPO activation as the result of their antioxidant protection weakening (Table 2).

Patients were registered to have significant increase of erythrocytes’ aggregation (Table 3) with the rise in their blood of the level of summary erythrocytes’ inclusion into aggregates (on 63.9%, rise of the very aggregates’ quantity (on 45.5%) and decrease in 56.9% of freely moving erythrocytes’ content in it.

And finally, the patients were found to have an evident acceleration of AH development with separate inductors and their combinations. The earliest AH appeared under collagen influence. A bit later it developed in response to ADP. Still later AH developed in response to ristomicin, thrombin, and adrenaline. At the same time, the number of freely circulating in patients’ blood thrombocyte aggregates of different size was significantly higher than control values.

Before the beginning of therapy, our patients had more active neutrophils’ aggregation than in control group in response to all the used inductors (with lectin on 58.3%, with concanavalin A on 34.4%, with phytohemagglutinin on 37.2%).

In 6 weeks of correction our patients already had evident optimization of blood lipid spectrum indices on the little rise of antioxidant activity and a decrease in plasma of acylhydroperoxides and thiobarbituric acid-products (Table 1). Reached positive dynamics increased to the 12th week of investigation, having provided the outlet of all the indices at the level of normal. Continuation of therapy perpetuated reached results having kept them to the end of the investigation.

All the patients on the background of correction were noted to have quick normalization of cholesterol content in erythrocytes’ membranes. Already after 6 weeks of treatment in red corpuscles’ membranes and 12 weeks of therapy in platelets’ and neutrophils’ membranes, we found a decrease of cholesterol content to the control values. Reached cholesterol level was kept to the end of investigation (Table 2).

Examined patients with AH and dyslipidemia on the background of treatment got fast LPO decrease in all the regular blood elements because of the rise of their antioxidant protectability. So, during six weeks of treatment in patients’ erythrocytes, we found normalization of superoxide dismutase and catalase. In platelets and neutrophils, it was reached in 12 weeks of therapy (Table 2).

Examined patients on the background of treatment were noticed to have a quick weakening of
<table>
<thead>
<tr>
<th>Registrated parameters</th>
<th>Initial state</th>
<th>Multimodality therapy, n=55, M±m</th>
<th>Control, n=26, M±m</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>erythrocytes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cholesterol of erythrocytes, mkmol/10^12 erythrocytes</td>
<td>1.34 ± 0.006</td>
<td>1.04 ± 0.008</td>
<td>1.03 ± 0.007</td>
</tr>
<tr>
<td>acylhydroperoxides of erythrocytes, D233/10^12 erythrocytes</td>
<td>4.54 ± 0.15</td>
<td>3.09 ± 0.07</td>
<td>3.07 ± 0.18</td>
</tr>
<tr>
<td>malonic dialdehyde of erythrocytes, nmol/10^12 erythrocytes</td>
<td>1.65 ± 0.13</td>
<td>1.15 ± 0.10</td>
<td>1.15 ± 0.14</td>
</tr>
<tr>
<td>catalase of erythrocytes, ME/10^12 erythrocytes</td>
<td>7457.5 ± 11.5</td>
<td>11194.0 ± 10.0</td>
<td>11198.0 ± 13.1</td>
</tr>
<tr>
<td>superoxidismutase of erythrocytes, ME/10^12 erythrocytes</td>
<td>1576.0 ± 2.08</td>
<td>1985.0 ± 3.21</td>
<td>1988.0 ± 6.42</td>
</tr>
<tr>
<td><strong>platelets</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cholesterol of thrombocytes, mkmol/10^9 thrombocytes</td>
<td>1.04 ± 0.006</td>
<td>0.84 ± 0.007</td>
<td>0.66 ± 0.008</td>
</tr>
<tr>
<td>acylhydroperoxides of thrombocytes, D233/10^9 thrombocytes</td>
<td>3.26 ± 0.04</td>
<td>2.70 ± 0.06</td>
<td>2.21 ± 0.05</td>
</tr>
<tr>
<td>malonic dialdehyde of thrombocytes, nmol/10^9 thrombocytes</td>
<td>1.33 ± 0.05</td>
<td>1.01 ± 0.04</td>
<td>0.67 ± 0.03</td>
</tr>
<tr>
<td>catalase of thrombocytes, ME/10^9 thrombocytes</td>
<td>5043.0 ± 15.36</td>
<td>7412.0 ± 15.40</td>
<td>9780.0 ± 20.13</td>
</tr>
<tr>
<td>superoxidismutase of thrombocytes, ME/10^9 thrombocytes</td>
<td>1156.0 ± 8.75</td>
<td>1401.8 ± 5.41</td>
<td>1647.6 ± 4.16</td>
</tr>
<tr>
<td><strong>neutrophils</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cholesterol of neutrophils, mkmol/10^9 neutrophils</td>
<td>0.82 ± 0.003</td>
<td>0.72 ± 0.007</td>
<td>0.62 ± 0.005</td>
</tr>
<tr>
<td>acylhydroperoxides of neutrophils, D233/10^9 neutrophils</td>
<td>3.52 ± 0.06</td>
<td>2.96 ± 0.07</td>
<td>2.37 ± 0.07</td>
</tr>
<tr>
<td>malonic dialdehyde of neutrophils, nmol/10^9 neutrophils</td>
<td>1.44 ± 0.05</td>
<td>1.10 ± 0.08</td>
<td>0.73 ± 0.05</td>
</tr>
<tr>
<td>catalase of neutrophils, ME/10^9 neutrophils</td>
<td>5249.0 ± 21.15</td>
<td>7604.1 ± 15.10</td>
<td>9959.2 ± 15.43</td>
</tr>
<tr>
<td>superoxidismutase of neutrophils, ME/10^9 neutrophils</td>
<td>1240.1 ± 4.29</td>
<td>1513.3 ± 5.02</td>
<td>1786.5 ± 4.35</td>
</tr>
</tbody>
</table>
Table 3  Aggregation ability of blood cells in patients on a background of complex treatment

