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Effect of telmisartan and enalapril on ventricular remodeling and kidney prognosis of patients with coronary artery disease complicated with diabetic nephropathy

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Abstract. The aim of the present study was to compare the value of telmisartan and enalapril on ventricular remodeling and kidney prognosis of patients with coronary artery disease complicated with diabetic nephropathy, and provide discussion on clinical reasonably chosen medicine. A total of 60 cases of coronary artery disease complicated with diabetic nephropathy were randomly divided for telmisartan (80 mg/day) treatment (n=32), enalapril (10 mg/day) treatment (n=28), while the rest of the therapy was kept the same. After 12 weeks, the clinical effects were compared between different groups. It was found that in comparison with enalapril group, the left ventricular ejection fraction of telmisartan group was significantly higher, and left ventricular end-diastolic diameter was significantly lower (P<0.05). The serum creatinine level and 24-h protein of telmisartan group were significantly lower than that for the enalapril group (P<0.05). In conclusion, the regular telmisartan treatment for patients with coronary artery disease complicated with diabetic nephropathy is better than enalapril on ventricular remodeling and kidney prognosis.

Introduction

Several studies on large-scale randomized controlled trials have confirmed that angiotensin-converting enzyme inhibitors (ACEI type) have an impact on high blood pressure and coronary artery disease, especially on patients with acute myocardial infarction of left ventricular remodeling, better than that with angiotensin receptor inhibitor [angiotensin receptor blocker (ARB) type] (1). The two drugs cannot be used simultaneously, and only patients sensitive to ACEI, such as those with irritating dry cough, may consider replacement by ARB. However, some researchers believe that ARB is superior to ACEI in kidney prognosis for patients with diabetic nephropathy, for example, a double dose of valsartan can obviously reduce urine protein level (2).

Based on this, the present study was designed to discuss the effect of telmisartan and enalapril on ventricular remodeling and kidney prognosis in patients with coronary artery disease complicated with diabetic nephropathy. The results provide clinical evidence for selection of drugs to treat hypertension and cardiovascular complications.

Patients and methods

Patients. We consecutively selected 60 patients with coronary artery disease complicated with diabetic nephropathy diagnosed at the Xinxiang Central Hospital (Henan, China) from June 2014 to June 2015. We chose acute myocardial infarction from coronary artery disease to shrink samples and increase positive rate. Diagnosis criteria were: i) Sudden chest pain, vomiting or dizziness and unawareness lasting for ≥30 min. ii) At least two adjacent leads of ST segments on urgent check ECG increase or descent with dynamic evolution. iii) Cardiac markers such as myocardial enzymes and positive cardiac troponins. Diabetic nephropathy conforms to WHO type 2 diabetes diagnostic criteria as well as protein-positive and 24-h protein >0.5 g, combining renal biopsy to confirm diagnosis if necessary. Inclusion criteria were: i) Age, 18-75 years. ii) Conforms to diagnostic criteria of acute myocardial infarction and diabetic nephropathy. iii) Good understanding with no unawareness obstacles and not participanting in other clinical research. Exclusion criteria were: i) Acute myocardial infarction with malignant arrhythmia; cardiogenic shock and acute left heart failure. ii) Acute and chronic renal failure, abnormal liver function and blood coagulation dysfunction. iii) Associated with other organ dysfunction, such as mechanical supplementary respiration, cerebrovascular disease, pregnancy, infections, autoimmune diseases, mental disorders, and poor compliance.

This study was approved by the Ethics Committee of the Xinxiang Central Hospital. Informed consent was obtained from patients or their family member. The patients were randomly divided into 32 cases constituting the telmisartan

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group and 28 cases comprising the enalapril group in accordance with admission order to the hospital. The telmisartan group had 19 males and 13 females aged 48-60 years and an average age of 55.6±9.2 years. The enalapril group had 16 males, and 12 females aged 49-72 years and average age of 55.8±9.5 years. The difference of gender and age of the two groups was of no statistical significance (P>0.05).

