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Original Research Article

Effect of combining valsartan and amlodipine in the treatment of type 2 diabetes mellitus complicated by hypertension

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Abstract

Purpose: *To investigate the efficacy of combining valsartan and amlodipine on patients who were co-morbid with type 2 diabetes mellitus (T2DM) and hypertension.*
Methods: *The medical records of 110 patients treated in North China Electric Power University Hospital, Beijing, China from July 2018 to October 2022 were retrospectively analyzed. Control group (CG; n = 50) was administered oral amlodipine (5 mg daily for 6 months), while the study group (SG; n = 60) received one tablet of co-formulated valsartan (80 mg)) and amlodipine (5 mg) daily for 6 months. All the patients, in addition to the above drugs, were also placed on insulin and atorvastatin calcium. After a 6-month treatment period, the therapeutic effect and incidence of adverse effects were compared between CG and SG. Blood glucose-related indices (glycosylated hemoglobin (HbA1c), 2 h postprandial blood glucose (2 h PG), and fasting blood glucose (FBG)) and blood pressure indices, viz, (diastolic blood pressure (DBP), systolic blood pressure (SBP)) were compared.*
Results: *Compared to the pre-treatment values, both groups showed significant decrease in 2 h PG, FBG, HbA1c, SBP and DBP after treatment ($p < 0.05$), but the 2 h PG, FBG, HbA1c, SBP and DBP in SG were significantly lower in comparison to CG ($p < 0.05$). The overall response rate (ORR) of CG was significantly lower in comparison to SG ($p < 0.05$). In SG, there was significant reduction in the incidence of adverse effects compared to CG ($p < 0.05$).*
Conclusion: *The combination of valsartan and amlodipine is effective in treating T2DM co-morbid with hypertension, and satisfactorily controls blood glucose level and blood pressure with a relatively high level of safety. Further experiments would be required to ascertain the reliability of these findings.*

Keywords: *Valsartan, Amlodipine, Type 2 diabetes mellitus, Hypertension*

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INTRODUCTION

Type 2 diabetes mellitus (T2DM), alternatively known as non-insulin-dependent diabetes or maturity-onset diabetes, is a chronic metabolic condition. Different from type 1 diabetes [1], T2DM is typically characterized by decreased responsiveness of the body to insulin [2,3]. It usually develops in middle-aged or elderly people aged 50 – 60 years, but in modern society, young people aged 20 – 45 years may also suffer from this disease [4]. In addition,

people with T2DM are often prone to hypertension, which may be related to poor insulin effect caused by T2DM. This may increase the tension of blood vessels and the retention of body fluids, thus leading to hypertension. On the other hand, hypertension may also affect the development and progression of diabetes by affecting the mechanism of blood glucose regulation [5].

The treatment of T2DM complicated by hypertension aims to control the blood glucose and blood pressure levels to fall within normal range so as to reduce the risk of complications [6]. Valsartan belongs to antihypertensive drugs, which are mainly used to antagonize angiotensin receptors, dilate blood vessels and lower blood pressure [7,8]. Amlodipine is a commonly used dihydropyridine calcium antagonist, which has good efficacy in treating hypertension and angina pectoris [9]. Amlodipine effectively lowers blood pressure, so it is a safe and effective oral antihypertensive drug [10]. Therefore, this study was designed to use valsartan combined with amlodipine to treat T2DM whose blood glucose control is complicated by hypertension and hence analyze the efficacy of this combination, which is aimed at offering valuable insights for clinical management and therapeutic approaches to this disease.

METHODS

Patients

The medical records of 110 patients treated in North China Electric Power University Hospital (Beijing) from July 2018 to October 2022 were retrospectively studied. The North China Electric Power University Hospital (Community Health Service Center of North China Electric Power University) is located in the north of the university campus, which is subordinate to North China Electric Power University. With a construction area of 3,030 square meters, the hospital has more than 20 clinical and auxiliary departments, such as internal medicine, surgery, emergency medicine, gynecology, stomatology, preventive medicine, general medicine (ophthalmology, ENT), traditional Chinese medicine and laboratory medicine, medical imaging (including radiology and B-ultrasound room), electrocardiogram room and pharmacy, with 26 beds. Based on different treatment methods, 50 patients with T2DM complicated by hypertension who received amlodipine were assigned to control group (CG), while 60 patients who were administered valsartan/amlodipine (co-formulation) were assigned to study group (SG). The research was ratified by the Medical Ethics Committee of North China Electric Power University Hospital, Beijing 102206, China (approval no. NCEPUH58432), and met the criteria in the Declaration of Helsinki [11].

Inclusion criteria

Patients who fulfilled the criteria for the diagnosis of T2DM [12] and hypertension-related diseases [13]; patients who had not received other medications before treatment; those with high degree of compliance and adherence; normal mental state; normal function of important organs such as the heart and liver and those with detailed medical records.

