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Clinical Observation on the Lisinopril plus Candesartan in the Treatment of Heart Failure Combined with Essential Hypertension

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ABSTRACT Objective: To observe and evaluate the efficacy and safety of clinical observation on the Lisinopril plus Candesartan in the treatment of heart failure(HF)combined with essential hypertension(EH). **Methods:** 69 patients with heart failure and hypertension were enrolled and randomly divided into three groups on the basis of different medications: The patients in group A were treated by the Lisinopril for 8 weeks, while the patients in group B were treated by the Candesartan for 8 weeks and the patients in group C were treated by the Lisinopril combined with the Candesartan for 8 weeks. Then the heart function which referred to the blood pressure, the NYHA classification, the level of brain natriuretic peptide (BNP), the echocardiography and the function of liver and kidney of patients were observed and compared among the three groups before and after the treatment. **Results:** Compared with group A and group B, the total effective rate of group C was improved obviously (P<0.05), and there was no significant difference in biochemical indexes before and after treatment between the three groups (P>0.05). **Conclusion:** The efficacy of Lisinopril combined with Candesartan in the treatment of heart failure and hypertension was much better than that of the single dosage of Lisinopril or Candesartan, which was worthy of being promoted in clinical trials.

Key words: Lisinopril; Candesartan; Heart failure; Hypertension; Combined therapy

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Introduction

Heart failure (HF) is a complicated clinical syndrome, which is a severe phase of many cardiac diseases. Ischemic heart disease is the most common cause of HF, HF combined with essential hypertension(EH) is a common problem in clinic and its prognosis is much worse [1]. So it is an important topic in the current angiocardiopathy sphere to enhance the research of therapy and improve the prognosis. The effect and safety of ACEI or ARB or ACEI combined with ARB has been proved by many researches. Both the medicines can improve the myocardium blood-supply and reduce the angina pectoris attacks, but there was few research on ACEI combined with ARB in the treatment of HF combined with EH. This research is aimed to explore the effect and safety of Lisinopril plus Candesartan in the treatment of HF combined with EH. The result will be reported as follows.

1 Materials and methods

1.1 Selection of samples

69 patients with chronic heart failure whose heart function were in grade II-Ⅳ (according to the standard of NYHA as the description of AHA standards) were selected. The patients with valvular heart disease, hypertrophic cardiomyopathy, peripartum cardiomyopathy, active myocarditis, acute myocardial infarction, systolic blood pressure< 90mmHg or with serious liver and kidney function lesion were excluded. As shown in Table 1, 69 patients with HF and EH were randomly divided into three groups, there was no statistical difference in the age, gender, etiology and course of disease among the 3 groups(P>0.05).

Table 1 The comparison of age, gender, etiology and course of disease among three groups

Group	Gender		Age	Weight	HF	NYHA		
	Male	Female	(year)	(kg)	(year)	II	III	IV
A	9	14	63.2± 5.6	61.5± 9.8	3.5± 9.8	5	12	6
B	10	13	63.1± 6.8	60.7± 8.9	3.6± 5.5	4	15	4
C	8	15	62.9± 7.8	60.9± 6.3	3.5± 7.5	6	11	6

1.2 Research methods

All the patients were given nitrates, aspirin, digitalis, diuretic and β -blockers according to their individuation, and then randomly divided into three groups as follows: group A was given Lisinopril (trade name is Zestril, produced by Astrazeneca drug manufactory limited company), the initial dose was 10mg qd, the maximal dose was 80mg/d; group B was given Candesartan(trade name is Blopress, produced by takeda pharmaceuticals drug manufactory limited company), and the initial dose was 8 mg qd, the maximal dose was 12 mg/d; group C was given the Lisinopril or Candesartan for one week, if the patients' blood pressure were stable and then received the combination of the two drugs, the initial

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and the maximal dose of the two drugs were the same as the group A and B. The dosages of the two drugs in the three groups were adjusted according to the patients' BP, heart function and their tolerance, which lasted for eight weeks. The patients' condition in detail were asked, detailed physical examinations were given, the cardiac functional grading were recorded, the blood routine, blood biochemistry, liver and kidney function, plasma level of BNP and doppler echocardiography were checked before and after treatment.

1.3 The standard of efficacy

1.3.1 The efficacy standard of heart function The change of heart function after treatment was taken as a judged standard. If the patients' heart function could reach grade Ⅰ or be improved for grade II or more which was recognized to significantly effective. If the heart function was improved for grade I, which was effective. If it didn't comply with the criteria mentioned above, which was nullity.

1.3.2 The efficacy standard of hypertension According to therapeutic effect evaluation standard of high blood pressure, the change of blood pressure of 69 patients before and after treatment were compared.

2 Results

2.1 Comparison of the efficacy of heart function among three groups

After treatment, the heart function of patients in three groups were improved obviously. There was no significant difference in the total effective rate (excellence rate+effective rate) between group A and B (P>0.05); but the total effective rate of Group C was significantly higher than that of both group A and B (P<0.05).

