Efficacy of the combination of valsartan and hydrochlorothiazide in the treatment of hypertensive heart disease

Xin Zhou, Yuefeng Chu*
Department of Cardiovascular Medicine, Lu'an Hospital of Anhui Medical University, Lu'an 237005, Anhui, China
*For correspondence: Email: Yuefeng_Chu@126.com

Sent for review: 9 May 2023
Revised accepted: 31 July 2023

Abstract

Purpose: To investigate the effectiveness of the combination of valsartan and hydrochlorothiazide in managing hypertensive heart disease.

Methods: From August 2020 to October 2022, the case data of 120 patients in Lu'an Hospital of Anhui Medical University, Lu'an, China were analyzed retrospectively. Based on the different treatment options, 54 patients with hypertensive heart disease who received valsartan alone (80 mg, once daily) for 3 months were placed in control group (CG), while 66 patients who received valsartan combined with Systolic blood pressure (SBP), therapeutic effect, diastolic blood pressure (DBP), and incidence of adverse effects were also recorded for CG and SG.

Results: In the SG, there were significant reductions in SBP, DBP, LVMI and LVPWT compared to CG, while EF showed significant increase after treatment (p < 0.05). In both groups, SBP, DBP, LVMI and LVPWT decreased significantly after treatment compared to pre-treatment values, but EF however showed a significant increase (p < 0.05). In the SG, there was a significant increase (p < 0.05) in the total effective rate compared to CG and there was also a significant reduction (p < 0.05) in the total incidence of adverse effects compared to CG.

Conclusion: Valsartan combined with hydrochlorothiazide is more effective in treating patients with hypertensive heart disease than valsartan monotherapy alone. However, the combination treatment should be subjected to further clinical trials prior to its introduction into clinical practice.

Keywords: Valsartan, Hydrochlorothiazide, Hypertensive heart disease, Cardiac function indices

INTRODUCTION

When hypertension is not effectively managed over a prolonged period, it leads to an increase in cardiac afterload. Additionally, the excessive release of hypertension mediators such as catecholamines and angiotensin, combined with other factors, contributes to left ventricular enlargement and left ventricular hypertrophy, thus affecting cardiac function. The heart disease arising, as a result, is called hypertensive heart disease [1].

According to statistics, of the 330 million cardiovascular patients, 245 million are patients with hypertension, accounting for 74.2%. There...
has been a notable increase in the number of people affected by hypertension globally over the years. It is estimated that at least 26.4 % of the global population is affected by this disease [2]. The predisposing factor of hypertensive heart disease is mainly related to hypertension and includes excessive cardiac load caused by hypertension and abnormal regulation of cytokines, which are the basic causes of hypertensive heart disease [3]. Moreover, infection, emotional stress, electrolyte imbalance and arrhythmia may also be predisposing factors for the development or aggravation of hypertensive heart disease [4].

Hypertensive heart disease is manifested as left ventricular dysfunction, including dyspnea, cough, expectoration and hemoptysis. Advanced left ventricular dysfunction can lead to right ventricular dysfunction, showing symptoms such as digestive system discomfort and edema [5]. Hypertensive heart disease will mainly cause lung congestion, decreased ventricular function, heart failure and insufficient blood supply. In severe cases, these complications can pose a significant threat to the patient’s life and health [6]. Therefore, it is crucial to properly diagnose and provide appropriate treatment for hypertensive heart disease which is aimed at controlling the patients’ blood pressure and treating their heart function on time using appropriate methods.

Presently, patients with hypertensive heart disease are mainly treated with drugs. Valsartan, an angiotensin II receptor antagonist (ARB), is an antihypertensive drug used mainly to antagonize angiotensin receptors and hence dilate blood vessels and lower blood pressure [7]. Valsartan is used to treat cardiovascular diseases such as myocardial infarction and hypertension. Its effect is long-lasting because of its long half-life and stable with a few side effects. Valsartan effectively treat refractory hypertension with high safety in heart failure patients whose blood pressure is still elevated after antihypertensive drug treatment [8]. Hydrochlorothiazide, as a diuretic, exerts its beneficial effects by inhibiting the reabsorption of sodium chloride in the anterior segment of the distal renal tubule and proximal tubule. This action promotes diuresis and enhances the excretion of sodium, leading to changes in renal hemodynamics and glomerular filtration function. Ultimately, this helps to reduce blood pressure in patients with hypertension [9]. The drug is used as a monotherapy or in combination with other anti-hypertension medicine to treat essential hypertension. Valsartan combined with hydrochlorothiazide effectively treats hypertension and the combined therapy is more effective than the single therapy of either drug [10].

