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Efficacy of felodipine and enalapril in the treatment of essential hypertension with coronary artery disease and the effect on levels of Salusin-β, Apelin, and PON1 gene expression in patients

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ABSTRACT

This study aimed to analyze the effect of felodipine combined with enalapril in the treatment of patients with essential hypertension and coronary artery disease. Also, the effect of these medicines was evaluated on the peripheral blood Salusin-β, Apelin levels, and PON1 gene expression. For this purpose, 110 patients with essential hypertension combined with coronary heart disease, admitted to the hospital from January 2019 to January 2021, were selected and randomly divided into two groups. The control group was given felodipine treatment alone, and the study group was treated with combined application of felodipine and enalapril. The treatment effect, peripheral blood Salusin-β, Apelin, PON1 gene expression, and the safety of medication were compared between the two groups. The results showed that the post-treatment systolic blood pressure in the study group was 119.77 ± 5.23 mm Hg and diastolic blood pressure was 86.84 ± 5.42 mm Hg, both of which were significantly lower than those in the control group (127.81 ± 6.92 mm Hg and 95.13 ± 6.08 mm Hg), with statistically significant differences ($p<0.05$). The effective rates of the study group and the control group were 92.73% and 74.54% respectively, with statistically significant differences ($P<0.05$). The post-treatment peripheral blood Salusin-βlevel in the study group was 3.77±0.53mmol/L, and Apelin was 1.94±0.58μg/L, with statistically significant differences compared to the control group ($P<0.05$). The PON1 gene expression in the study group was higher than those in the control group after treatment ($P<0.05$). Also, the results showed that there was no statistical difference in adverse reactions between the two groups ($P>0.05$). According to these results, the combination of felodipine and enalapril in patients with essential hypertension combined with coronary artery disease can effectively lower the patients' blood pressure and improve their peripheral blood Salusin-β, Apelin levels, and PON1 gene expression, thus enhancing the patients' therapeutic effect with few adverse effects and high safety.

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Introduction

Hypertension and coronary heart disease are both relatively common chronic clinical conditions, with a high prevalence especially in the elderly population (1). Hypertension can be divided into two types, primary and secondary, of which primary hypertension is more common, and patients with primary hypertension are prone to coronary heart disease and other diseases, causing a great impact on the quality of life of patients (2). Felodipine is a calcium antagonist that dilates the small arteries of patients, thus effectively lowering their blood pressure levels, but the effect of this drug alone is limited and is usually used in combination with other drugs (3). Some studies have shown that the combination of felodipine and enalapril has good efficacy and a good safety profile (4).

Studies with various models of hypertension, such as inhibition of nitric oxide synthesis by L-NAME, strongly suggest that the development of cardiac fibrosis is associated with inflammatory processes induced by the uptake of cells such as macrophages into the left ventricle (5-7). There is also evidence of increased oxidative stress and decreased antioxidant defense in hypertensive conditions (8). Paraoxonase (PON) is a glycoprotein enzyme that binds to the surface of high-density HDL lipoproteins, and its activity is highly correlated with cardiovascular disease and tissue damage in some organs. Its levels have been studied in patients with hypertension (9).

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Studies show that PON1 also plays an important role in preventing LDL and HDL lipid peroxidation (10). Paraoxonase, as an antioxidant, has a supportive and protective role for the oxidation of LDL lipid markers and is associated with increased changes in HDL and LDL compounds (11). The pathophysiological effects of hypertension, such as impaired cell function and imbalance between vasoconstrictors and vasodilators, cause changes in blood vessels, including vascular wall hyperplasia and accelerated atherosclerosis, leading to coronary artery disease. Therefore, treatment of hypertension is necessary to reduce the risk of cardiovascular disease (12).

