Effects of milrinone on serum IL-6, TNF-α, Cys-C and cardiac functions of patients with chronic heart failure

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Received December 4, 2017; Accepted August 24, 2018

DOI: 10.3892/etm.2018.6672

Abstract. Effects of milrinone on serum interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), cystatin C (Cys-C) and cardiac functions of patients with chronic heart failure were analyzed to investigate the value of milrinone in chronic heart failure. A total of 70 patients diagnosed with chronic heart failure were selected and randomly divided into treatment group (n=35) and control group (n=35). All patients were treated with conventional anti-heart failure therapy, and patients in the treatment group received milrinone on the basis of conventional therapy. The general data of patients, such as age, sex and course of chronic heart failure, were collected; the levels of serum IL-6, TNF-α and Cys-C before and after treatment were compared between the groups, and the cardiac function indexes were also compared, including cardiac output (CO), stroke volume (SV), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVSd) and brain natriuretic peptide (BNP) level. Besides, the curative effects and adverse reactions in the two groups were recorded. The results revealed that serum IL-6, TNF-α and Cys-C levels had no significant difference between the two groups before treatment; however, the curative effect in the treatment group was significantly superior to that in control group ($p<0.05$); after treatment, CO, SV and LVEF in both groups were obviously increased, but LVDd, LVSd and BNP levels were obviously decreased; the curative effect in the treatment group was significantly superior to that in control group ($p<0.05$); heart rate in both groups was obviously decreased after treatment ($p<0.05$); the total effective rate in the treatment group was significantly higher than that in control group after treatment ($p<0.05$). In conclusion, based on the conventional anti-heart failure therapy, the application of milrinone can reduce the serum IL-6, TNF-α and Cys-C levels and improve the cardiac functions of patients effectively.

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Key words: milrinone, heart failure, interleukin-6, tumor necrosis factor-α, cystatin C, cardiac functions

Introduction

Clinically, chronic heart failure is one of the most common critical diseases, whose main clinical manifestation is chronic cardiac insufficiency. The main treatment method is the application of diuretics and digitalis, but they are not applicable in all cases (1). Digitalis can cause digitalism, induce arrhythmia again, and increase the mortality rate (2). Under the over-response of inflammatory system, the cystatin C (Cys-C) level is also increased (3); the increased inflammatory factor and Cys-C levels will also promote the occurrence and development of chronic heart failure, aggravate the ventricular remodeling and negative inotropic effect of patients with heart failure, and decrease the cardiac functions, causing a vicious cycle (4,5). With the continuous improvement in clinical treatment, milrinone, as a new non-digitalis positive inotropic drug, significantly increases the survival rate of patients with chronic heart failure and improves the prognosis, and is applied increasingly widely in clinic currently (6). Milrinone can also inhibit the over-response of inflammatory system in patients with chronic heart failure, thus inhibiting the ventricular remodeling and negative inotropic effect (7,8). When patients suffer from congestive heart failure, especially advanced heart failure, it will aggravate the heart failure, or even cause cardiogenic shock and lead to death, if the treatment is not timely or appropriate (9). Many studies have shown that milrinone is one of the effective positive inotropic agents in the treatment of chronic heart failure, especially advanced heart failure, which can significantly improve the cardiac functions, regulate the levels of inflammatory factors and reduce the mortality rate of patients (10).

Patients and methods

General data. A total of 70 patients diagnosed with chronic heart failure in Shouguang People's Hospital (Weifang, China)

from March 2012 to February 2016 were selected and divided into treatment group (n=35) and control group (n=35) using a random number table. There were 42 males and 28 females aged 56-78 years with an average of 65.25 years. According to New York Heart Association (NYHA) classification of cardiac function, there were 16 cases of cardiac function in class III and 19 cases of cardiac function in class IV in the treatment group, and 17 cases of cardiac function in class III and 18 cases of cardiac function in class IV in the control group, respectively. Among all patients enrolled, there were 14 cases of coronary heart disease, 21 cases of hypertensive heart disease, 17 cases of myocardial infarction, 6 cases of rheumatic cardiomyopathy, 4 cases of valvular heart disease, 5 cases of ischemic cardiomyopathy and 3 cases of other diseases. Exclusion criteria: patients with severe hepatic or renal dysfunction; patients with malignant tumors; patients with electrolyte disorders; patients with mental disorders; patients with acute myocardial infarction; pregnant or lactating women; patients with a drug allergy history; patients with incomplete clinical data or patients who quit halfway. The study was approved by the Ethics Committee of Shouguang People's Hospital and informed consents were signed by the patients or the guardians.

