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Effect of adjuvant levosimendan therapy on neuroendocrine hormones and cytokines in elderly patients with chronic heart failure

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ABSTRACT

Objective: To discuss the effect of adjuvant levosimendan therapy on neuroendocrine hormones and cytokines in elderly patients with chronic heart failure. **Methods:** A total of 100 elderly patients with chronic heart failure who were treated in the hospital between March 2014 and March 2017 were divided into control group and levosimendan group by random number table, each with 50 cases. Control group received clinical routine therapy for chronic heart failure, and levosimendan group received routine therapy combined with adjuvant levosimendan therapy. The differences in serum levels of RAAS indexes, thyroid hormones, myocardial damage indexes and endothelial function indexes were compared between the two groups before and after treatment. **Results:** At T0, there was no statistically significant difference in serum levels of RAAS indexes, thyroid hormones, myocardial damage indexes and endothelial function indexes between the two groups. At T1, serum RAAS indexes PRA, Ang Ⅱ and ALD levels of levosimendan group were lower than those of control group; serum thyroid hormones TT3, TT4, FT3 and FT4 levels of levosimendan group were higher than those of control group; serum myocardial damage indexes cTn Ⅰ, H-FABP and NT-proBNP levels of levosimendan group were lower than those of control group; serum endothelial function index NO level of levosimendan group was higher than that of control group while ET-1 level was lower than that of control group. **Conclusion:** Adjuvant levosimendan therapy for elderly patients with chronic heart failure can effectively adjust the secretion of neuroendocrine hormones and reduce the myocardial and vascular endothelial damage.

1. Introduction

Chronic heart failure (CHF) is the myocardial injury caused by composed of a variety of reasons, such as cardiomyopathy, myocardial infarction and inflammation, it will eventually result in the decline in ventricular pumping and/or filling ability, and how to delay the progression of myocardial remodeling and reduce the mortality of heart failure is the focus of current clinical research[1,2]. In view of the occurrence mechanism of chronic heart failure, diuresis and vascular dilation, cardiotonic therapy by digitalis and so on are all the basic therapies for the disease, but the curative effect of some patients is not obvious and the disease even progresses, so some scholars recommend adding levosimendan in the overall therapy. Levosimendan is a powerful calcium sensitizer, which changes the calcium-binding information transmission to eventually strengthen the myocardial contractility and optimize the cardiac function[3−5]. In this research, levosimendan and conventional therapy were used together for clinical treatment of elderly patients with CHF, and the role of the scheme in optimizing patients' condition was explored so as to provide a reference for subsequently selecting the therapy for similar diseases.

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2. Information and methods

2.1 Case information

A total of 100 elderly patients with CHF who were treated in the hospital between March 2014 and March 2017 were enrolled for study, and the patients themselves/family members signed informed consent. Random number table was used to divide the patients into control group and levosimendan group, each with 50 cases. Control group included 27 male cases and 23 female cases that were 60-79 years old; levosimendan group included 28 male cases and 22

female cases that were 62-75 years old. The distribution of general information was not significant between the two groups, and the hospital ethics committee examined and approved the study.

Inclusion criteria: (1) in accordance with the clinical diagnosis for CHF; (2) 60 years old; (3) without history of levosimendan application or allergy; (4) cooperating with the whole treatment and inspection. Exclusion criteria: (1) combined with cardiac dysfunction caused by infective endocarditis, viral myocarditis and other infections; (2) combined with severe liver, liver and kidney insufficiency; (3) combined with hyperthyroidism, hypothyroidism, pheochromocytoma and other endocrine diseases; (4) combined with malignant tumor diseases.

2.2 Therapy

Control group of patients received clinical routine therapy for chronic heart failure, including furosemide for diuresis, nitrates for vascular dilation, cardiotonic therapy by digitalis preparation, etc. Based on conventional treatment, levosimendan group received levosimendan treatment, specifically as follows: levosimendan loading dose 12 μg/kg, by intravenous injection (finished in 10 min), then maintenance dose 0.1 μg/kg min, micro-pump intravenous injection, for 24 h. The treatment was repeated once after 5 d in same way.

2.3 Observation indexes

Before treatment (T0) and after 10 d of treatment (T1), morning fasting cubital venous blood serum samples were obtained from two groups of patients, and the ria method was used to to detect the contents of renin - angiotensin - aldosterone system (RAAS) indicators, including renin (PRA), angiotensin Ⅱ (Ang Ⅱ) and aldosterone (ALD); ria method was used to detect serum levels of thyroid hormones, including total triiodothyronine (TT3), total thyroxine (TT4), free triiodothyronine (FT3) and free thyroxine (FT4); enzyme-linked immunosorbent assay method was used to detect the serum contents of myocardial injury indexes, including cardiac troponin Ⅰ (cTn Ⅰ), heart type fatty acid binding protein (H-FABP) and N-terminal pro-brain natriuretic peptide (NT-proBNP); enzyme-linked immunosorbent assay was used to determine the serum contents of endothelial function indexes, including nitric oxide (NO) and endothelin-1 (ET-1).

