Amlodipine/atorvastatin has an effect on vascular function and normal lipid levels.

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Abstract

Objective: To investigate whether the use of amlodipine/atorvastatin can affect vascular endothelial function as well as blood vessel elasticity and lipid level compared with hypotensor alone.

Method: There were 162 participants selected into domestic compound hypotensive tablets (Group 1), amlodipine tablets (Group 2) and amlodipine/atorvastatin group (Group 3) randomly. After 3 months, 144 participants remained. Each participant’s medical history was collected, and each participant underwent a blood biochemical examination including high-sensitivity C-Reactive Protein (hs-CRP), Flow-Mediated-Dilation (FMD) and Endothelium-Independent Dilatation (EID), and carotid-Femoral Pulse Wave Velocity (c-f PWV) before and after the 3-month follow-up period.

Results: Compared with baseline, the FMD values of all groups improved significantly. Group 3 showed the greatest difference, followed by Groups 2 and 1. In contrast, no difference in EID was noted (P>0.05 in three groups). After treatment, the c-f PWV of Groups 2 and 3 turned to be significantly better (P<0.05), while that of Group 1 did not change. There was no statistical significant difference among three groups. The lipid levels of the participants in Group 3 decreased, while those in Groups 1 and 2 did not change. The hs-CRP levels of Groups 2 and 3 decreased significantly, whereas that of Group 1 did not change.

Conclusions: In conclusion, we found that Amlodipine/atorvastatin combination pills can improve vascular endothelial function as well as vascular elasticity, and down-regulate the level of hs-CRP.

Keywords: Vascular endothelial function, Pulse wave velocity, Amlodipine/atorvastatin.

Introduction

Cardiovascular disease, a major cause of death worldwide, has the following risk factors: hypertension, age, smoking, glucose tolerance, family history of premature cardiovascular events, obesity, high homocysteine level, and dyslipidaemia. Hypertension is the most important factor among which. Framingham risk score showed that, of hypertensive patients, 78% of men and 82% of women have at least one risk factor [1].

Hypertension and dyslipidaemia are the main reasons for endothelial dysfunction and decreasing arterial elasticity. Studies have indicated that the occurrence and development of cardiovascular disease are related to decreased arterial elasticity [2]. The co-existence of hypertension and high cholesterol can accelerate endothelia dysfunction, causing atherosclerotic plaque formation, the main cause of cardiovascular disease [3]. Most experiments have shown that the rate of death can be decreased by the combination of the treatment of hypertension and hyperlipidaemia [4,5]. Therefore, drug and non-drug methods of controlling blood pressure and lipid levels can reduce cardiovascular mortality rates and improve patient quality of life.

Pulse Wave Velocity (PWV) is a sensitive indicator that can evaluate the arterial elasticity in early clinical trials, and carotid-femoral PWV (c-f PWV) in particular is a reliable predictor of cardiovascular events and mortality [6]. Flow-Mediated Dilatation (FMD) is the most common non-invasive method for evaluating endothelial function. Most patients with hypertension also have dyslipidaemia. Evidence-based
medicine studies mainly focus on patients with dyslipidaemia and fail to focus on patients with normal lipid levels and one or two cardiovascular risk factors (such as hypertension, age, smoking, glucose tolerance, family history of premature cardiovascular events, obesity, high homocysteine level, and dyslipidaemia mentioned above). Additionally, based on the use of hypotensors and statins, especially amlodipine/atorvastatin, helps reduce the incidence and mortality rates of cardiovascular disease in patients with hypertension. However, few studies have examined the early atherosclerotic changes caused by amlodipine/atorvastatin in patients with hypertension, in whom endothelial function and arterial elasticity are the two main indexes. Because of the obvious relationship between morning blood pressure and the incidence of cardiovascular disease, controlling morning blood pressure can reduce the incidence of cardiovascular disease. As such, this study investigated whether the combined use of amlodipine/atorvastatin and a hypotensor can affect patients’ vascular endothelial function and blood vessel elasticity compared to use of the hypotensor alone. Here we studied patients with hypertension without hyperlipidaemia but with one or two cardiovascular risk factors.

Materials and Methods

Materials

The 162 participants in this survey were chosen from among inpatients between March and December 2012 who were administered domestic compound hypotensive tablets, amlodipine tablets, or amlodipine/atorvastatin. The patients were 30-75 years of age, did not have hyperlipidaemia, and had one or two cardiovascular risk factors or being treated at baseline. Both genders were included. After 3 months, 144 participants remained: 44 were included in Group 1 (domestic compound hypotensive tablets); 48 in Group 2 (amlodipine tablets), and 52 in Group 3 (amlodipine/atorvastatin). The basic participant characteristics—incorporating age, gender, body mass index, smoking history, TG, LPL-C, total cholesterol, high-density lipoprotein, and hs-CRP did not differ statistically among the three groups (Table 1).