Exclusion criteria

Patients with grade Ⅲ hypertension; patients with drug allergy and contraindications to medications administered in this study; comorbidity with other endocrine disorders; coagulation dysfunction; and patients whose condition was complicated by infectious or immune diseases.

Therapeutic schemes

All patients were given routine treatment, which included hypoglycemic and lipid-lowering treatments. The patients were injected with insulin subcutaneously to control blood glucose, and statins were given to control blood lipids. Isophane protamine recombinant human insulin injection (Jiangsu Wanbang Biochemical Pharmaceutical Group Co. Ltd, approval no. S20060001) was used to control blood glucose, administered twice daily, with dosage adjusted based on patient's blood sugar levels. Atorvastatin calcium tablets (Lepu Pharmaceutical Technology Co. Ltd, approval no. H20163270) were used to control blood lipids, with a dosage of 20 mg per dose, taken orally once daily, for 6 months.

Control group

In addition to the routine treatment described above, patients also took amlodipine besylate tablets (Suzhou Yushi Pharmaceutical Co. Ltd, SFDA approval no. H20103315, specification: 5 mg/tablet) orally, 5 mg/daily for 6 months.

Study group

In addition to previously described routine treatment, patients also took valsartan and amlodipine tablets (Zhejiang Huahai Pharmaceutical Co. Ltd., SFDA approval no. H20213253, specification: 80 mg valsartan + 5

mg amlodipine tablet orally, once daily for 6 months.

Evaluation of parameters/indices

2 h postprandial blood glucose

After fasting, the venous blood (5 mL) was withdrawn from the participants in both groups in the morning, and the median elbow vein (3 mL) was withdrawn 2 h after meal to measure the concentration of 2 h postprandial blood glucose (2 h PG).

Blood glucose-related indices

An automated biochemical analyzer was employed to assess the blood glucose-related indices before and after therapy, including glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG) and 2 h PG.

Therapeutic outcomes

Therapeutic effects were compared between CG and SG. The criteria for evaluating efficacy are presented in Table 1. The blood glucose-related indices (FBG, 2h PG, HbA1c) and blood pressure levels (diastolic blood pressure (DBP), and systolic blood pressure (SBP)) were analyzed before and after treatment. The occurrence rate of adverse effect was compared between CG and SG. The overall response rate (R) was calculated using Eq 1.

$$R = \{(ME+E)/N\}100 \quad \text{..... (1)}$$

where N is the overall patient population.

Statistics

Statistical Package for Social Sciences (SPSS) 20.0 (SPSS Inc., Chicago, IL, USA) was utilized to analyze the collected data. GraphPad Prism 8 was utilized to draw the pictures for the data. Chi-squared test was utilized to compare classified variables. Paired t-tests were utilized for conducting intra-group comparisons, while inter-group comparisons were conducted using independent sample *t*-tests. The statistical significance of the results was assessed at $p < 0.05$.

RESULTS

General patient information

Comparing the basic clinical data, the results showed that the two groups exhibited similarities in age, body mass index (BMI), gender, course of diabetes, course of hypertension, place of residence and blood pressure classification ($p > 0.05$; Table 2).

Blood glucose-related indices

When comparing the blood glucose-related indices, no significant differences were found in the FBG, HbA1c and 2 h PG between CG and SG before treatment ($p > 0.05$). Nevertheless, after therapy, OG demonstrated significantly lower FBG, 2 h PG and HbA1c in comparison to CG ($p < 0.05$). Furthermore, intra-group comparison revealed that FBG, 2 h PG and HbA1c in both groups decreased significantly after treatment compared to before therapy ($p < 0.05$; Figure 1).

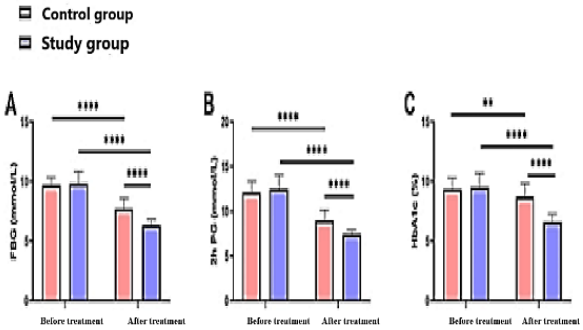

Figure 1: Comparison of blood glucose-related indices. (A) Comparison of FBG level before and after therapy, (B) Comparison of 2 h PG level before and after therapy, (C) Comparison of HbA1c level before and after therapy. ***Key:*** $^{**}P < 0.01$ and $^{****}P < 0.0001$ significance between groups being compared

Table 1: Criteria for evaluating clinical efficacy

Efficacy rating	Evaluative criteria
Markedly effective (ME)	Clinical symptoms such as hyperphagia, drowsiness and headache disappear, and blood pressure and heart rate return to normal.
Effective (E)	Clinical symptoms such as hyperbiosis, drowsiness and headache improve, and blood pressure and heart rate stabilized.
Ineffective	Clinical symptoms such as hyperbiosis, drowsiness and headache have not improved or rather worsened, and blood pressure and heart rate are unstable.