2.4 Statistical methods

RAAS indexes, thyroid hormones, myocardial injury indexes and endothelial function indexes were all in terms of mean ± standard deviation and compared by t test. Data calculation was by software SPSS 25.0 and $P<0.05$ indicated statistical significance in differences in statistic.

3. Results

3.1 RAAS indexes

Comparison of serum RAAS indexes PRA (ng/mL), Ang Ⅱ (ng/L) and ALD (pg/mL) levels between the two groups at different points in time was as follows: at T0, there was no significant difference in serum PRA, Ang Ⅱ and ALD levels between the two groups ($P>0.05$). At T1, serum PRA, Ang Ⅱ and ALD levels of both groups were lower than those at T0, and serum PRA, Ang Ⅱ and ALD levels of levosimendan group were lower than those of control group ($P<0.05$), shown in Table 1.

3.2 Thyroid hormones

Comparison of serum thyroid hormones TT3 (μmol/L), TT4 (μmol/L), FT3 (pmol/L) and FT4 (pmol/L) levels between the two groups at different points in time was as follows: at T0, there was no significant difference in serum TT3, TT4, FT3 and FT4 levels between the two groups ($P>0.05$). At T1, serum TT3, TT4, FT3 and FT4 levels of both groups were higher than those at T0, and serum TT3, TT4, FT3 and FT4 levels of levosimendan group were higher than those of control group ($P<0.05$), shown in Table 2.

Table 1.

Comparison of serum RAAS index levels.

Groups	n	PRA		Ang Ⅱ		ALD	
		T_0	T_1	T_0	T_1	T_0	T_1
Control group	50	4.38±0.49	3.17±0.35*	294.27±33.85	261.49±27.83*	45.81±5.63	37.94±4.52*
Levosimendan group	50	4.35±0.47	2.38±0.27*	291.69±30.74	198.36±25.41*	45.76±5.72	28.57±3.46*
t		0.281	6.298	0.176	17.382	0.254	12.153
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group at T_0, *$P<0.05$.

Table 2.

Comparison of serum thyroid hormone levels.

Groups	n	TT3		TT4		FT3		FT4	
		T_0	T_1	T_0	T_1	T_0	T_1	T_0	T_1
Control group	50	0.83±0.09	0.97±0.12*	115.83±14.67	120.64±13.50*	2.74±0.35	3.38±0.36*	17.48±1.74	17.95±2.03*
Levosimendan group	50	0.82±0.09	1.22±0.15*	114.79±13.58	137.92±15.63*	2.78±0.32	4.17±0.48*	17.62±1.69	18.63±1.94*
t		0.214	6.912	0.176	13.284	0.204	6.038	0.163	4.282
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group at T_0, *$P<0.05$.

Table 3.

Comparison of serum myocardial damage index levels.

Groups	*n*	cTnⅠ		H-FABP		NT-proBNP	
		T_0	T_1	T_0	T_1	T_0	T_1
Control group	50	0.27±0.04	0.15±0.02*	6.29±0.75	4.18±0.53*	6 421.97±743.88	4 728.94±537.62*
Levosimendan group	50	0.28±0.03	0.09±0.01*	6.24±0.72	3.07±0.38*	6 529.71±785.63	3 015.27±384.48*
t		0.182	5.271	0.264	7.298	0.294	13.287
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group at T_0, *$P<0.05$.

Table 4.

Comparison of serum endothelial function index levels.

Groups	*n*	NO		ET-1	
		T_0	T_1	T_0	T_1
Control group	50	43.28±5.19	57.15±6.09*	59.28±6.21	51.59±6.32*
Levosimendan group	50	43.76±4.88	68.64±7.53*	59.77±6.48	45.72±5.18*
t		0.217	14.382	0.198	9.364
P		>0.05	<0.05	>0.05	<0.05

Note: compared with same group at T_0, *$P<0.05$.

3.3 Myocardial damage indexes

Comparison of serum myocardial damage indexes cTnⅠ (ng/mL), H-FABP (ng/mL) and NT-proBNP (pg/mL) levels between the two groups at different points in time was as follows: at T0, there was no significant difference in serum cTnⅠ, H-FABP and NT-proBNP levels between the two groups ($P>0.05$). At T1, serum cTnⅠ, H-FABP and NT-proBNP levels of both groups were lower than those at T0, and serum cTnⅠ, H-FABP and NT-proBNP levels of levosimendan group were lower than those of control group ($P<0.05$), shown in Table 3.

3.4 Endothelial function indexes

Comparison of serum endothelial function indexes NO (μmol/L) and ET-1 (ng/L) levels between the two groups at different points in time was as follows: at T0, there was no significant difference in serum NO and ET-1 levels between the two groups ($P>0.05$). At T1, serum NO levels of both groups were higher than those at T0 while ET-1 levels were lower than those at T0; serum NO level of levosimendan group was higher than that of control group while ET-1 level was lower than that of control group ($P<0.05$), shown in Table 4.

