The Effect of Combination Therapy on Indices of Endothelial Dysfunction in Women with Hypertension and Menopausal Syndrome

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Abstract

Aim of the study was to evaluate the efficiency of the effect of combination therapy on indices of endothelial dysfunction in women with hypertension and menopausal syndrome.

Methods: For the purpose of implementation of the tasks set, we performed a comprehensive survey and follow-up of 60 hypertensive women in postmenopause of 1 to 5 years. The first group consisted of 30 hypertensive patients - women with mild climacteric syndrome of the average age of 54.17±2.59 years, MRS score = 3.50 points [3; 4]. The second group consisted of 30 hypertensive patients - women with moderate climacteric syndrome of the average age of 53.30±3.34 years, MRS score = 7.00 points [7; 8].

Results: According to our observations, no significant difference of nitrite dynamics between the groups was reported; in the first group Sl = 1.15 mmol/l /
3 months (95% CI 0.51; 1.79) vs SI = 0.95 mmol/l / 3 months (95% CI 0.24; 1.66) in the second group (p > 0.05). Significantly the nitrate level increase during the observation period was larger in the second group: SI = 3.43 mmol/l / 3 months (95% CI 2.37; 4.50) vs SI = 2.82 mmol/l / 3 months (95% CI 2.15; 3.49) in the first group (p < 0.05). The NOx level increase during a 6-months observation period was significantly larger in the second group: SI = 4.38 mmol/l / 3 months (95% CI 3.15; 5.62) vs SI = 3.97 mmol/l / 3 months (95% CI 2.93; 5.01) in the first group (p < 0.05).

Keywords: hypertension in women, climacteric syndrome, vasoregulating function

Introduction

Hypertension (HT) is the first largest contributor to mortality from cardiovascular disease and forms the basis for the development of many cardiovascular diseases and complications. A large number of articles on hypertension so far published contain though a rather scarce and controversial information concerning gender differences. Although hypertension develops in women later than in men, its course is much heavier and with a greater number of complications, and the degree of cardiovascular risk in women after 60 years is higher than in men [1].

Hypertension in women of menopausal age in 40-80% of cases is associated with the climacteric syndrome (CS), which not only deteriorates health status of patients, but also aggravates the clinical course of the disease [2]. The initial manifestation of endothelial dysfunction preceding its organic damage, is a violation of its local vasoregulating function. The available publications provide evidence for endothelial dysfunction in atherosclerosis and arterial hypertension in men, at the same time, there are insufficient studies describing the state of the endothelium in hypertension in post-menopausal women [3].

Aim of the study: The aim of this study is to evaluate the efficiency of the effect of combination therapy on indices of endothelial dysfunction in women with hypertension and menopausal syndrome.

Material and methods

For the purpose of implementation of the tasks set, we performed a comprehensive survey and follow-up of 60 hypertensive women in post-menopause of 1 to 5 years. In the study group were included patients with the manifestations of climacteric syndrome of mild and moderate severity, whose average age was 53.76±4.27 years. The patient groups were comparable in age, the average systolic (SBP) and diastolic blood pressure (DBP), as well as the average duration of HT in both groups.

Criteria for inclusion in the study: Documented stage I-II hypertension with moderate and high risk of cardiovascular complications; absence of
menstruation for at least 12 months; the age over 45-65 years; the presence of sinus rhythm; signed informed consent to participate in the study.

Criteria for exclusion from the study: intractable arterial hypertension; symptomatic arterial hypertension; chronic heart failure III-IV FC according to NYHA; confirmed stable angina; previous cerebral stroke or transient ischemic attack; diabetes mellitus; peripheral arterial disease; congenital or acquired heart valvular disease; the creatinine level of blood plasma more than 124 μmol/l; mental illness and any other conditions that limit the ability of the patient to understand the informed consent.