<table>
<thead>
<tr>
<th>No. (M/F)</th>
<th>G1 44 (25/19)</th>
<th>G2 48 (22/26)</th>
<th>G3 52 (25/27)</th>
<th>P 0.12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48.84 ± 13.73</td>
<td>49.12 ± 12.55</td>
<td>48.41 ± 11.16</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.08 ± 2.60</td>
<td>25.01 ± 2.72</td>
<td>26.26 ± 3.29</td>
<td>0.22</td>
</tr>
<tr>
<td>Smoking</td>
<td>4 5 6</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>155.9 ± 10.6</td>
<td>155.2 ± 11.7</td>
<td>154.1 ± 10.3</td>
<td>0.25</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>97.3 ± 9.6</td>
<td>95.9 ± 10.2</td>
<td>96.3 ± 8.2</td>
<td>0.48</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>113.92 ± 20.73</td>
<td>114.77 ± 26.39</td>
<td>120.33 ± 25.31</td>
<td>0.13</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>45.45 ± 8.44</td>
<td>44.98 ± 8.94</td>
<td>47.56 ± 9.56</td>
<td>0.26</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>184.19 ± 33.17</td>
<td>186.08 ± 38.58</td>
<td>194.13 ± 36.91</td>
<td>0.99</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>138.6 ± 111.32</td>
<td>160.3 ± 117.02</td>
<td>163.02 ± 90.79</td>
<td>0.16</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>18.4 ± 0.5</td>
<td>20.3 ± 0.8</td>
<td>19.8 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>CRE (ummol/L)</td>
<td>48.4 ± 6.5</td>
<td>46.3 ± 7.8</td>
<td>47.3 ± 6.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Vascular endothelial function

The mean FMD of all groups improved significantly, Group 3 showed the highest degree of improvement, followed by Groups 2 and 1. However, no difference in EID was seen (Table 2 and Figure 1).

Vascular elasticity

After treatment, the c-f PWV of Groups 2 and 3 were significantly improved, whereas that of Group 1 did not
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change. There were no statistically significant changes among the three groups (Table 2 and Figure 2).

**Table 2. Changes in vascular function (x̄ ± S).**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Baseline</th>
<th>3 month</th>
<th>Baseline</th>
<th>3 month</th>
<th>Baseline</th>
<th>3 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMD (%)</td>
<td>8.7 ± 4.6</td>
<td>13.4 ± 4.6*</td>
<td>8.9 ± 3.4</td>
<td>16.8 ± 6.2**</td>
<td>9.7 ± 4.6</td>
<td>19.4 ± 3.7*</td>
</tr>
<tr>
<td>EID (%)</td>
<td>15.7 ± 6.5</td>
<td>17.1 ± 7.3</td>
<td>17.2 ± 4.5</td>
<td>18.2 ± 3.6</td>
<td>16.7 ± 4.5</td>
<td>17.4 ± 5.4</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>7.69 ± 3.59</td>
<td>7.53 ± 2.95</td>
<td>7.81 ± 3.63</td>
<td>7.29 ± 1.63*</td>
<td>8.58 ± 4.29</td>
<td>7.82 ± 2.84*</td>
</tr>
</tbody>
</table>

NOTE: *P<0.05, **P<0.01 (The comparison of the three groups before and after the treatment); #P<0.05 vs. G1, P<0.05 vs. G2 post-treatment.

**Table 3. Changes in lipid and hs-CRP levels (x̄ ± S).**

<table>
<thead>
<tr>
<th>Groups</th>
<th>LDL-C (mg/dl)</th>
<th>HDL-C (mg/dl)</th>
<th>TC (mg/dl)</th>
<th>TG (mg/dl)</th>
<th>hs-CRP (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 Baseline</td>
<td>113.92 ± 20.73</td>
<td>45.45 ± 8.44</td>
<td>184.19 ± 33.17</td>
<td>138.6 ± 111.32</td>
<td>1.44 ± 1.01</td>
</tr>
<tr>
<td>3 month</td>
<td>113.15 ± 20.55</td>
<td>45.1 ± 8.54</td>
<td>182.50 ± 32.50</td>
<td>135.25 ± 90.24</td>
<td>1.42 ± 0.03</td>
</tr>
<tr>
<td>G2 Baseline</td>
<td>114.77 ± 26.39</td>
<td>44.98 ± 8.94</td>
<td>186.08 ± 38.58</td>
<td>160.3 ± 117.02</td>
<td>1.40 ± 0.91</td>
</tr>
<tr>
<td>3 month</td>
<td>113.27 ± 24.39</td>
<td>43.98 ± 9.01</td>
<td>184.79 ± 38.41</td>
<td>151.52 ± 98.25</td>
<td>1.30 ± 0.13*</td>
</tr>
<tr>
<td>G3 Baseline</td>
<td>120.33 ± 25.31</td>
<td>47.56 ± 9.56</td>
<td>194.13 ± 36.91</td>
<td>163.02 ± 90.79</td>
<td>1.43 ± 0.54</td>
</tr>
<tr>
<td>3 month</td>
<td>105.5 ± 21.14*</td>
<td>47.52 ± 9.35</td>
<td>177.33 ± 35.2*</td>
<td>148.06 ± 75.93*</td>
<td>1.32 ± 0.17*</td>
</tr>
</tbody>
</table>

Note: *P<0.05 (The comparison of the three groups before and after the treatment); #P<0.05 vs. G1 post-treatment.