4. Discussion

Without proper treatment, CHF may early progress into cardiac functional decompensation, and this is also one of the main causes of death of inpatients in Department of Cardiology. After routine diuretic, vascular dilation drug, digitalis preparation and other therapies, the illness is not obviously improved in some patients, and the drugs with other mechanisms of action are needed for combination therapy to reverse the disease. Levosimendan is a new type of calcium sensitizer, and unlike the traditional positive inotropic drugs, it optimizes the cardiac function mainly through the following ways: (1) by increasing cell contraction protein sensitivity to Ca^{2+}, opening K^+ channels and increasing myocardial contractility; (2) by activating ATP-sensitive potassium channels to dilate d blood vessels and reduce the cardiac preload and afterload; (3) it has certain inhibitory effect on phosphodiesterase when used in large dosages, increases the concentration of cAMP in myocardial cells and exerts the additional positive inotropic effect[6,7]. In this study, levosimendan was used as adjuvant drug and used for the treatment of elderly patients with CHF, and the optimization effect of combined treatment on the condition of such patients was discussed. There is excessive activation of the neuroendocrine system in patients with CHF. Early RAAS activation has certain compensatory effects on the decline of cardiac function, but excessive activation can lead to the continuous deterioration of cardiac function. The current studies have confirmed that there is generally excessive RAAS activation in patients with CHF, which is characterized by the increased secretion of its downstream molecules PRA, AngⅡ and ALD, and results in further increase of vascular contraction and cardiac afterload as well as the continuous decline of cardiac pumping function[8–10]. RAAS indexes can indirectly reflect the illness severity and treatment outcomes of patients with CHF, and it was found in the study that compared with those at T0, serum PRA, AngⅡ and ALD levels of both groups were lower at T1, indicating that both treatments help to suppress the activity of RAAS; further compared with those of control group, serum PRA, AngⅡ and ALD contents of levosimendan group were low at T1, indicating that adjuvant levosimendan therapy can more effectively inhibit the excessive activation of RAAS, which is one of the important ways for it to achieve therapeutic effect.

In addition to sympathetic excitement, the changes in thyroid hormone levels in CHF patients have also received much attention from at home and abroad at present. thyroid hormone signal transduction system expression decreases in heart tissue in the case of heart failure, T3 and T4 levels drop, T3 level drops most obviously, and the worse the cardiac function, the lower the thyroid hormone levels[11–13]. It was found in the study that compared with those at T0, serum TT3, TT4, FT3 and FT4 levels of both groups increased at T1, which indicates that both treatments are helpful to optimize the cardiac function of CHF patients; further compared with those of control group, serum TT3, TT4, FT3 and FT4 contents of levosimendan group were higher at T1, showing that adjuvant levosimendan therapy can more effectively enhance the cardiac function of patients with CHF, and the increase of thyroid hormone levels is the main expression of its treatment effectiveness.

Myocardial cell function damage is the root cause of the cardiac

function decline in patients with CHF, and many factors associated with myocardial cell function can be abnormally synthesized and secreted, and become the objective indexes to indirectly judge the existence and severity of myocardial injury. cTnⅠ is closely associated with myocardial remodeling, myocardial cell degradation and structural protein loss can both result in increased serum levels of cTnⅠ, and excessive cTnⅠ is also a sign of poor prognosis in patients with heart disease[14]. H-FABP is released into the blood early after myocardial injury, and some studies have indicated that its high expression can activate Fas/FasL system function and promote myocardial cell apoptosis[15]. NT-proBNP is the proBNP split product that is massively synthesized and secreted when myocardial cells are pulled, which can more sensitively evaluate cardiac function and has become a diagnostic index for cardiac dysfunction[16,17]. It was found in the study that compared with those at T0, serum cTnⅠ, H-FABP and NT-proBNP contents of both groups decreased at T1; further compared with those of control group, serum cTnⅠ, H-FABP and NT-proBNP contents of levosimendan group were lower at T1, indicating that adjuvant levosimendan therapy can effectively reduce the myocardial injury in patients with CHF.

Vascular endothelial cells have a powerful secretion function and regulate vascular activity by secreting NO, ET-1 and other factors. There is vascular endothelial cell damage in CHF patients, it results in the decreased secretion of vasodilator factor NO and the increased secretion of vasoconstrictor factor ET-1, and the they cause vasomotor imbalance and increase cardiac pumping resistance together, are the initiating factors in the occurrence of heart failure, and also become the indirect indexes to judge CHF condition[18–20]. It was found in the study that compared with those at T0, serum NO levels of both groups increased while ET-1 levels decreased at T1; further compared with those of control group, serum NO level of levosimendan group was higher while ET-1 level was lower at T1, indicating that adjuvant levosimendan therapy can reduce vascular endothelial injury, and indirectly confirming its efficiency in anti-heart failure.

Levosimendan combined with conventional therapy can be more effective than routine anti-heart failure treatment to optimize the neuroendocrine system function and alleviate myocardial injury and vascular endothelial injury in elderly patients with CHF, and it is expected to become a new way for future CHF treatment.

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