In the current study, we evaluated the clinical efficacy of felodipine and enalapril in the treatment of essential hypertension combined with coronary artery disease, and the effect of these medicines was considered on levels of Salusin-β, Apelin, and PON1 gene expression among these patients

Materials and methods

General information

110 cases were included, all of which were patients with primary hypertension combined with coronary heart disease treated in our hospital from January 2019 to January 2021. The cases were equally divided into two groups according to the order of admission, with 55 cases in the study group, including 37 males and 18 females, aged 52-81 years, with a mean age of (69.55±3.88) years, and the duration of the disease ranged from 2 to 10 years, with a mean of (4.58 ± 0.87) years. The patients' hypertension was graded as grade I in 18 cases, grade II in 22 cases and grade III in 15 cases. The cardiac function classification (NYHA) was class I in 17 cases, class II in 26 cases and class III in 12 cases. There were 55 cases in the control group, including 36 males and 19 females, aged51-83 years, with a mean age of (69.62±3.90) years, and the duration of the disease ranged from 2 to 10 years, with a mean of (4.60±0.88) years. The patients' hypertension was graded as grade I in 16 cases, grade II in 23 cases and grade III in 16 cases. The cardiac function classification (NYHA) was class I in 19 cases, class II in 24 cases and class III in 12 cases. The general information of the study group was compared with that of the control group at P> 0.05, which met the requirements for comparison. Inclusion criteria: (i) All patients met the relevant diagnostic criteria for hypertension in the 2010 edition of the Chinese Guidelines for the Prevention and Treatment of Hypertension and the diagnostic criteria for coronary artery disease established by the International Society of Cardiology;(ii) The patient's electrocardiogram showed myocardial ischaemia and coronary artery stenosis of more than 50%; (iii) All patients and families were aware of the study and agreed to cooperate. Exclusion criteria: (i) severe hepatic and renal dysfunction; (ii) malignancy; (iii) severe organic disease; (iv) secondary hypertension; (v) psychiatric disease; (vi) uncooperative patients.

Methods

The control group was given felodipine treatment((Manufacturer: Hangzhou Sublime Nanyang Pharmaceutical Co., Ltd; Approval No.: State Drug Administration H20064340), orally, using a dose of 2.5mg/dose once daily for one week. In the study group, felodipine was given in combination with enalapril. The dose and method of felodipine were the same as that of the control group, and enalapril (manufacturer: Shanghai Modern Pharmaceutical Co., Ltd.; approval No.: State Drug Administration H31021937) was given orally at 5mg/dose once a day for 7 days, and if the patient's blood pressure was still above 140/90mmHg, the dose of the drug could be increased and continued for 1 week. Plasma Salusin-β and Apelin levels were measured in both groups before and 1 week after treatment by fasting for 9h, collecting 5ml of fasting venous blood early in the morning on day 2, anticoagulating with anticoagulant edetate disodium, standing for 10min, centrifuging for 15min at 3000r/min and storing in a low-temperature refrigerator at -20°C. Plasma Salusin-β and Apelin levels were measured using a microparticle enzyme-linked immunoassay.

Observation indicators

Systolic and diastolic blood pressure levels were measured in both groups before and after 1 week of treatment. Plasma Salusin-β and Apelin levels were compared between the two groups before and 1 week after treatment. The incidence of adverse reactions such as dizziness, diarrhea, nausea and palpitations during administration were counted and compared between the two groups.

Evaluation of PON1 gene expression

From all subjects, 3ml of blood was prepared and transferred to the laboratory to extract RNA in tubes containing EDTA. In order to extract RNA from patients' blood samples, all steps were performed according to the protocol of the Hybrid-RTM Blood RNA kit (GeneAll, South Korea). The extracted product was examined using conventional PCR to ensure that the obtained RNA was not contaminated with genomic DNA. The final product was elucidated in free-RNase tubes and stored at -80°C. A nanodrop device was used to evaluate the quality of the extracted RNA.

In total, one pair of primer was designed for the PON1 gene and one pair of primer was designed for GapDH as a housekeeping gene by referring to the sequences in the NCBI database. After the design, the primer sequences were also blasted by NCBI and Gene Runner to fully examine their specificity. Designed primers were made by the Europhins Company (France). The sequence of primers is shown in Table 1.