<table>
<thead>
<tr>
<th>Registrated parameters initial state</th>
<th>Multimodality therapy, n=55, M±m</th>
<th>Control, n=26, M±m</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>erythrocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sum of all the erythrocytes in an aggregate</td>
<td>68.7 ± 0.10</td>
<td>41.7 ± 0.09</td>
</tr>
<tr>
<td>quantity of aggregates</td>
<td>13.1 ± 0.11</td>
<td>8.9 ± 0.06</td>
</tr>
<tr>
<td>quantity of free erythrocytes</td>
<td>152.9 ± 1.16</td>
<td>240.8 ± 0.32</td>
</tr>
<tr>
<td>platelets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT with ADP, s</td>
<td>23.6 ±0.05</td>
<td>28.1 ± 0.09</td>
</tr>
<tr>
<td>AT with collagen, s</td>
<td>22.5 ± 0.10</td>
<td>26.9 ± 0.14</td>
</tr>
<tr>
<td>AT with thrombin, s</td>
<td>34.0 ± 0.12</td>
<td>43.6 ± 0.10</td>
</tr>
<tr>
<td>AT with ristomycin, s</td>
<td>27.4 ± 0.11</td>
<td>32.4 ± 0.15</td>
</tr>
<tr>
<td>AT with epinephrine, s</td>
<td>71.2 ± 0.12</td>
<td>83.5 ± 0.13</td>
</tr>
<tr>
<td>Number of little aggregates (in 100 free thrombocytes)</td>
<td>12.3 ± 0.12</td>
<td>8.7 ± 0.06</td>
</tr>
<tr>
<td>Number of medium and large aggregates (in 100 free thrombocytes)</td>
<td>4.30 ± 0.06</td>
<td>2.50 ± 0.05</td>
</tr>
<tr>
<td>neutrophils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggregation with lectin, %</td>
<td>24.7 ± 0.10</td>
<td>20.2 ± 0.07</td>
</tr>
<tr>
<td>Aggregation with concanavalin A, %</td>
<td>19.9 ± 0.13</td>
<td>17.3 ±0.09</td>
</tr>
<tr>
<td>Aggregation with phytohemagglutinin, %</td>
<td>42.0 ± 0.05</td>
<td>36.3 ± 0.04</td>
</tr>
</tbody>
</table>
initially intensive aggregative ability of regular blood elements. So, patients receiving therapy were noted to have normalization of summary erythrocytes’ quantity in an aggregate, quantity of aggregates themselves and quantity of free erythrocytes to the 6th week of investigation (Table 3).

Therapy was accompanied in patients by weakening to control the level of platelets’ aggregation process in vitro and in vivo in 12 weeks of treatment. By this period of treatment, patients kept collagen as the most active inductor, time of AH development with it turned out to be the least one (33.1 ± 0.14 s). The second place as far as the speed of AH development is concerned belonged to ADP. A bit later AH appeared with ristomicin, with thrombin and adrenaline. It was accompanied by gradual quantity reduction of freely moving in blood thrombocyte aggregates which reached the level of control indices to the 12th week of investigation.

Therapy application led patients to the quick evident weakening of neutrophils’ aggregation with all the used inductors, mostly seen to the end of the investigation. So, by the 12th week of treatment, we noticed a summary evident lowering of their aggregation in response to lectin on 58.3%, to concanavalin A on 35.4%, to phytohemagglutinin on 37.2% what allowed given indices reach control level.