Table 2: Comparison of general patient information

Factor	Item	CG (n=50)	OG (n=60)	χ^2	*P*-value
Age (years)				0.535	0.464
	≤ 65	26	27		
	> 65	24	33		
Gender					
	Male	32	39	0.012	0.913
	Female	18	21		
BMI (kg/m^2)				0.441	0.507
	≤25	21	29		
	>25	29	31		
Course of diabetes				0.031	0.860
	≤6 years	20	25		
	>6 years	30	35		
Course of hypertension				1.171	0.279
	≤7 years	26	25		
	>7 years	24	35		
Blood pressure classification				0.201	0.654
	Grade I	17	18		
	Grade II	33	42		
Place of residence				0.147	0.702
	City	26	29		
	Rural	24	31		

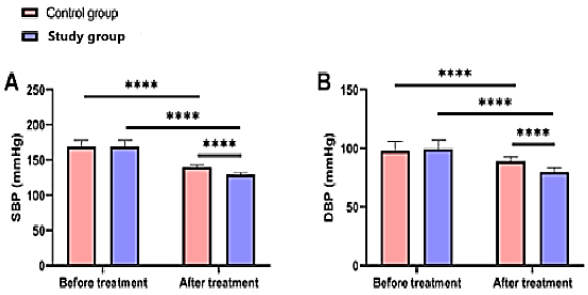

Figure 2: Comparison of blood pressure levels (A) Comparison of SBP level before and after therapy, (B) Comparison of DBP level before and after therapy. ***Key***: ****P < 0.0001 significance between groups being compared

Blood pressure levels

When comparing the blood pressure levels before and after treatment, no significant differences were found in the SBP and DBP between CG and SG before treatment (p > 0.05), Nevertheless, after therapy, the SG demonstrated significantly lower SBP and DBP compared to CG (p < 0.05). Furthermore, intra-group comparison revealed that the SBP and DBP in the two groups decreased significantly after treatment compared to before therapy (p < 0.05; Figure 2).

Therapeutic effect

The treatment outcomes were analyzed and compared between CG and OG. The results showed that in OG, there was significant increase in the overall response rate compared to CG (p = 0.029; Table 3).

Adverse reactions

The adverse effects were analyzed and compared between CG and OG. The findings showed that in OG, there was a significant reduction in the total rate of adverse effects in comparison to CG (p = 0.037; Table 4).

DISCUSSION

With the rapid development of urbanization and the convenience of life, more and more unhealthy lifestyles have emerged, such as prolonged sitting, sedentary lifestyles, high-energy diets and stress. These factors will increase the risk of T2DM which is also called non-insulin-dependent diabetes mellitus because patients' insulin levels are usually normal or higher than normal, but their body cells have insufficient insulin response, resulting in elevated blood glucose levels [14].

Table 3: Comparison of treatment outcomes

Group	Markedly effective	Effective	Ineffective	Overall response rate
CG (n=50)	18 (36.00)	23 (46.00)	9 (18.00)	41 (82.00)
OG (n=60)	26 (43.33)	31 (51.67)	3 (5.00)	57 (95.00)
χ^2				4.742
P-value				0.029

Table 4: Comparison of adverse reactions

Group	Facial flushing	Foot edema	Gastrointestinal discomfort	Dizziness	Headache	Total adverse reactions
CG (n=50)	2 (4.00)	2(4.00)	0	4(8.00)	2 (4.00)	10 (20.00)
OG (n=60)	1 (1.67)	0	1(1.67)	1(1.67)	1 (1.67)	4 (6.67)
χ^2						4.365
P-value						0.037

If the disease is not effectively controlled, it may cause other health problems. T2DM complicated by hypertension is a common chronic disease, and the two mutually affect and aggravate each other. According to relevant surveys, in 2019, there were more than 460 million adults with diabetes worldwide, of which about one-third also suffered from hypertension [15]. In China, currently, nearly 3 out of every 10 adult patients suffer from both hypertension and diabetes, and the incidence rates of these two diseases are constantly increasing [16].