Therefore, this study was designed to use valsartan combined with hydrochlorothiazide to analyze the clinical efficacy and influence on heart functional indexes and blood pressure in treating patients with hypertensive heart disease. This is necessary to provide a reliable reference for the treatment and diagnosis of the disease in clinical practice.

**METHODS**

**Clinical data**

From August 2020 to October 2022, the case data of 120 patients admitted in the Department of Cardiovascular Medicine, Lu’an Hospital of Anhui Medical University were collected and analyzed retrospectively. The control group (CG) consisted of 54 patients with hypertensive heart disease who underwent valsartan therapy, while the study group (SG) consisted of 66 patients who underwent a combination therapy of valsartan and hydrochlorothiazide. The research was ratified by the Ethics Committee of Lu’an Hospital of Anhui Medical University, and it adhered to the ethical principles outlined in the Declaration of Helsinki [11]. All patients and/or their statutory guardians affixed written informed consent.

**Inclusion and exclusion criteria**

**Inclusion criteria**

Those who were in conformity with the diagnostic criteria for hypertensive heart disease and hypertension-related diseases [12]; Patient who were diagnosed with an ultrasound blood pressure monitoring; and those with complete clinical data.

**Exclusion criteria**

Patients with drug allergy and contraindications to drugs used in this study; patients in the emergency unit with hypertension; patients with poor compatibility and compliance; comorbidity with other endocrine diseases; coagulation dysfunction; patients with mental disorders; and patients whose health condition was complicated by infectious or immune diseases.

**Therapeutic schemes**

Control group (CG): Patients were treated with valsartan. The patient took oral valsartan capsules [13] (Tianda Pharmaceutical (Zhuhai)

*Trop J Pharm Res, August 2023; 22(8): 1742*
Co., Ltd., SFDA Approval No. H20030777, specification: 80 mg×14 capsules), once daily, one capsule at a time, with breakfast. The course of treatment lasted for three months. According to the patient's disease development, the dosage was adjusted to 160 mg/day.

Study Group (SG): Patients in the SG took oral hydrochlorothiazide (Yunpeng Pharmaceutical (Shanxi) Co. Ltd, SFDA approval no. H14020796, specification: 25 mg) in combination with Valsartan (same dose used in the CG), with a first dose of 6.5 mg/day, for a total duration of 3 months. In the course of treatment, the dosage was adjusted to 13 mg/day, according to the patient's treatment response.

Assessment of cardiac function indices

Heart function indices, including left ventricular posterior wall thickness (LVPWT), left ventricular mass index (LVMI) and left ventricular ejection fraction (EF) were determined by Philips IU22 color ultrasonic diagnostic instrument (Florida, USA) before and after treatment (end of 3 months).

Evaluation of parameters/outcomes

Main outcome measures: Changes in cardiac function indices (LVMI, LVPWT, EF) in both groups were compared before and after therapy. Therapeutic effect was calculated using Eq 1 and compared between the two groups.

\[
TE = (ME + E/TC)100 \quad \text{(1)}
\]

where TE = Total effective rate; ME = markedly effective cases; E = effective cases; TC = total cases.

The evaluation criteria of efficacy are shown in Table 1. Alterations in diastolic blood pressure (DBP) and systolic blood pressure (SBP) were recorded for CG and SG. Secondary outcome measures: The baseline data and incidence of adverse effects were compared between CG and SG.

**Statistical analysis**

Data were analyzed using SPSS 20.0 (SPSS Inc, Chicago, IL, USA). GraphPad Prism 8 was utilized for data visualization. Chi-squared test was utilized for comparison of classified variables. Intra-group comparisons were conducted using paired t-test, while inter-group comparisons were conducted using independent sample t-test. The statistical significance of the results was determined with a threshold of \( p < 0.05 \).

**RESULTS**

**Clinical data**

Upon comparing the basic clinical data, it was observed that there were no statistically significant differences in the duration of disease, body mass index (BMI), gender, age, educational level and place of residence between the CG and SG (\( p > 0.05 \); Table 2).

**Blood pressure indices**

Upon comparing the blood pressure indices, no significant difference in the SBP and DBP was found between the CG and SG before therapy (\( p > 0.05 \)). Nevertheless, after therapy, the SG showed significantly lower SBP and DBP compared to the CG (\( p < 0.05 \)). Furthermore, intra-group comparison revealed that the SBP and DBP in both groups decreased significantly after treatment compared to before therapy (\( p < 0.05 \)) (Figure 1).

**Cardiac function indices**

A comparison of the cardiac function indices, before and after therapy, is presented in Figure 2. There was no significant difference in LVMI, LVPWT and EF levels in both groups before therapy (\( p > 0.05 \)). However, compared to the CG after therapy, the SG demonstrated significantly lower LVMI and LVPWT levels but the EF was significantly higher (\( p < 0.05 \)).