Table 1. The primer sequences for the PON1 gene and GapDH gene

Gene		Primer Sequence
PON1	Forward	5' CCTGCAATAATATGAAACAACCTG 3'
	Reverse	5'CTAGAACACGAAAAGTGAAAGAAAAC 3'
GapDH	Forward	5′ CTCTCTGCTCCTCCTGTTCG 3′
	Reverse	5′ ACGACCAAATCCGTTGACTC 3′

One-step RT-PCR method was used for RT-PCR. In this method, cDNA production and PCR reaction are performed simultaneously in one step (13). To do this, a ready-made HyperScript kit (Gene All, South Korea) was used. The RAD-BIO 96-well thermocycler (USA) was used to perform the reaction. 1µl (10 Pmol) primer, 2µl sample (extracted RNA), and 7µl RNase -free water was added to the master mix with a volume of 10µl. Reaction temperature program was at one stage for cDNA production at 55°C for 60 minutes, primary denaturation at 94°C for 5 minutes and 35 cycles with 94°C for 30 seconds (secondary denaturation), 59°C for 30 seconds (to bind primers), 72°C for 45 seconds (extension) and finally 8 minutes at 72°C for the final extension.

Efficacy assessment criteria

The efficacy of the treatment was assessed according to the improvement of the clinical symptoms of the patient, if the patient's blood pressure returned to normal after treatment, no angina attack, and the ST-segment-T wave of the ECG returned to the isotonic line could be judged as effective; Patients with a basic return to normal blood pressure, a reduction in the number of angina attacks by more than 50%, ST-segment recovery of 1.5 mm or more at rest and upright T waves were considered effective; If the frequency of angina attacks was reduced by less than 10% after treatment and no change in the ST-segment-T wave of the ECG were considered ineffective. The total effective rate (significant rate + effective rate) was compared between the two groups.

Statistical methods

The data were entered into SPSS 23.0 for processing, and the measurement data were expressed as (Mean ± Standard Error) with t-test between groups, and the count data were expressed as (%) with $\chi 2$ test. Statistically significant differences were expressed as $P<0.05$.

Results and discussion

Comparison of blood pressure levels between the two groups before and after treatment

There was no significant difference between the blood pressure levels of the two groups before treatment ($P>0.05$), but after treatment, the systolic and diastolic blood pressure in the study group were significantly lower compared with the control group ($P<0.05$),a statistically significant difference (Figure 1).

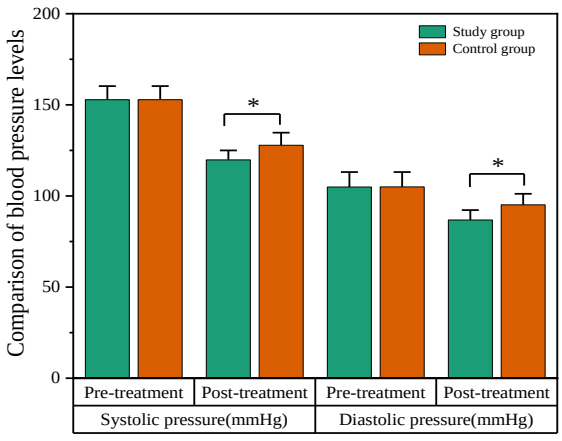

Figure 1. Comparison of blood pressure levels between the two groups before and after treatment; Note: compared with the control group *P<0.05

Comparison of clinical treatment effects between the two groups

The total effective rate of the study group was significantly higher compared with the control group, P<0.05, with significant differences between the groups. See Table 2.

Table 2. Comparison of treatment effects between the study group and the control group

Group	Cases	Significant Effects	Effective	Invalid	Total Efficiency
Study Group	55	34 (61.82%)	17 (30.91%)	4 (7.27%)	51 (92.73%)
Control Group	55	20 (36.36%)	21 (38.18%)	14 (25.46%)	41 (74.54%)
χ^2 value					6.382
P value					0.016

Comparison of peripheral blood Salusin-β and Apelin levels between the two groups

The peripheral blood Salusin-β levels in the study group were lower than those in the control group after treatment, and Apelin levels were significantly higher than those in the control group, with significant differences (P<0.05) (Figure 2).