Objective examination, instrumental and laboratory diagnostic methods were performed according to European recommendations on arterial hypertension (ESH/ESC 2013). In order to objectify the severity of the symptoms of menopause and to monitor the efficiency of treatment the menopause rating scale (MRS) \cite{4, 5} was used. By the severity of somatic-vegetative symptoms women were divided into two groups: the first group (3-4 points) with mild climacteric syndrome; the second group (5-8 points) with climacteric syndrome of moderate severity.

The first group consisted of 30 hypertensive patients - women with mild climacteric syndrome of the average age of 54.17±2.59 years, MRS score = 3.50 points \cite{3; 4}. The second group consisted of 30 hypertensive patients - women with moderate climacteric syndrome of the average age of 53.30±3.34 years, MRS score = 7.00 points \cite{7; 8}.

For measuring NO\textsubscript{X} level in the blood plasma we used the method based on reduction of nitrate to nitrite using Griess Reagent. The optical density was measured using SF-46 spectrophotometer (photoelectrocalorimeter) with wavelength of 540 nm. The level of nitrite was calculated using a calibration schedule based on the concentration of nitrite.

The level of Endofelin-1 (ET-1) in blood plasma was determined by ELISA method using standard reagent kits made by DRG (USA) according to the method described in the application instruction for these test systems. The analysis was performed using "SUNRISE TS" (Austria) immunoassay analyzer.

The patients involved in the study received treatment according to the recommendations of ESH/ESC (2013). Patients in both groups received combination antihypertensive therapy with Moexipril (Moex®, Schwarz Pharma AG) and Diltiazem (Diacordin 90 retard, Lechiva a.s.). In addition, patients received standard lipid-lowering and antiplatelet therapy according to current treatment protocols of patients with cardiovascular risk. Moexipril starting dose was 7.5 mg once per day with consequent increase in doses up to achievement of BP target value or 30 mg once per day. Diltiazem dose was 90 mg 2 times a day. At failure to achieve the target BP other medications were administered additionally to the current therapy, and the respective patients were excluded from the study. The follow-up period made 6 months.
Statistical analysis of the results

We calculated the median and interquartile range (Me [25; 75]) the p-value is indicated in the comparison groups. Difference at p < 0.05 was considered to be a reliable value. Statistical processing of obtained results was performed using methods of nonparametric statistics. Dynamics of indicators in response to the therapy was estimated using the Delta check method. The slope (SL) was calculated in the mixed effects in model 3 the values of the trends. For statistical data processing PSPP statistical software package (0.7.9 version, GNU GPL License) was used.

Results

The dynamics of the levels of NOx and Endothelin-1 in the examined persons are presented in Table 1. The women of the first and the second groups being examined had no significant differences in the level of nitrite (p > 0.05). The nitrite concentration after 3 months of treatment increased by +12.5% in the group of women with mild CS and by +13.3% in the group with the climacteric syndrome of moderate severity; there was no significant difference between the examined groups (p > 0.05). Within the next 3 months, the growth of nitrite made +11.8% in the group with mild CS and +8.7% in the group with moderate severity of the CS. According to our observations, no significant difference of nitrite dynamics between the groups was reported; in the first group Sl = 1.15 mmol/l / 3months (95% CI 0.51; 1.79) vs Sl = 0.95 mmol/l / 3months (95% CI 0.24; 1.66) in the second group (p > 0.05).

The nitrate level was significantly lower in the group with moderate severity of the CS making 12.5 mmol/l vs 19.0 mmol/l in the group with mild CS (p < 0.05). The increase of nitrate level after the first 3 months by 34.9% was observed in the group of women with moderate severity of the CS, which was not significantly higher than the increase in the nitrate level making 13.1% in the group with mild CS (p> 0.05). Within the next 3 months, the nitrate level increased by 34.3 % in the group of women with moderate severity of the CS, and the growth of this indicator was significantly larger as compared to 13.6% in the group with mild CS (p < 0.05).