**Table 1: Evaluation criteria for clinical effects**

<table>
<thead>
<tr>
<th>Efficacy grade</th>
<th>Evaluative criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markedly effective</td>
<td>Blood pressure returns to normal, and clinical symptoms such as heart failure and arrhythmia are significantly improved.</td>
</tr>
<tr>
<td>Effective</td>
<td>Blood pressure is obviously reduced, and clinical symptoms such as heart failure and arrhythmia are improved.</td>
</tr>
<tr>
<td>Ineffective</td>
<td>The effect on blood pressure control is not ideal, and the clinical symptoms such as heart failure and arrhythmia have not improved but rather worsened.</td>
</tr>
</tbody>
</table>
Table 2: Comparison of clinical data

<table>
<thead>
<tr>
<th>Factor</th>
<th>CG (n=54)</th>
<th>SG (n=66)</th>
<th>$\chi^2$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60 years old</td>
<td>33</td>
<td>29</td>
<td>3.507</td>
<td>0.061</td>
</tr>
<tr>
<td>&gt;60 years old</td>
<td>21</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31</td>
<td>38</td>
<td>0.000</td>
<td>0.985</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤21 kg/m²</td>
<td>32</td>
<td>31</td>
<td>1.799</td>
<td>0.180</td>
</tr>
<tr>
<td>&gt;21 kg/m²</td>
<td>22</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 years</td>
<td>24</td>
<td>28</td>
<td>0.049</td>
<td>0.824</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>30</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below junior college</td>
<td>28</td>
<td>41</td>
<td>1.282</td>
<td>0.258</td>
</tr>
<tr>
<td>Junior college and above</td>
<td>26</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>City</td>
<td>24</td>
<td>31</td>
<td>0.076</td>
<td>0.782</td>
</tr>
<tr>
<td>Rural</td>
<td>30</td>
<td>35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Comparison of blood pressure changes (A) Comparison of SBP before and after therapy (B) Comparison of DBP before and after therapy. **** $P < 0.0001$. SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Furthermore, intra-group comparison showed that LVMI and LVPWT levels in both groups decreased significantly after treatment compared to before therapy, while EF showed a significant increase ($p < 0.05$).

Therapeutic effect

The therapeutic effect were analyzed between the CG and SG. The findings showed that in the SG, there was a significant increase in the total effective rate compared to CG ($p = 0.007$; Table 3).

Incidence of adverse reactions

The adverse reactions were analyzed between the CG and SG. The findings showed that in the SG, there was a significant reduction in the total rate of adverse effects compared to CG ($p = 0.001$; Table 4).

DISCUSSION

In recent years, with the change in lifestyle, the incidence of hypertension among young and middle-aged people is increasing. If hypertension is not effectively managed for 3 - 5 years, it leads to structural and functional changes in the heart, which is known as hypertensive heart disease. The elderly are the common population suffering from hypertension.
With the increase in age, the elderly begin to show manifestations such as decreased vascular elasticity and arteriosclerosis, which leads to unsatisfactory control of the blood pressure, thus causing hypertension. Secondly, metabolic disorders caused by obesity, or unhealthy living habits such as sedentary lifestyle, smoking and drinking can also induce hypertension [13].

Early symptoms of hypertension are generally atypical, such as mild headache and chest tightness, which are not easy to detect. If the disease continues to progress and is not taken seriously, it will lead to more serious complications and even threaten health and life. Long-term hypertension easily cause the aggravation of cardiac afterload. When the pressure of the arterial system increases, the heart needs to compensate moderately, thus leading to myocardial ischemia and heart disease [14]. If hypertensive heart disease is not controlled and treated on time, it leads to left heart failure, which is life-threatening. At present, drugs are the main treatment for hypertensive heart disease and angiotensin receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEI), Beta (β)-blockers and aldosterone receptor antagonists are the drugs of choice for controlling patients’ blood pressure as well as improve cardiac function [15]. In daily life and diet, patients also need to strictly control the intake of salt, quit smoking and alcohol, develop an exercise culture and maintain a peaceful state of mind to avoid the aggravation of diseases caused by excessive emotions.

In the treatment of hypertensive heart disease, it is crucial to control blood pressure effectively. Therefore, selecting an appropriate antihypertensive drug that quickly restore blood pressure to normal levels with minimal adverse reactions is crucial for prognosis. Valsartan is a commonly used antihypertensive drug in treating minor and moderate hypertension with good efficacy and less side effects. It works by reducing arterial pressure and has been shown to be particularly effective in treating hypertension for elderly patients, thus, helping to maintain blood pressure within a normal range [16]. Valsartan not only has a good antihypertensive effect but also does not affect the heart rate. It is thus a potential drug in treating hypertensive heart disease. In addition, combining valsartan with diuretics further enhances its antihypertensive effect. Hydrochlorothiazide, a diuretic drug, helps patients with hypertension via diuresis and also lowers blood pressure concurrently. For this reason, valsartan is often combined with hydrochlorothiazide to further enhance the treatment effect [17].