The T2DM complicated by hypertension causes significant harm to the body and have varying degrees of impact. If it is not effectively managed and kept under control on time, it leads to cardiovascular and cerebrovascular diseases, stroke, nephropathy and other serious complications, and the normal metabolism and function of various organs in the body is negatively impacted. When both diseases coexist, these negative effects are exacerbated. Hypertension increase the burden on the heart, increase the risk of health problems and lead to other cardiovascular diseases. Elevated blood glucose levels damage the vascular endothelial cells and nervous system, resulting in diabetic complications such as diabetic retinopathy, peripheral neuropathy and diabetic nephropathy [17]. Therefore, it is important to actively control T2DM and hypertension by taking correct treatment measures as a way of preventing further deterioration of the disease.

In addition to changing unhealthy lifestyles, it is necessary to take appropriate medications to control both disease conditions, relieve symptoms and prevent complications. The selection of the treatment plan for T2DM and hypertension should be determined by qualified healthcare professionals based on the individual patient's specific condition, in other to achieve the best treatment effect. Amlodipine has a significant antihypertensive effect [18]. Furthermore, multiple clinical trials have revealed the efficacy of valsartan in managing diabetic nephropathy, and this reduces the risk of cardiovascular events, such as heart attack and deterioration of renal function. However, the curative effect of valsartan monotherapy on T2DM complicated by hypertension may not give the best ideal effect.

Therefore, this study was designed to combine these two drugs (amlodipine and valsartan) and explore the efficacy of the combined drugs. The overall response rate in study group (SG) who received both drugs was better than that of control group (CG) that received only amlodipine, indicating that in comparison to monotherapy, the combination of these two medicines complement each other synergistically, explore their advantages maximally, and significantly improve the therapeutic outcome of patients.

In addition, we also analyzed and compared the parameters related to blood glucose and blood pressure levels of the patients before and after therapy. In comparison to the pre-treatment period, FBG, 2 h PG, HbA1c, SBP and DBP in both groups were significantly reduced after treatment, and the SG exhibited significantly lower levels of FBG, 2 h PG, HbA1c, SBP and DBP compared to CG, indicating that the blood sugar and blood pressure indices of the participants treated with valsartan and amlodipine were significantly improved in comparison to amlodipine alone, and the treatment effect of the combination was remarkable. Amlodipine alone may have some limitations for different patients in the treatment of T2DM complicated by hypertension. Therefore, the combination of amlodipine and valsartan result in a synergistic effect, thereby further enhancing the effect of blood sugar and blood pressure control and relieving symptoms. A study by Ferdinand et al. [19] revealed that the combined therapy with amlodipine and valsartan demonstrated a more pronounced impact on hypertensive patients compared with the use of either drug alone. This is a reasonable choice for patients in which monotherapy is ineffective and this is similar to the findings of this study.

Finally, the incidence of adverse effects was analyzed and compared. Consistent with the findings of Miura *et al* [20], the results indicated a significantly lower overall occurrence rate of adverse effects in the SG compared to CG, indicating that during treatment, valsartan and amlodipine not only significantly improved blood glucose and blood pressure and enhanced the

therapeutic effect, but also did not increase the incidence of adverse reactions, thus exhibiting a high safety profile. If monotherapy is ineffective, it is a common strategy to combine several drugs for treatment. In this case, amlodipine combined with valsartan is a reasonable choice. Conversely, it is necessary during treatment with both drugs to closely monitor changes in blood pressure and pay attention to possible drug interactions to avoid them as they lead to adverse reactions.

Limitations of this study

These findings reveal that combined therapy with valsartan and amlodipine produced a more substantial effect in managing patients with T2DM complicated by hypertension already receiving insulin and statins. Nevertheless, it is essential to acknowledge the shortcomings present in this research. For instance, this research is characterized as a retrospective study with a restricted sample size, which may have biased the experimental results of this study. Secondly, due to the inability to conduct follow-up investigations on patients, it is impossible to compare the effects of prolonged treatment and prognosis.

CONCLUSION

Valsartan combined with amlodipine is effective in treating patients co-morbid with T2DM and hypertension and are already receiving insulin and statins. The combination satisfactorily controls both blood glucose level and blood pressure, with a high level of safety. Further experiments would be required to ascertain the reliability of these findings.

DECLARATIONS

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Funding/Sponsorship

None provided.

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. Hongyan Chen and Xiuxiu Yin conceived and designed the study, and drafted the manuscript. Hongyan Chen, Wenfang Niu and Chunling Liu collected, analyzed and interpreted the experimental data. Wenfang Niu and Xiuxiu Yin revised the manuscript for important intellectual content. All authors read and approved the final draft of the manuscript.

Ethical Approval

This study was approved the Medical Ethics Committee of North China Electric Power University Hospital, Beijing 102206, China (approval no. NCEPUH58432),

Availability of Data and Materials

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

***Use of Artificial Intelligence*/Large Language Models**

None provided.

Use of Research Reporting Tools

None provided.

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