**DISCUSSION**

AH development among working population without any doubt has in its basic genetic component,30,31,32 and different negative environmental impacts.33,34

It is equally fair in relation to the combination of AH with dyslipidemia when hereditary factors of their development35,36 are burdened by irrational way of life what leads to the development of large-scale pathology.37

Taking into consideration all the peculiarities of AH and dyslipidemia pathological displays it was decided to fulfill correction of such patients with the help of hypolipidemic diet, graduated exercise and simvastatin. The last one showed earlier in the course of significant monotherapy activity influencing aggregative-disaggregative blood features of this patients’ category.21

On the background of therapy fulfillment, persons with AH and dyslipidemia reached quick growth of antioxidant blood plasma protection with LPO normalization in it. Optimization of cholesterol quantity in their blood during 12 weeks of treatment was accompanied by normalization of cholesterol content in regular blood elements’ membranes in the same period.

On the background of fulfilled treatment, the patients were noticed to have a quick lowering of erythrocytes’ aggregative ability what is mostly the basis for optimization of their blood rheological characteristics. It is evident that normalization of erythrocytes’ aggregation of patients with AH and dyslipidemia having received simvastatin on the background of non-medication was caused by quick optimization of their important aggregation mechanism, which is an increase of erythrocytes’ surface electronegativity because of growth of proteins with a negative charge on their membrane.37

Generation weakening of oxygen active forms lowers oxidative alteration of electronegative membrane’s proteins and globular plasma proteins fulfilling the role of “bridges” between separate erythrocytes, lowering, at the same time, forces of cells’ cohesion in developing aggregates.38

Erythrocytes’ aggregation weakening on the background of c therapy is evidently provided by an increase in healthy people’s values of adenylate cyclase activity in them. It leads to the rise in erythrocytes’ cytoplasm of cyclic adenosine monophosphate level, to lowering of Ca2+ inflow into cells with suppression of phosphodiesterase activity.52,59

Quick AH inhibition to control level in patients having received therapy turned out to be possible mostly because of normalization of plasma lipid composition and LPO level in it and platelets40 at normalization of cholesterol level in their membranes.51 It influenced quickly and positively their receptor and post-receptor mechanisms of aggregation realization.42,43 Prolongation of AH period till control level in response to ristomycin in patients having received treatment can be explained by lowering till healthy persons’ values of von Willebrand Factor content in blood, and on platelets’ surface, the number of receptors to it.44,45

In the basis of reaching AH normalization there was also activity optimization of some significance for aggregation intrathrombocyte mechanisms of thromboxane formation66,47 and evidence of secretory process from platelets.48 At the same time, normalization of AH period of coming with separate inductors provided activity optimization in patients’ organisms of not only initial stage of hemostasis but also all the rest its mechanisms.50,51,52

Neutrophils’ aggregation normalization in patients during 12 weeks of therapy was provided by cholesterol decrease in their membranes and locus quantity in the composition of glycoprotein receptors connecting lectins.53 So, phytohemagglutinin can interact mostly with glycoproteins’ bD-galactose parts, lectin of wheat germ with N-acetyl-D-glucosamine and N-acetyl-neuraminic (sialic) acid, and concanavalin A with containing mannose N-glycans.54

Decrease of lectin-stimulated neutrophils’ aggregation in patients with AH and dyslipidemia
having received treatment took place in the result of weakening of adhesion receptors’ expression having in their composition some parts which contain N-acetyl-D-glucosamine, N-acetyl-neuraminic acid and mannose what can be charged by lowering of neutrophils’ aggregative response to lectin impact of wheat germ and concanavalin A.\textsuperscript{25,26} Normalization on the background of therapy of induced aggregation evidence under the impact of phytohemagglutinin should be connected with lowering in their receptors of glycoproteins’ parts containing B-D-galactose.\textsuperscript{5,7}

CONCLUSION

Patients with AH and dyslipidemia can be characterized by the increase of plasma LPO and regular blood elements with evident strengthening of erythrocytes, platelets and neutrophils to aggregation. Simvastatin intake on the background of non-medication normalizes, in patients with AH and dyslipidemia, lipid composition and LPO level in plasma and regular blood elements for 12 weeks of investigation. Complex therapy of patients with AH and dyslipidemia lowers erythrocytes’ aggregative abilities in 6 weeks, while platelets and leukocytes in 12 weeks of therapy. In this connection, we can consider that simvastatin application in combination with non-medication during six weeks, in the case of persons with AH and dyslipidemia, provides aggregation normalization of basic regular blood elements for 12 weeks what can significantly lower risk of thrombus formation in the given category of patients.

CONFLICT OF INTEREST

No conflict of interest to declare.

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