Original Article
Effects of combination treatment with amlodipine and telmisartan on blood pressure and inflammatory endothelial factors in patients with primary hypertension

Jianzhi Shao*, Wenhui Lin*, Bin Lin, Qizeng Wang, Yunpeng Chen, Huiting Chen

Department of Cardiovascular Medicine, The First People’s Hospital of Wenling, Wenling 317500, Zhejiang, China.
*Equal contributors and co-first authors.

Received April 3, 2020; Accepted June 12, 2020; Epub September 15, 2020; Published September 30, 2020

Abstract: Hypertension is defined as a common clinical disease in which the circulating load in the cardiac blood vessels is persistently elevated. The aim of this study is to explore the effects of combination treatment with amlodipine and telmisartan on the blood pressure and inflammatory endothelial factors of patients with primary hypertension. Patients (n = 106) admitted to our hospital for primary hypertension treatment were selected as the observation subjects and were equally divided into a control group (n = 53) and an observation group (n = 53) using the method of a Random Number Table. The control group was treated with amlodipine tablets + compound amiloride hydrochloride tablets, while the observation group received treatment with amlodipine tablets + telmisartan. Following treatment, both groups showed a dramatic elevation in the levels of NO and serum adiponectin, but compared with the control group, the observation group had significantly higher levels of NO and serum adiponectin but lower intima-media thickness (P < 0.05). There was no significant difference between the two groups in terms of incidence of adverse reactions (P > 0.05). The efficacy of combination treatment with amlodipine and telmisartan for primary hypertension has been established, and its mechanism is thought to be related to the inhibition of intravascular inflammatory reactions and platelet activation, improvement of vascular endothelial functions, and up-regulation of serum adiponectin level. Meanwhile, combination treatment can also inhibit the progression of atherosclerosis with less adverse reactions.

Keywords: Primary hypertension, amlodipine, telmisartan, blood pressure, inflammatory factor, endothelial factor

Introduction
Hypertension is mainly found in middle-aged and elderly people. Primary hypertension is a type of hypertension in which the causes are not readily identifiable. It has a case rate higher than 90% of all other hypertension diseases [1]. Primary hypertension chronically impairs the organs of the body, including the heart, brain, and kidney. It compromises the patients' bodily functions and is therefore a risk factor for a number of diseases such as cerebral apoplexy, coronary disease, and renal disease [2, 3]. As one of the pathological characteristics of most cardiovascular diseases, changes in vascular endothelial cells (VECs) result in vascular endothelial dysfunction, reducing tonic regulation of blood vessels, and leading to atherosclerosis. Meanwhile, such changes contribute to intravascular inflammatory reactions and stimulate an increased expression of multiple factors [4]. Correlational studies showed that patients with hypertension have impaired vascular endothelial function, activated platelets and intravascular inflammatory reactions [5, 6]. Therefore, improvements in vascular endothelial function, inhibition of intravascular inflammatory reactions, and platelet activation play a significant role in improving the patients' conditions and prognosis.

Amlodipine is a calcium antagonist and has the effect of reducing blood pressure. Telmisartan is an angiotensin II specific receptor antagonist
Effects of combination treatment with amlodipine and telmisartan

and has the effect of promoting vasoconstriction [7]. Previous studies have shown that amlodipine combined with telmisartan in the treatment of primary hypertension can effectively control the blood pressure level of patients [8]. However, there are few studies on the effects of amlodipine and telmisartan on inflammatory endothelial factors in patients with primary hypertension. Based on this, the present study combined amlodipine with telmisartan in the treatment of patients with primary hypertension to observe its clinical value and effects on patients' intravascular inflammatory reaction and vascular endothelial function, in order to provide a reference for the clinical formulation of drug treatment regimens for primary hypertension, which is reported here.

Materials and methods

General materials

Patients (n = 106) who were admitted to our hospital for primary hypertension treatment from January 2018 to January 2019 were selected as the observation subjects according to the following inclusion criteria: compliance with relevant diagnosis criteria in 2010 Chinese Guidelines for the Management of Hypertension [9]; aged between 50-79; SBP > 140 mmHg and (or) DBP > 90 mmHg; no antihypertensive drugs administered in the past 2 weeks, and awareness of the study facts and having signed the informed consent documents. Patients who had any of the following conditions were excluded: secondary hypertension; severe organ insufficiency; acute cardio-cerebrovascular conditions within the past 3 months; complicated severe infection; malignant tumor; UAP; complicated gout; allergy to drugs used; or history of mental illness. Patients included were equally divided into the control group (n = 53) and the observation group (n = 53) by the method of Random Number Table. This study has been approved by the Ethics Committee of The First People's Hospital of Wenling. All study participants provided written informed consent before participating in the study.