Table 2 Comparison of the efficacy of heart function among three groups

Group	Num	NYHA heart function			
		Excellence	Utility	Inefficacy	Total efficacy
A	23	6 (26%)	11 (48 %)	6(26 %)	74 %
B	23	9 (39 %)	8 (35 %)	6(26 %)	74 %
C	23	12 (52%)	9 (39 %)	2 (8.7 %)	91 %*

Note: Compared with group A and group B, *P < 0.05.

2.2 Comparison of the blood pressure before and after treatment among 3 groups

After treatment, the systolic and diastolic blood pressures of patients in three groups all decreased obviously than those before treatment, and the systolic and diastolic blood pressures of patients in Group C was significantly lower than those of group A or B (P<0.01).

Table 3 Comparison of the blood pressure before and after treatment among 3 groups ($\bar{x}\pm s$,mmHg)

Parameter (mmHg)	Group A (n = 23)		Group B (n = 23)		Group C (n = 23)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
SBP	141.9± 13.8	124.1± 1.9*	141.6± 14.7	123.1± 4.3*	142.1± 13.2	117.9± 3.5*△
DBP	95.1± 9.7	76.4± 2.3*	94.9± 7.9	75.9± 8.4*	95.2± 2.7	71.8± 6.5*△

Note: Compared with before treatment, *P < 0.01; Compared with group A and group B, △P < 0.01.

2.3 Comparison of the plasma BNP before and after treatment among 3 groups

After treatment, the plasma BNP levels all dropped apparently than those before treatment in three groups (P<0.01), and the plasma BNP level of group C was significantly lower than those of group A or B (P<0.01).

Table 4 The comparison of BNP before and after treatment among the three groups (ng / L,$\bar{x}\pm s$)

Parameter	Group A		Group B		Group C	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Num	23	23	23	23	23	23
BNP	489 ± 41	152 ± 57*	490 ± 56	153 ± 37*	496 ± 23	106 ± 54*△

Note: Compared with before treatment, *P < 0.01; Compared with group A and group B, △P < 0.01.

2.4 Comparison of the change of echocardiography before and after treatment among 3 groups

CHF usual meaned the function of the myocardium contraction decreased significantly, the cardiac output was reduced and the left ventricular end-diastolic volume was increased. In the clinical, CHF often caused pulmonary congestion, around the loop hypoperfusion and the merger existed different level etc. it was mainly due to the heart abnormal diastolic and systolic function results in the decrease of pump function and circulating blood characterized clinical syndrome [2]. As shown in Table 5, the left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) of 3 groups were all significantly lower than

those before treatment(P<0.01). While the left ventricular ejection fraction (LVEF), cardiac output (CO), cardiac index (CI) of 3 group were all markedly lower than those before treatment, which were significantly higher in the group C than those of group A or B(P<0.05).

Table 5 Comparison of the change of echocardiography before and after treatment among 3 groups ($\bar{x}\pm s$)

Group		Num	LVEDV(ml)	LVESV(ml)	LVEF(%)	CO(L/min)	CI(L/min·m^2)
A	Before treatment	23	203.8± 66.4	143.9± 68.8	30.5± 4.6	3.7± 0.9	2.8± 0.7
	After treatment	23	163.7± 54.9*	114.9± 34.7*	36.9± 2.7*	4.6± 1.4*	3.4± 0.5*
B	Before treatment	23	204.5± 64.6	142.7± 48.9	30.7± 4.8	3.8± 1.1	2.8± 0.5
	After treatment	23	162.5± 65.4*	115.6± 40.7*	36.6± 2.1*	4.6± 2.5*	3.4± 0.2*
C	Before treatment	23	203.6± 57.3	144.2± 57.7	29.9± 7.8	3.8± 1.5	3.0± 0.8
	After treatment	23	128.4± 22.1*△	94.58± 14.2*△	40.3± 1.9*△	5.2± 0.8*△	4.0± 0.8*△

Note: Compared with before treatment, *P < 0.01; Compared with group A and group B after treatment, △ P < 0.05.

2.5 Comparison of the change of blood parameter values before and after treatment among 3 groups

As shown in Table 6, There was no significant difference in serum potassium, sodium, magnesium, urea nitrogen and creatinine before and after treatment in three groups(P>0.05).

Table 6 Comparison of the change of blood parameter values before and after treatment among 3 groups ($\bar{x}\pm s$)

Group	K^+(mmol/L)		Na^+(mmol/L)		Mg^+(mmol/L)		BUN(mmol/L)		Cr(μmol/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
A(n=23)	4.3± 0.1	4.3± 0.1	137± 16	137± 7	0.9± 2.5	1.0± 0.4	9.8± 1.2	9.9± 0.7	134± 18	135± 23
B(n=23)	4.3± 0.4	4.2± 0.9	138± 8	139± 4	0.9± 3.6	0.9± 0.8	9.9± 2.4	9.9± 1.3	135± 15	136± 25
C(n=23)	4.2± 0.9	4.2± 0.8	138± 12	138± 18	0.9± 1.9	1.0± 0.3	9.8± 5.6	9.9± 7.8	133± 23	134± 13

2.6 Comparison of the incidence of Adverse reactions during treatment among 3 groups

Three patients had paroxysmal dry cough in group A, and two had dizziness; four patients had dizziness in group B; one patient had paroxysmal dry cough in group A, and three had dizziness. The symptom of dry cough disappeared after symptomatic treatment; dizziness was tolerable and disappeared after two-three days, there was no statistical difference in the incidence of adverse reactions during treatment significance among three groups(P>0.05).