Previous research [18] has shown that in the treatment of elderly patients with hypertension, combining valsartan with amldipine or hydrochlorothiazide has been found to be effective in improving vascular endothelial function and lowering blood pressure, which would be a better choice for them. In this study, valsartan combined with hydrochlorothiazide was used to treat patients with hypertensive heart disease. The findings revealed that in the study group (SG), there was a notable increase in the total effective rate compared to the control group (CG), indicating that compared with single drug treatment, the combination of these two drugs complement each other, work synergistically to explore their advantages and as such, significantly improve the therapeutic effect on patients. In addition, the changes in blood pressure and cardiac function indices before and after therapy were analyzed and compared. The results showed that in the SG, there were significant reductions in SBP, DBP, LVMl and LVPWT compared to CG, while the EF showed a significant increase after treatment. Compared

Table 3: Therapeutic effectiveness

<table>
<thead>
<tr>
<th>Group</th>
<th>Markedly effective</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Total effective rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG (n=54)</td>
<td>10 (18.5)</td>
<td>33 (61.1)</td>
<td>11 (20.37)</td>
<td>43 (79.63)</td>
</tr>
<tr>
<td>SG (n=66)</td>
<td>24 (36.36)</td>
<td>39 (59.09)</td>
<td>3 (4.55)</td>
<td>63 (95.45)</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td></td>
<td></td>
<td></td>
<td>7.217</td>
</tr>
<tr>
<td>$P$-value</td>
<td></td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
</tbody>
</table>

Table 4: Incidence of adverse reactions (N (%))

<table>
<thead>
<tr>
<th>Groups</th>
<th>Headache</th>
<th>Vertigo</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Dry cough</th>
<th>Oedema</th>
<th>Total adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG (n=54)</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>17 (31.48)</td>
</tr>
<tr>
<td>SG (n=66)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>6 (9.09)</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.611</td>
</tr>
<tr>
<td>$P$-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
</tbody>
</table>

Zhou & Chu

Trop J Pharm Res, August 2023; 22(8): 1745
with pre-treatment conditions, SBP, DBP, LVMI and LVPWT in both groups decreased significantly, while EF showed a significant increase post-treatment, which indicate that the blood pressure and cardiac function of patients receiving valsartan plus hydrochlorothiazide were notably improved and that the treatment effect was remarkable.

Valsartan alone may have some limitations for different patients with hypertensive heart disease. Therefore, valsartan combined with hydrochlorothiazide further enhances the antihypertensive effect and improve the cardiac function of patients involved. In this regard, the findings of this research are similar to a previous study [19]. Valsartan has a notable antihypertensive effect and also ameliorates the heart function of patients. However, the combined use of valsartan and hydrochlorothiazide further enhance the therapeutic outcome and reduce the damage to the target organs of the body.

Finally, the incidence of adverse reactions of patients in both groups revealed that in the SG, there was a significant reduction in the total rate of adverse reactions compared to CG, indicating that combination therapy effectively reduces the incidence of adverse effects and has a high safety profile. This result is consistent with the findings of a previous study [20].

Limitations of this study

Valsartan combined with hydrochlorothiazide has been shown to be effective in treating patients with hypertensive heart disease. Nevertheless, there are still some shortcomings. For instance, this research is a retrospective one and the sample size is limited, so it can't be as uniform as a randomized controlled experiment. Secondly, due to the lack of follow-up in this study, it is not possible to compare and observe the long-term effect and prognosis of the patients.

CONCLUSION

The combination of valsartan and hydrochlorothiazide is effective in treating patients with hypertensive heart disease. It effectively ameliorates blood pressure, improves cardiac function and lowers the incidence of adverse reactions. Sample size should be expanded, and proper and follow-up of patients done in large-scale randomized experiments conducted in future studies to validate these present findings.

DECLARATIONS

Acknowledgements
None provided.

Funding
None provided.

Ethical approval
This study was approved by the Ethics Committee of Lu’an Hospital of Anhui Medical University, China.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest
No conflict of interest associated with this work.

Contribution of Authors
We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Xin Zhou conceived and designed the study and drafted the manuscript. Xin Zhou and Yuefeng Chu collected, analyzed and interpreted the experimental data. Yuefeng Chu revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Open Access
This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

REFERENCES