Methods

The control group received oral administration of amlodipine benzenesulfonate tablets (Shan-xi Kanglisheng Pharmaceutical Co., Ltd., GYZ Zi H20073835, specification: 2.5 mg) at a dose of 2.5 mg/time per day, and compound amlodipine hydrochloride tablets (Suzhou Dawnrays Pharmaceutical Co., Ltd., GYZ Zi H20053836, specification: each tablet contains 25 mg amiloride hydrochloride and 25 mg hydrochlorothiazide) at a dose of half a tablet per day. The observation group received oral administration of amlodipine benzenesulfonate tablets at the same dose as the control group and telmisartan (Shanghai Modern Pharmaceutical Co., Ltd., GYZ Zi H20053836, specification: 40 mg) at a dose of 40 mg per day orally. Both groups were treated for 2 months.

Observation indicators

Blood pressure measurement: DBP and SBP measured with hamnatodynamometer before and after treatment.

Test of inflammatory factors levels: Blood (5 mL) was drawn from the veins of patients in a fasting state before and after treatment, centrifuged for 10 minutes at a centrifugal radius of 10 cm and speed of 3000 r/minute. We then obtained serum samples to test the levels of interleukin (IL)-1, IL-7, and Hs-CRP using an ELISA kit (R&D Systems, USA).

Test of endothelial active factor levels: Blood samples were taken before and after treatment to test ET-1 levels using an ELISA kit (Nanjing Camillo Biological Engineering Co., Ltd.), the level of NO using a NiRs test kit (Beijing Lingbao Tech Co., Ltd.), and the level of VEGF using an ELISA kit (Beijing Jianping Jinxing Biological Tech Co., Ltd.).

Test of platelet activating factors: Blood samples were taken before and after treatment to test the positive expression rate of platelet activating factor CD62P and glycoprotein GPIIb/IIa by a flow cytometer (MK-3 Company, USA) with a test kit from Shanghai Sunbio Co., Ltd.

Test of serum adiponectin and intima-media thickness (IMT): Blood samples were taken before and after treatment to test the level of serum adiponectin by ELISA (Beijing Kangtai Biological Co., Ltd.) and the IMT at the carotis communis, its branch, and initial segment were measured by ALOKA5500 CDU diagnostic apparatus.
Effects of combination treatment with amlodipine and telmisartan

Recording adverse reactions: Adverse reactions, including headaches, edema of lower extremity, and kaliopenia, etc., were recorded and counted.

Evaluation criteria of efficacy: Markedly effective: DBP declined by 10 mmHG and recovered to normal levels or declined by 20 mmHg after treatment. Effective: DBP declined less than 10 mmHg and recovered to normal levels or declined by 10-19 mmHg, and SBP declined at least 30 mmHg after treatment. Ineffective: DBP fails to decline to normal levels or SBP declined less than 30 mmHg after treatment. Total effective rate = 100% - ineffective rate.

Statistical analysis

SPSS 19.0 was used for statistical analysis. Measurement data are expressed as mean ± standard deviation (SD) and analyzed with a t-test; nominal data are expressed as percentage values and analyzed with χ² test. P < 0.05 was considered statistically significant.

Results

Group comparison of general clinical data

There was no significant difference between the two groups in respect to baseline data such as gender, age, body mass index (BMI), pathogenesis, and history of smoking (P > 0.05), as shown in Table 1.

Group comparison of efficacy

The observation group (96.23%) showed significantly increased total rate of effectiveness compared with control group (84.91%) (P < 0.05).

Note: amlodipine and telmisartan as a combination treatment for patients with primary hypertension can significantly improve clinical efficacy, as shown in Table 2.

Group comparison of blood pressure

After treatment, both groups experienced a significant decline in SBP and DBP, and the observation group was significantly lower than the control group (P < 0.05). Note: amlodipine and telmisartan as a combination treatment for patients with primary hypertension can significantly reduce the patient’s blood pressure, as shown in Figure 1.

Group comparison of levels of serum inflammatory factors

After treatment, both groups experienced a significant decline in IL-1, IL-7 and Hs-CRP, and the observation group was significantly lower than the control group with a statistical difference (P < 0.05). Note: amlodipine and telmisartan as a combination treatment for patients with primary hypertension can significantly reduce the patient’s levels of serum inflammatory factors, as shown in Figure 2.