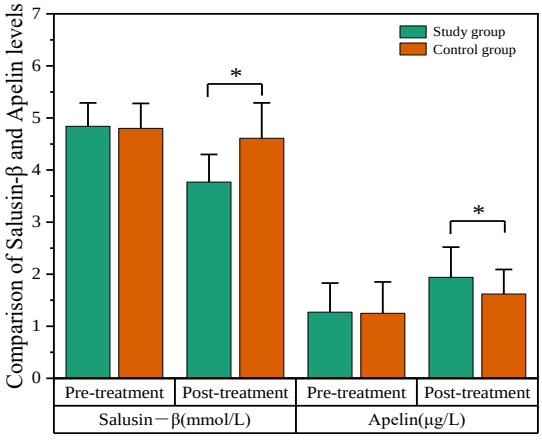

Figure 2. Comparison of peripheral blood Salusin-β and Apelin levels between the two groups; Note: compared with the control group *P<0.05

Comparison of PON1 gene expression between the two groups

The PON1 gene expression in the study group was higher than those in the control group after treatment (P<0.05) (Figure 3).

Comparison of adverse reactions

5 cases of adverse reactions occurred in the study group after administration, with an overall incidence of 8.88%. Adverse reactions occurred in 7 cases in the control group, with an incidence of 13. 33%. There was no significant difference in the comparison of adverse reactions between the two groups, P>0.05 (Table 3).

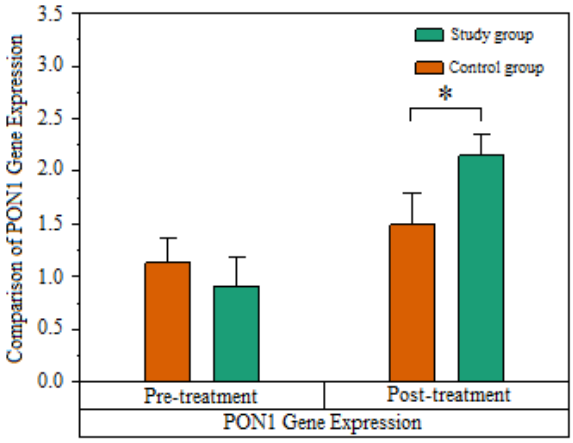

Figure 3. Comparison of PON1 gene expression between the two groups; Note: compared with the control group *P<0.05

Table 3. Comparison of adverse reactions between the study group and the control group

Group	Cases	Diarrhea	Nausea & Vomiting	Dizziness	Palpitation	Total Incidence
Study group	55	0 (0.00%)	2 (3.64%)	2 (3.64%)	1 (1.82%)	4 (9.10%)
Control group	55	1 (1.82%)	3 (5.46%)	2 (3.64%)	1 (1.82%)	7 (12.74%)
χ^2 value						0.417
P value						0.532

Hypertension and coronary heart disease are major chronic diseases that affect people's quality of life and life safety. Chronically hypertensive patients can exacerbate atherosclerosis formation and trigger coronary heart disease, which in turn increases the death rate of patients (14). The number of patients with hypertension and coronary heart disease both showed a yearly increase. There is also a significant increase in patients with essential hypertension in combination with coronary artery disease (15). Primary hypertension is a type of blood pressure in which the cause of the increase in blood pressure is not clear, and the proportion of primary hypertension in the population with hypertension is over 90%. The main clinical symptoms are dizziness, fatigue, insomnia and excessive dreaming. If the patient's condition is not effectively controlled for a long time, it may further progress to primary hypertension

combined with coronary artery disease, aggravating the patient's condition (15, 16). Therefore, it is extremely important to find a clinically safe and reliable option to treat primary hypertension combined with coronary artery disease (16).

Vascular endothelial cell injury can impair vascular barrier function, allowing for the deposition of large amounts of lipids and monocytes in the blood in the subendothelial space, which in turn leads to foam cell formation and is an important factor in triggering early atherosclerosis (17). Inflammation of the blood vessel wall is an important process in atherosclerosis. Infection of the extravascular or vascular wall can be triggered by a variety of pathogens. The development of primary hypertension combined with coronary artery disease is associated with atherosclerosis and high blood pressure. When treating this condition, clinical attention should be given to strictly controlling the patient's blood pressure and lipid levels, minimizing endothelial damage and reducing the patient's inflammation level (18).