Methods. All patients were treated with conventional anti-heart failure therapy, including the oxygen inhalation, bed rest, diuretics, vasodilators, β-blockers. The patients in the treatment group received milrinone based on conventional anti-heart failure therapy [intravenous injection of 2 mg milrinone at first, and continuous intravenous infusion later at a rate of 0.225-0.650 μg/(kg·min)] every day (12-16 h/day). Both courses of treatment in the treatment and control group were 8 days.

Determination of serum interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), Cys-C and brain natriuretic peptide (BNP) levels: patients were fasting for solids and liquids for 10 h overnight at 1 day before treatment and 5 days after treatment, and 10 ml peripheral blood was extracted. Then the upper-layer serum was taken to detect the levels of IL-6, TNF-α and Cys-C via immunoturbidimetry and the level of BNP via radioimmunoassay. The reagents and instruments were provided by Shandong Scenker Biotechnology, Co., Ltd. (Shandong, China).

Determination of cardiac functions: cardiac output (CO), stroke volume (SV), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVDd), and left ventricular end-systolic diameter (LVSd) of patients were detected by professional medical technicians using the Vivid 7 Dimension ultrasound (GE Healthcare, Boston, MA, USA) instrument at 1 day before treatment and 5 days after treatment.

Recording of curative effects and side-effects: according to NYHA classification of cardiac function, the curative effects on all patients were assessed after treatment. Remarkably effective: disappearance or significant improvement in clinical manifestations of heart failure, and significant improvement in cardiac function classification; effective: increase in NYHA classification of cardiac function by one class; ineffective: no improvement in NYHA classification of cardiac function, aggravation of clinical manifestations or death. During and after treatment, the heart rate, systolic pressure, diastolic pressure and treatment-related adverse reactions of patients, including ventricular arrhythmia, ventricular fibrillation, premature beat, tachycardia, decreased blood pressure, headache and gastrointestinal reactions, were closely monitored.

Statistical methods. Statistical Product and Service Solutions (SPSS) 19.0 software (IBM Corp., Armonk, NY, USA) was used for data processing. Data are presented as $\bar{x}\pm s$. t-test was used for the comparison of measurement data, and Chi-square test was used for the comparison of enumeration data. $P<0.05$ suggested that the difference was statistically significant.

Results

Comparison of general conditions between treatment and control group before treatment. There were no statistically significant differences in age, sex, course of chronic heart failure, LVEF and BNP level between treatment and control group before treatment ($p>0.05$), and the data were comparable (Table I).

Comparison of inflammatory factors between treatment and control group before and after treatment. Serum IL-6 and TNF-α levels had no significant difference between treatment and control group before treatment, but the levels were significantly decreased in both groups after treatment; the curative effect in the treatment group was significantly superior to that in control group, and the difference was statistically significant ($p<0.05$) (Table II).

Comparison of Cys-C levels between treatment and control group before and after treatment. The serum Cys-C levels in treatment and control group had no significant difference before treatment, but the levels were decreased significantly in both groups after treatment; the curative effect in the treatment group was significantly superior to that in control group, and the difference was statistically significant ($p<0.05$) (Table III).

Comparison of cardiac function indexes between treatment and control group before and after treatment. There was no significant difference in CO, SV, LVEF, LVDd, LVSd and BNP level between treatment and control group before treatment; after treatment, CO, SV and LVEF in both groups were obviously increased, but LVDd, LVSd and BNP level were obviously decreased; the curative effect in the treatment group was significantly superior to that in control group, and the difference was statistically significant ($p<0.05$) (Tables IV and V).

Comparison of heart rate and blood pressure between treatment and control group before and after treatment. Heart rate, systolic and diastolic pressure had no significant difference between treatment and control group before treatment; heart rates in both groups were obviously decreased after treatment ($p<0.05$), but there were no statistically significant differences in systolic and diastolic pressure ($p>0.05$) (Table VI).

Comparison of effective treatment rates between treatment and control group after treatment. After different anti-heart

Table I. Comparison of general conditions between treatment and control group.

Group	Age (years)	Sex (male/female)	Course of disease (years)	LVEF (%)	BNP (x1,000 pg/ml)
Treatment group	64.59±7.23	22/13	11.56±2.21	38±5	4.92±0.73
Control group	65.92±6.92	20/15	9.92±1.98	38±7	4.95±0.66
P-value	0.864	0.792	0.695	0.882	0.912

LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide.

Table II. Comparison of inflammatory factors between treatment and control group before and after treatment.