Group comparison of levels of endothelial factors

After treatment, both groups experienced a significant decline in ET-1 and VEGF, and significant elevation in NO level. However, the observation group had significantly lower levels of ET-1 and VEGF than the control group, and higher levels of NO level, with a statistical difference (P < 0.05). Note: amlodipine and telmisartan as a combination treatment for patients with primary hypertension can significant-

Table 1. Group comparison for general clinical data (X ± s, n)

<table>
<thead>
<tr>
<th>Group Type</th>
<th>n</th>
<th>Gender</th>
<th>Average Age (Year)</th>
<th>BMI (kg/m²)</th>
<th>Pathogenesis (Year)</th>
<th>History of Smoking (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation group</td>
<td>53</td>
<td>27 (50.94)</td>
<td>26 (49.06)</td>
<td>56.68 ± 6.79</td>
<td>24.96 ± 1.82</td>
<td>6.77 ± 1.35</td>
</tr>
<tr>
<td>Control group</td>
<td>53</td>
<td>25 (47.17)</td>
<td>28 (52.83)</td>
<td>57.21 ± 6.44</td>
<td>25.21 ± 1.76</td>
<td>6.80 ± 1.41</td>
</tr>
<tr>
<td>χ²/t</td>
<td>0.151</td>
<td>0.412</td>
<td>0.719</td>
<td>0.112</td>
<td>0.158</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.698</td>
<td>0.681</td>
<td>0.474</td>
<td>0.911</td>
<td>0.691</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Group comparison for clinical efficacy [n (%)]

<table>
<thead>
<tr>
<th>Group Type</th>
<th>n</th>
<th>Markedly Effective</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Total Effective Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>53</td>
<td>28 (52.83)</td>
<td>23 (43.40)</td>
<td>2 (3.77)</td>
<td>51 (96.23)</td>
</tr>
<tr>
<td>Control group</td>
<td>53</td>
<td>20 (37.74)</td>
<td>25 (47.17)</td>
<td>8 (15.09)</td>
<td>45 (84.91)</td>
</tr>
<tr>
<td>χ²</td>
<td>10.920</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effects of combination treatment with amlodipine and telmisartan

Figure 1. Group comparison for blood pressure. After treatment, both groups had a significant decline in SBP and DBP, and the observation group was significantly lower than the control group. Note: compared with conditions before treatment, ***P < 0.001; compared with control group, ###P < 0.001.

Figure 2. Group comparison for level of serum inflammatory factors. After treatment, both groups had a significant decline in IL-1, IL-7, and Hs-CRP, and the observation group was significantly lower than the control group. Note: compared with conditions before treatment, ***P < 0.001; compared with control group, ###P < 0.001.

Figure 3. Group comparison for level of endothelial factors. After treatment, both groups had a significant decline in ET-1 and VEGF, and a significant elevation in NO level. The observation group had significantly lower levels of ET-1 and VEGF, and higher levels of NO level than the control group. Note: compared with conditions before treatment, ***P < 0.001; compared with control group, ###P < 0.001.

Figure 4. Group comparison of platelet activating factors. After treatment, both groups experienced a significant decline in CD62P and GPIIb/IIIa, with the observation group showing significantly lower levels than the control group (P < 0.05). Note: amlodipine and telmisartan as a combination treatment of patients with primary hypertension can significantly improve the activation status of platelets in the body of patients, as shown in Figure 4.

Figure 5. Group comparison of serum adiponectin and IMT. After treatment, both groups experienced significant elevation in the levels of serum adiponectin, and significant decline in IMT. The observation group had significantly higher levels of serum adiponectin and lower levels of IMT than the control group (P < 0.05). Note: amlodipine and telmisartan as a combination treatment for patients with primary hypertension can significantly improve the level of serum adiponectin in the body of patients, and inhibit the progress of atherosclerosis, as shown in Figure 5.

Group comparison of adverse reactions

The total incidence of adverse reactions in the observation group was 7.55%, which was not statistically different from the 11.32% of the control group. Note: amlodipine and telmisartan as a combination
Effects of combination treatment with amlodipine and telmisartan

Figure 4. Group comparison for positive expression rate of platelet activating factors. After treatment, both group had a significant decline in CD62P and GPIIb/IIIa, and the observation group was significantly lower than the control group. Note: compared with conditions before treatment, ***$P < 0.001$; compared with control group, ###$P < 0.001$.

Figure 5. Comparison between the two groups for serum adiponectin and IMT. After treatment, both groups had a significant elevation in the levels of serum adiponectin and a significant decline in IMT, and the observation group had higher levels of serum adiponectin and lower levels of IMT than the control group. Note: compared with conditions before treatment, ***$P < 0.001$; compared with control group, ###$P < 0.001$.