Significantly the nitrate level increase during the observation period was larger in the second group: Sl = 3.43 mmol/l / 3months (95% CI 2.37; 4.50) vs Sl = 2.82 mmol/l / 3 months (95% CI 2.15; 3.49) in the first group (p < 0.05).
Table 1. Dynamics of the level of NOX and ET-1 in plasma in women with arterial hypertension and climacteric syndrome (Me [25;75])

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nitrite, mmol/l</th>
<th>Nitrates, mmol/l</th>
<th>NOX, mmol/l</th>
<th>ET-1, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>The group surveyed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>persons</td>
<td>Group 1 (n=30)</td>
<td>Group 2 (n=30)</td>
<td>p-value</td>
<td>Group 1 (n=30)</td>
</tr>
<tr>
<td>Trend begins</td>
<td>8.00 [7.00; 9.00]</td>
<td>8.00 [6.75; 9.00]</td>
<td>0.88</td>
<td>19.00 [17.75; 20.25]</td>
</tr>
<tr>
<td>After 3 months</td>
<td>9.00 [7.00; 12.25]</td>
<td>8.50 [5.75; 12.25]</td>
<td>0.58</td>
<td>22.00* [19.00; 24.25]</td>
</tr>
<tr>
<td>Δ % 3 months</td>
<td>12.50 [11.90; 68.75]</td>
<td>13.33 [-0.33; 64.73]</td>
<td>0.53</td>
<td>13.06 [0.00; 30.83]</td>
</tr>
<tr>
<td>After 6 months</td>
<td>10.00* [8.00; 12.25]</td>
<td>9.50* [6.00; 13.25]</td>
<td>0.54</td>
<td>24.50* [22.00; 28.00]</td>
</tr>
<tr>
<td>Δ % 3-6 months</td>
<td>11.81 [0.00; 14.29]</td>
<td>8.71 [0.00; 14.29]</td>
<td>0.63</td>
<td>13.63 [5.42; 17.85]</td>
</tr>
<tr>
<td>Slope</td>
<td>1.15 (95% CI 0.51; 0.79)</td>
<td>0.95 (95% CI 0.24; 1.66)</td>
<td>0.53</td>
<td>2.82 (95% CI 2.15; 3.49)</td>
</tr>
</tbody>
</table>

Note: * the significance of differences in the group under the influence of treatment.
Changes in the total content of metabolites of nitric oxide (NOx) were similar to nitrate dynamics. The NOx level increase during a 6-months observation period was significantly larger in the second group: $SI = 4.38 \text{ mmol/l } / 3 \text{ months}$ (95% CI 3.15; 5.62) vs $SI = 3.97 \text{ mmol/l } / 3 \text{ months}$ (95% CI 2.93; 5.01) in the first group ($p < 0.05$).

The group of women with moderate severity of CS featured a significantly higher level of ET-1 with $0.535 [0.503; 0.705] \text{ ng/ml}$ vs $0.410 [0.358; 0.530] \text{ ng/ml}$ in the group with mild CS ($p < 0.05$). The dynamics of this indicator showed no significant difference between both groups after 3 months of observation, whereas after 6 months, the decrease in the level of ET-1 was -21.4% more accentuated in the second group with moderate severity of CS vs -5.7% in the first group with mild CS ($p < 0.05$).

**Discussion**

Sympathetic activity increases during postmenopausal period. Increase of sympathetic activity serves as the general mechanism both for hypertension emergence and occurrence of hot flashes [6].

Our findings are consistent with studies showing that endothelial dysfunction increases in women with the CS, which is associated with decreased levels of estrogen [7, 8], because they have the ability to cause vasodilation by affecting the synthesis of nitric oxide (NO). Dynamics of the content of nitric oxide metabolites in the blood plasma in women with arterial hypertension having climacteric syndrome can be used in the evaluation of the efficiency of the administered therapy.

**Conclusion**

According to our observations, in response to the combination therapy with Moexipril and Diltiazem endothelial function has been significantly improved, which was manifested both in increased production of nitric oxide and decrease in the content of ET-1 in blood plasma.

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**Ethical Declaration.** The study was approved by the local ethics committee of State Institute «Zaporizhzhia Medical Academy of Postgraduate Education of Ministry of Health of Ukraine». The study was carried out in conformity with the Declaration of Helsinki.

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