Study methods. Two groups of patients were given standard medical treatment according to related guides. Treatment included acute myocardial infarction for dual anti-platelet, anticoagulant, blood lipid, anti-myocardial ischemia and emergency revascularization. Diabetes was treated by reasonable oral hypoglycemic agents or subcutaneous injection of insulin with control of fasting blood glucose <7.0 mmol/l, postprandial blood glucose 2H <11.1 mmol/l, and glycosylated hemoglobin <7.0%. Diabetic nephropathy was treated with a combination of traditional Chinese and Western medicine of blood protein in reducing urinary protein, blood creatinine of which the telmisartan group received 80 mg/day qd morning dose while the enalapril group for 10 mg/day qd morning dose, used for 12 weeks continuously. Close attention was paid to the blood pressure level, and potential allergies.

Indicators observed. The differences between left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDd), average systolic and diastolic blood pressure were compared. In addition, Scr, 24-h protein, average fasting blood sugar before three meals and average blood sugar after 2 h of three meals were also compared.

Statistical analysis. SPSS 20.0 software (Chicago, IL, USA) was used to conduct statistical analysis. The measurement data were expressed as mean ± standard deviation, and comparisons were made between groups using t-test. Enumeration data were expressed as percentage, and comparisons were made between groups using the χ^2 test. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of ventricular remodeling indicators. The differences of LVEF and LVEDd before treatment showed no statistical significance (P>0.05). After treatment, LVEF of the two groups increased, LVEDd decreased, and compared with the enalapril group, LVEF of telmisartan was significantly higher whereas LVEDd was significantly lower (P<0.05). The differences of average systolic and diastolic blood pressure before and after treatment did not show statistical significance (P>0.05) (Tables I and II).

Comparison of indicators of kidney prognosis. The differences of quantitative comparison between Scr and 24 h protein before treatment was not statistically significant (P>0.05). After treatment, Scr and 24 h protein of the two groups descend and the telmisartan group was significantly reduced compared to the enalapril group (P<0.05). The differences of average fasting blood sugar 2 h after meals, before and after treatment, was of no statistical significance (P>0.05; Tables III and IV).

Discussion

Abnormal activation of Renin-angiotensin-aldosterone system (RAAS) is important in the acute and recovery period of acute myocardial infarction, especially with a leading role in the occurrence and development of ventricular remodeling. After myocardial infarction, cardiac output decreases, and renal perfusion is insufficient. The sympathetic nerves, renal vasoconstriction, activation of juxtaglomerular cell receptor and the secretion of rennin all lure the activation of RAAS and produce corresponding biological effects. The oligo-peptide of eight poly amino acid angiotensin-II (Ang-II) (1) transformed from angiotensin-original has main effect on RAAS, e.g., myocardial hypertrophy, apoptosis and interstitial fibrosis. Moreover, it promotes the release of norepinephrine and aldosterone, activates the sympathetic nerves, increases the biological synthesis and activity of aldosterone, and inhibits the decomposition and increases collagen synthesis of fibroblasts I and III to induce fibrosis (2). It disrupts the balance between matrix metalloproteinases (MMPS) and tissue inhibitors of metalloproteinases (TIMPs) and increases the ratio of MMPS/TIMPs. The normal collagen degraded by the elevated MMPS and replaced by fibrous mass lack connection structures, which potentially leads to atherosclerosis and ventricular remodeling (3). It is proven that the blockage of the RAAS activation can reverse the ventricular remodeling of hypertension, acute myocardial infarction, and chronic systolic heart failure patients, increasing the survival rate (4).

Due to high blood sugar and changes of blood flow dynamics, the localized kidney Ang-II increases in patient with diabetes (5). It induces and transforms the expression of biologically active molecules such as growth factor-β, monocyte chemoattractant protein 1 and plasminogen activator inhibitor 1 promoting renal interstitial fibroblast proliferation and differentiation (6). It results in a large number of mononuclear macrophage infiltrating glomerular, the extracellular matrix synthesis is increased and degradation reduced (6). The findings of Cha *et al* (7) showed that in the glomerular cells and renal tubular epithelial cells, aldosterone directly activates nuclear factor-κB in a concentration-dependent manner, thus stimulating the transcription, expression and protein synthesis of monocyte chemotactic factor and macrophage migration inhibitory factor (7). Animal experiments also showed that aldosterone can improve the expression of a variety of pro-inflammatory factors and profibrotic cytokines to stimulate the production of reactive oxygen species and induce cell apoptosis mechanism, leading to the deduction of glomerular filtration rate, renal fibrosis and renal failure (7). The RENAAL test suggested that with a high ratio of urine albumin/creatinine, losartan can prevent the blood creatinine from increasing and can reduce the fatality rate of developing to end-stage renal disease (8).