Felodipine, a drug commonly used in clinical practice for the treatment of hypertension, can effectively inhibit the inward flow of extracellular calcium ions, enhance cardiac index and cardiac output, thereby reducing cardiac load, and has a better effect on both coronary vascular and peripheral vasodilation without affecting the patient's myocardial and cardiac contractile function (19). In addition, the drug is rapidly absorbed orally and has a long-lasting effect, making it widely used in clinical practice. However, in patients with essential hypertension and coronary artery disease, the effect of this drug alone is limited and needs to be combined with other drugs as appropriate (20). Enalapril, one of the commonly used antihypertensive drugs, can effectively inhibit angiotensin II converting enzyme activity and has a good vasodilatory effect, which is important in lowering blood pressure in patients (21). Some studies have reported that the combination of felodipine and enalapril significantly improves the therapeutic effect in patients with hypertension combined with coronary artery disease, and the efficacy is better than that of treatment with felodipine alone (22, 23). The analysis may be because enalapril not only reduces the expression of angiotensin II and promotes the decrease of blood pressure. It also helps to enhance left ventricular systolic function, reduce cardiac load and improve patients' cardiac function (24). Felodipine and enalapril can work synergistically to increase coronary blood flow and reduce angina pectoris, thereby improving patient outcomes. A number of studies have reported that giving enalapril to patients with hypertension and coronary artery disease in addition to felodipine treatment does not increase adverse effects and has a good safety profile (25-27).

Some studies have reported that vascular endothelial cell damage and local inflammatory responses have a greater relationship with the development of hyperemia and coronary heart disease (28), which can increase vascular tension and exacerbate thrombosis, among which Sa-lusin-β can promote the release of inflammatory factors in the body and aggravate the degree of damage to vascular endothelial cells, which in turn induces coronary heart disease and is expected to become an important marker for predicting the development of coronary heart disease. Serum Apelin has diuretic, vasodilating and vascular regenerative effects, and is a protective factor in coronary artery disease. Some studies have confirmed that Apelin enhances L-arginine transport capacity and nitric oxide synthase activity, which can promote NO production and thus play a role in vasodilating and lowering blood pressure, effectively inhibiting and delaying the progression of coronary artery disease (29). Some studies have shown that the simultaneous application of felodipine and enalapril in the treatment of patients with hypertension combined with coronary heart disease can significantly reduce the serum Salusin-β level and promote the level of Apelin, which can inhibit and reduce the inflammatory response of patients (29).

The results of this study showed that the systolic and diastolic blood pressure of patients in the study group treated with felodipine and enalapril were significantly lower than those in the control group after treatment, indicating that the combined treatment had a better effect on blood pressure control. The peripheral blood Apelin and Salusin-β levels in the study group improved better than those in the control group after treatment and the treatment efficiency was higher than that in the control group, suggesting that the combined treatment helped to reduce the inflammatory response of patients and protect the

vascular endothelial function of patients, thus improving the efficacy of patients.

Paraoxonase-1 (PON-1) is a calcium-dependent serum of the paraoxonase family that binds to HDL (30). Although all paraoxonases can hydrolyze long-chain aromatic and aliphatic lactones, PON-1 has arylesterase activity, too. There is ample evidence that PON-1 may have a protective effect on atherogenesis (9). PON-1 seems to be the main factor in the anti-inflammatory function of HDL by preventing LDL oxidation. On the other hand, the prevalence of coronary artery diseases such as atherosclerosis and their mortality is increasing globally (26, 31). Therefore, finding compounds that can increase the activity of this enzyme will be very effective in preventing atherosclerosis (9). The result of the current study showed that the combination of felodipine and enalapril in the treatment of essential hypertension with coronary artery disease can significantly enhance PON1 gene expression in the study group in comparison with the control group.

In terms of the safety of the two-drug treatment groups, there was no statistically significant difference between the groups, indicating that the combination treatment was safe, clinically feasible and did not increase adverse effects in patients.

In conclusion, the combination of felodipine and enalapril in the treatment of essential hypertension combined with coronary artery disease can effectively reduce patients' blood pressure, enhance their efficacy, improve their peripheral blood Salusin-β, Apelin, PON1 gene expression and have a high safety profile, which can be enhanced in clinical use.

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None.

Interest conflict

None.

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