**Lipid and hs-CRP levels**

After treatment, the lipid levels of the participants in Group 3 decreased, while those in Groups 1 and 2 did not change. The hs-CRP levels of Groups 2 and 3 also significantly declined, whereas that of Group 1 did not change. The differences in hs-CRP levels in Groups 2 and 3 were statistically different from those in Group 1 but not statistically different from each other (Table 3).

**Discussion**

The “China Cardiovascular Disease Report 2011” shows that China currently has 230 million patients with cardiovascular disease and that 350 million succumb to it yearly, accounting for 41% of all deaths [6]. As is known to all, the cardiovascular diseases such as hypertension and coronary heart disease share the same physiological and pathological basis-atherosclerosis. In the presence of hypertension, vascular endothelial cells are stimulated by growth factor and vasoactive substances, leading to an increase in the migration of vascular smooth muscle cells and promoting the development of molded fibrous [8,9]. Long-term uncontrolled hypertension is the main cause of cardiovascular disease, particularly when accompanied by genetic factors, environmental factors, and structural abnormalities of blood vessels. Therefore, the treatment for hypertension also focuses on changes in vascular function.
In the clinical setting, there are many measurement methods for vascular function, including PWV, FMD, urinary microalbumin/creatinine, and Nitric Oxide (NO).

The main forms of atherosclerosis are vasoconstriction and endothelium dysfunction, which finally causes the partial or complete close-up of vascular. So for the patients with hypertension, it is crucial to prevent and treat Atherosclerosis. The 2010 ESC/ESH hypertension management guidelines changed the c-f PWV standard from 12 m/s to 10 m/s. Generally speaking, the larger the value, the greater the degree of stiffness. Benetos et al. found the accelerated artery stiffness can be affected by blood pressure, heart rate, and c-f PWV after they had been following up the treated patients with hypertension and the participants with normal blood pressure for 6 years [10].

In addition, Laurent et al. examined 1,715 patients with hypertension for as long as 7.9 years and found that as the c-f PWV increased by 4 m/s, the patients’ relative risk of stroke increased to>1.72 and that after adjustment for cardiovascular risk factors, c-f PWV remained a significant indicator (relative risk=0.39, P<0.02) [11].

Endothelial dysfunction is the contributing factor for atherosclerosis and a common cause of atherosclerosis and hypertension. Atherosclerotic vascular abnormalities, primarily vasoconstriction and endothelial dysfunction, can ultimately lead to partial or complete occlusion of the blood vessels in patients with hypertension, so the prevention and treatment of atherosclerosis are critical. FMD is the most common non-invasive inspection method for evaluating endothelial function, which can predict cardiovascular disease events [12].

The ACTION study [13] found that amlodipine demonstrated some anti-atherosclerotic properties, stimulated NO production, act as an anti-oxidant, and regulate matrix deposition. This study found that after treatment of amlodipine or amlodipine/atorvastatin, vascular function is obviously improved; in contrast, vascular function is not improved by Guo compound antihypertensive drugs, as found in early research. Therefore, vascular function is best improved by amlodipine/atorvastatin treatment. Atorvastatin interferes with the development of atherosclerosis through non-lipid-related and pleiotropic effects, including improved endothelial function, reduced vascular smooth muscle cell proliferation, stabilized athermanous plaques, reduced inflammation, and reduced platelet aggregation [14]. In an open-label study of 21 hypertensive, hypercholesterolemic patients, 3 months of amlodipine treatment improved large and small vessel arterial compliance by 26% and 38%, respectively, and reduced systemic vascular resistance by 10% (all P<0.0001 vs. baseline) [15]. The addition of atorvastatin for an additional 3 months improved small-vessel arterial compliance by an additional 42% (P<0.001 vs. month 3) and reduced systemic vascular resistance by an additional 5% (P<0.05 vs. month 3). In contrast, large-vessel compliance was not further improved by combination therapy. What’s more, Azushima et al. also found the effects of single pill-based combination therapy of amlodipine and atorvastatin on within-visit blood pressure variability and parameters of renal and vascular function in hypertensive patients with chronic kidney disease.

In conclusion, we found that Amlodipine/atorvastatin combination pills can improve vascular endothelial function as well as vascular elasticity, and down-regulate the level of hs-CRP.

References
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