Table 3. Group comparison for adverse reactions [n (%)]

<table>
<thead>
<tr>
<th>Group Type</th>
<th>n</th>
<th>Headache</th>
<th>Edema of Lower Extremity</th>
<th>Kaliopenia</th>
<th>Total Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>53</td>
<td>3 (5.66)</td>
<td>1 (1.89)</td>
<td>0 (0.00)</td>
<td>4 (7.55)</td>
</tr>
<tr>
<td>Control</td>
<td>53</td>
<td>2 (3.77)</td>
<td>2 (3.77)</td>
<td>2 (3.77)</td>
<td>6 (11.32)</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.442</td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.506</td>
</tr>
</tbody>
</table>

treatment for patients with primary hypertension has proven to be safe, with no increase in adverse reactions in the patients, as shown in Table 3.

Discussion

Primary hypertension is a clinically common disease affecting a wide range of people. According to World Health Organization (WHO) statistics, it has a case rate of 40% in the population aged 25 years and older. It is an independent risk factor leading to coronary heart disease, heart failure, and similar cardiovascular diseases; therefore, it poses a severe health threat [10]. In recent years, changes to lifestyle and diet, have contributed to an increase in the case rates of hypertension. Epidemiologic studies revealed that the incidence of primary hypertension in China is about 243-455 in 10,000 and is higher in middle-aged and elderly males who smoke [11]. In addition to measures such as controlling salt intake and avoiding smoking and drinking alcohol, long-term administration of antihypertensive drugs, including diuretics, calcium channel antagonists, and angiotensin receptor antagonists is required to treat primary hypertension, in order to control the patient’s blood pressure within the standard range.

Amlodipine is a long-lasting dihydropyridine calcium channel antagonist with a half-life of around 3.5 h and a capacity to reduce blood pressure in the long run. It works by affecting the movement of calcium into the smooth muscle cells of the heart and blood vessels. As a result, amlodipine relaxes the smooth muscle cells of blood vessels, dilating them and reducing their workload [12]. Telmisartan is an Ang II receptor (AT1 type) antagonist, which inhibits the activity of Ang II through selective affinity to AT1 type receptors and then stops blood vessels from contracting, suppressing sympathetic excitation and reducing the synthesis and release of aldosterone. Studies of pharmacokinetics found that the half-life of telmisartan is about 18-24 hours. It can reduce and flatten blood pressure with minimum toxic side effects.
and a high margin of safety [13]. It is clinically found that primary hypertension patients with a large fluctuation of blood pressure are more likely to suffer from cardiovascular and cerebrovascular diseases. By observing the changes of blood pressure before and after treatment, the patient’s conditions can be managed, which is conducive to their prognosis. This study revealed that the observation group excelled compared to the control group in respect of total effective rate and decline in SBP and DBP, but there was no significant difference regarding adverse reactions, which is consistent with previous reports [14]. This study establishes the efficacy of combination treatment with amlodipine and telmisartan for primary hypertension with less adverse reactions and better efficacy than the combination treatment of amlodipine and compound amiloride hydrochloride.

For patients with hypertension, inflammatory reactions of the vascular wall due to vascular endothelial dysfunction results in increased levels of various inflammatory factors [15]. Hs-CRP, an acute-phase protein produced by the liver, may increase due to inflammatory reactions or tissue damage. Correlational studies have shown that Hs-CRP is a risk factor for dyslipidemia and hypertension and is significantly higher in patients with hypertension than in healthy people [16]. IL-1 is a type of proinflammatory factor produced by activated Th2 cells to accelerate the proliferation of VSMCs and also plays a key role in the formation and development of hypertension [17]. Correlational studies have revealed that levels of serum IL-1 in patients with primary hypertension are significantly higher than those in healthy people (control group) [18]. IL-7 is a pleiotropic cytokine present in lymphocytes, bone marrow cells, and vascular endothelial cells expressing its receptor, and has a widespread immunological effect [19]. Primary hypertension plays a proinflammatory role while vascular endothelial dysfunction activates immunological cells to reduce T-suppressor cells. IL-7 works on T-cells for immune dysregulation and participates in the development of primary hypertension. Studies have indicated that in patients with primary hypertension, IL-7 levels are significantly higher than those in healthy control groups [20]. Results from this study showed an obvious decline in levels of serum IL-1, IL-7, Hs-CRP in both groups after treatment, and overall, the observation group had significantly lower levels than the control group, which is consistent with previous reports [21]. This indicates that the combination treatment of amlodipine and telmisartan can inhibit the vascular inflammatory reactions in patients with primary hypertension.