Findings have shown that synthesis of Ang-II cannot only come from invertase, but also from chymotrypsin, cathepsin G and gastric and pancreatic enzymes (9). Long-term ACEI treatment may lead to the ACE escape phenomenon, thus, the ACEI-blocking RAAS system is incomplete. The proximal renal tubule Ang-II production concentration is 10,000-fold the one in circulating plasma and ACEI's inhibitory effect of locally high concentration Ang-II weakens. While ARBs

Table I. Comparison of ventricular remodeling indicators.

	LVEF, %				LVEDd, mm			
Group	Before	After	t-test	P-value	Before	After	t-test	P-value
Telmisartan	43.6±4.2	54.5±5.3	4.128	0.038	57.2±2.3	54.4±2.7	4.027	0.039
Enalapril	45.5±4.6	49.8±5.1	3.968	0.041	56.8±2.4	55.5±2.6	3.867	0.042
t-test	0.632	4.675			0.854	4.559		
P-value	0.124	0.035			0.721	0.036		

LVEF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic diameter.

Table II. Comparison of ventricular remodeling indicators.

	nSBP, mm Hg				nDBP, mm Hg			
Group	Before	After	t-test	P-value	Before	After	t-test	P-value
Telmisartan	103.6±5.2	100.5±4.6	0.657	0.218	66.7±3.4	65.9±3.7	0.936	0.857
Enalapril	105.7±5.3	101.7±4.8	0.745	0.327	66.8±3.3	65.3±3.5	0.864	0.639
t-test	0.127	0.325			0.425	0.387		
P-value	0.321	0.426			0.332	0.516		

nSBP, nocturnal systolic blood pressure; nDBP, nocturnal diastolic blood pressure.

Table III. Comparison of kidney prognosis indicators.

	Cr, μmol/l				24 h protein, g			
Group	Before	After	t-test	P-value	Before	After	t-test	P-value
Telmisartan	365.7±36.5	284.5±32.3	4.365	0.036	1.5±0.4	0.7±0.2	4.569	0.032
Enalapril	359.8±32.4	312.4±34.7	4.023	0.039	1.3±0.2	0.9±0.2	4.127	0.037
t-test	0.557	4.756			0.427	5.124		
P-value	0.236	0.027			0.326	0.019		

Table IV. Comparison of kidney prognosis indicators.

	Fasting blood sugar, mmol/l				Blood sugar after meals, mmol/l			
Group	Before	After	t-test	P-value	Before	After	t-test	P-value
Telmisartan	6.9±1.3	6.7±1.4	0.869	0.546	9.6±1.6	9.5±1.7	0.129	0.329
Enalapril	6.8±1.4	6.7±1.5	0.754	0.527	9.4±1.5	9.4±1.6	0.632	0.756
t-test	0.754	0.632			0.754	0.965		
P-value	0.125	0.203			0.426	0.823		

mostly act as AT1 receptor antagonist and can block the downstream cascade reaction with the strongest activity, but without reducing the content of bradykinin and prostaglandin, the long-term benefits on the body are better (5). Findings of the HEAAL study have shown that patients with heart failure who cannot use ACEI are recommended

to use 150 mg losartan per day for a significant reduction in the mortality rates, and heart failure hospitalization rates, than those who use 50 mg per day (10). The VALIANT (11) and OPTIMAAL (12) experiments also showed that ARB is good for inhibiting left ventricular remodeling. Mauer *et al* (13) suggested that RAAS blockade system before the advent of protein in urine of patients with type 2 diabetes cannot retard progress of the early histological lesions of diabetes kidney. However, the losartan group progression to microalbumin in urine was less than that of the enalapril and placebo groups.

Thus, the LVEF of telmisartan group significantly increased, whereas LVEDd, Scr level and 24-h protein were significantly decreased. In conclusion, routine application of telmisartan for patients with coronary artery disease complicated with diabetic nephropathy is better than enalapril on ventricular remodeling and kidney prognosis.

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