3 Discussions

ACEI reduce the levels of Angiotensin II and Aldosterone, through inhibiting the effects of ACE on the transition from AngI to AngⅡ,thus delay even terminate the development of heart failure. However, only 30% AngⅡ in heart are produced by the way of Convertase, which induce Aldosterone escape[3]. ACEI can't restrain AngⅡ formed from the non ACEI, so ACEI blocking of Ang is not completely. ARB can directly block the effect of AngⅡ from the level of receptor more thoroughly [4]and selectively block the combination of AngⅡ and AT1, and lower the blood pressure and risk of target organs [5]. All these provide theories why ARB can enhance the effect of anti-heart failure when the efficacy of ACEI is not ideal or the two drugs are given concurrently. In this study, there is no difference between the efficacy of Candesartan or Lisinopril on alone in the treatment of HF (P>0.05). Many reports indicate that ACEI plus ARB can enhance the therapeutic effect on HF. Val—HeFT is the first clinical test about the differences in the efficacy between ACEI plus ARB and ACEI alone[6]. ACEI plus ARB can decrease rehospitalization rate and significantly improve the heart function classification, increase the ejection fraction, relieve the clinical symptoms and improve the quality of life. RESOIVD preliminary test [7] draw a conclusion that the effect of combined therapy is better than ACEI or ARB sole treatment in preventing left artrium reconstruction. The goal of treatment of HF is not just to improve the symptoms and quality of life, more importantly, it is aimed to prevent and delay the development of cardiac muscle reconstruction, reduce the fatality rate[8]. This research suggests that the heart function of all patients in three groups all improved, especially the total effectiveness of combined treatment is significantly higher than sole treatment (P<0.05), and the echocardiography index improve more significantly(P<0.05), the pressure are markedly lower(P<0.01). ZHAO Ji-hong [9] et al found that the level of BNP increased with the development of heart failure and heart function rank, a remarkably positive correlation is existed, but it has a negative correlation with LVEF. In this study, BNP levels are significantly decreased in combined treatment than those of sole treatment, which suggest that the combined treatment is more effective in the improvement of heart function of patients with HF and EH.

Both ACEI and ARB can treat angina pectoris and improve myocardial ischemia through decreasing cardiac oxygen consumption, reducing coronary artery tension and improving myocardial reconstruction. PERTINET proves that vascular endothelial cells function can be improved significantly after long term treatment

with ACEI. EUROPA observes that ACEI not only has the function of depressing blood pressure but also anti-atherosclerosis. LI Lu [10] et al find myocardial fibrosis levels of AP is much higher than that of the healthy persons, which can be improved by Candesartan treatment. ACEI and ARB were unanimously reported to be able to prevent or reverse the vessel wall hypertrophy anginal [11]. ACEI plus ARB have the potential complementary effect through blocking RAS and playing a role in bradykinin, which can be achieved better than with a class of drugs alone[12].

The common adverse reactions of ACEI and ARB are hypotension, renal functional lesion, hyperkalemia, etc. Meanwhile, the adverse reactions of ACEI also include dry cough, angioedema, etc. ARB have not cough side effects, which protect heart head blood-vessel by enhancing the role of AT2 and reduce the incidence of cerebral apoplexy[13]. ARB and ACEI have similar effect on the decrease of high-risk of myocardial infarction, but the tolerance are better[14]. In this study, no significant difference is observed in the incidence of adverse reactions between the combined treatment and solo treatment, which suggests that the combination of ACEI and ARB also have high safety in the treatment of HF and EH.

In a conclusion, the combination of Lisinopril and Candesartan on the basis of routine therapy can significantly enhance the therapeutic effect on HF patients with EH and has mild adverse reaction, which is a new way for HF combined with EH and worthy of being promoted to the clinical trials.

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赖诺普利联合坎地沙坦治疗心力衰竭合并原发性高血压

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摘要 目的：观察和评价赖诺普利联合坎地沙坦治疗心力衰竭(HF)合并原发性高血压(EH)的疗效。**方法**：将我院收治的 EH 合并 HF 患者 69 例，在给予个体化治疗的基础上随机分为：A 组赖诺普利治疗组，B 组坎地沙坦治疗组，C 组赖诺普利和坎地沙坦联合治疗组，三组疗程均为 8 周。观察治疗前后的血压、心功能分级、BNP 水平、心脏彩色多普勒及肝肾功检查。**结果**：与对照组比较，联合组的总有效率明显增高，差异有统计学意义；治疗前后所有患者肝肾功能等生化指标未见明显变化。**结论**：赖诺普利与坎地沙坦联合治疗心力衰竭合并原发性高血压的疗效明显优于单用赖诺普利或坎地沙坦的疗效，且安全性好，值得广泛推广和应用。

关键词：赖诺普利；坎地沙坦；心力衰竭；高血压；联合治疗

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