Currently, it is generally believed that vascular endothelial cell injury and functional change are the important pathological mechanisms for the occurrence of primary hypertension, and hypertension will reduce the activity of oxidase, enhance the lipid peroxidation, lead to the metabolic disorder of oxygen free radicals, and damage the vascular endothelial cells. Both ET-1 and NO are produced by vascular endothelial cells, which are vasoactive substances and have the biological function of maintaining the structure of vascular intima and regulate the function of vasoconstriction. Among them, ET-1 is a regulator of vasoconstriction. When vascular endothelial function is impaired, ET-1 can be increased, while too high of a concentration of ET-1 can promote the proliferation of endothelial cells, smooth muscle cells, and aggravate the condition of patients [22]. NO is a type of vasodilatation factor, and when vascular endothelial function is impaired, NO level can be decreased. As a factor to maintain the survival of vascular endothelial cells, VEGF plays an important role in the occurrence of hypertension, which can repair damaged endothelial cells, improve vascular permeability, and help maintain the physiological functions of vascular endothelial cells. It has been reported that the VEGF level of patients with primary hypertension is higher than that of the normal control group, and when the vascular endothelial injury and dysfunction occur, the VEGF level can be increased [23]. When the serum levels of ET-1, VEGF and NO were abnormal, the endothelial function was impaired, the blood pressure was increased, and the condition was aggravated. Results from our study revealed that both groups experienced a decline in serum ET-1 and VEGF, and an increase in NO levels after treatment. However, ET-1 and VEGF were lower in the observation group than the control group and NO levels were higher in the observation group than the control group. This indicates that the combination treatment of amlodipine with telmisartan can improve vascular endothelial function.
Both CD62P and GPIIb/IIIa are markers of platelet activation. More specifically, CD62P, an activated platelet membrane glycoprotein, directly reflects the extent to which platelets are activated, while GPIIb/IIIa binds to hematein to participate in the process of platelet aggregation (PA), and exists as an important substance reflecting the activation degree of platelets. Correlational studies have shown that patients with hypertension suffer from an abnormal increase in expression levels of platelet activating factors [24]. Results from our study revealed that after treatment, both groups experienced a significant decline in positive expression rates of CD62P and GPIIb/IIIa. Overall, levels in the observation group were significantly lower than those in the control group, indicating that combination treatment with amlodipine and telmisartan reduces the degree of platelet activation in patients with primary hypertension.

Adiponectin is a protective factor secreted by adipose cells. It plays the role of inhibition and protection during the development of primary hypertension and is negatively correlated to blood pressure [25, 26]. IMT can directly reflect the degree of atherosclerosis, and primary hypertension is one of the risk factors for the formation of atherosclerosis. Therefore, observation of IMT in patients with primary hypertension can reveal the atherosclerotic lesions of the patients [2]. Patients with hypertension are vulnerable to atherosclerosis [27] as they suffer from increased hypertensive turbulences, lipid metabolism disorder, damaged BVE, and vascular inflammatory reaction, which results in changes such as PA, formation of carrier lipoprotein B complex and fat accumulation on vascular walls. Results from this study indicated that both groups experienced an elevation in serum adiponectin and a reduction in IMT. Overall, the observation group had higher levels of serum adiponectin than the control group and lower levels of IMT than the control group, findings which are similar to previous reports [28]. These results indicate that amlodipine and telmisartan can up-regulate serum adiponectin levels and inhibit progression of atherosclerosis in patients with primary hypertension.

In conclusion, the efficacy of combination treatment with amlodipine and telmisartan for primary hypertension has been established. Its mechanism of action is thought to be linked to the inhibition of intravascular inflammatory reactions, platelet activation, improvement of vascular endothelial functions, and up-regulation of serum adiponectin level. In addition, combination treatment can inhibit progression of atherosclerosis with less adverse reactions, and therefore is worth promoting. However, due to the small number of samples collected in this study and the short observation time, the results may be biased. In the future, the clinical study scale can be expanded for more in-depth exploration.

Disclosure of conflict of interest

None.

Address correspondence to: Huiting Chen, Department of Cardiovascular Medicine, The First People's Hospital of Wenling, No. 333, Chuan'an South Road, Chengxi Street, Wenling 317500, Zhejiang, China. Tel: +86-15867061921; E-mail: chchenht@163.com

References

Effects of combination treatment with amlodipine and telmisartan


Effects of combination treatment with amlodipine and telmisartan