		TNF-α (pg/ml)		IL-6 (ng/l)	
Group	n	Before treatment	After treatment	Before treatment	After treatment
Treatment group	35	11.51±2.32	8.22±1.56	17.03±9.53	8.23±5.15
Control group	35	10.98±3.01	9.56±2.21	16.87±8.78	10.05±4.22
P-value		0.792	0.001	0.673	0.001

TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.

Table III. Comparison of Cys-C levels between treatment and control group before and after treatment.

		Cys-C (mg/l)	
Group	n	Before treatment	After treatment
Treatment group	35	1.95±1.13	0.89±0.56
Control group	35	1.83±0.54	1.37±0.39
P-value		0.956	<0.001

Cys-C, cystatin C.

Table IV. Comparison of cardiac function indexes between treatment and control group before and after treatment.

	CO (l/min)		SV (ml)		LVEF (%)	
Group	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Treatment group (n=35)	4.46±0.88	6.04±0.63	53.92±5.96	69.04±6.13	38±5	51±8
Control group (n=35)	4.39±0.82	4.62±0.38	52.88±6.17	59.63±7.56	38±7	43±6
P-value	0.987	<0.001	0.897	<0.001	0.882	0.001

CO, cardiac output; SV, stroke volume; LVEF, left ventricular ejection fraction.

failure therapies, the total effective rates in treatment and control group were 97.14 and 74.28%, respectively. The total effective rate in the treatment group was significantly higher than that in control group after treatment ($p<0.05$) (Table VII).

Comparison of adverse reactions between treatment and control group. The incidence rate of adverse reactions in the treatment group was 22.86%, while that in control group was 25.71%, and the difference was not statistically significant ($p>0.05$) (Table VIII).

Table V. Comparison of cardiac function indexes between treatment and control group before and after treatment.

Group	LVDd (mm)		LVSd (mm)		BNP (x1,000 pg/ml)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Treatment group (n=35)	68.03±8.11	52.77±6.34	47.59±4.33	36.20±2.99	4.92±0.73	3.01±0.42
Control group (n=35)	67.59±7.38	59.46±6.06	47.92±3.03	41.77±3.21	4.95±0.66	4.02±0.61
P-value	0.678	0.001	0.791	0.001	0.912	<0.001

LVDd, left ventricular end-diastolic diameter; LVSd, left ventricular end-systolic diameter; BNP, BNP, brain natriuretic peptide.

Table VI. Comparison of heart rate and blood pressure between treatment and control group before and after treatment.

Group	Heart rate (beats/min)		Systolic pressure (mmHg)		Diastolic pressure (mmHg)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Treatment group (n=35)	90.5±5.9	83.2±4.5	138.2±7.6	140.7±6.8	75.3±7.6	80.2±5.9
Control group (n=35)	91.3±6.2	87.6±4.3	136.9±7.8	141.3±7.0	73.7±6.5	79.9±5.1
P-value	0.535	0.021	0.627	0.492	0.392	0.411

Table VII. Comparison of effective treatment rates between treatment and control group.

Group	n	Remarkably effective	Effective	Ineffective	Total effective rate (%)
Treatment group	35	15	19	1	97.14
Control group	35	7	19	9	74.28
P-value					<0.001

Table VIII. Comparison of adverse reactions between treatment and control group.

Adverse reaction	Treatment group (n=35)		Control group (n=35)		P-value
	n	Incidence rate (%)	n	Incidence rate (%)	
Ventricular arrhythmia	2	5.71	2	5.71	
Ventricular fibrillation	0	0	0	0	
Premature beat	1	2.86	2	5.71	
Tachycardia	1	2.86	2	5.71	
Decreased blood pressure	1	2.86	1	2.86	
Headache	1	2.86	1	2.86	
Gastrointestinal reactions	2	5.71	1	2.86	
Total	8	22.86	9	25.71	0.909

Discussion

Chronic heart failure is one of the common complications of cardiovascular disease in clinic with a high mortality rate and poor prognosis, and the main pathogenesis is that the poor ejection fraction or damaged filling function lead to decreased CO, and disable the tissues to participate in various metabolic activities (11). Over-activation of the inflammatory system and excessive release of inflammatory cytokines accelerate the pathophysiological process of chronic heart failure, resulting in ventricular remodeling and negative inotropic effect (12). IL-6 and TNF-α are active in patients with chronic heart failure; as a result, the left ventricular volume and pressure are increased and cardiac function is impaired, thus aggravating the chronic heart failure (13). Patients with chronic heart failure are in a relatively hypoxic-ischemic state for a long time, which leads to the over-synthesis and secretion of IL-6 and TNF-α, and worsening of the cardiac contractility (14); at the same time, myocardial cells, stimulated by inflammatory cytokines, can produce a kind of inducible nitric oxide synthase (iNOS) oxidase, and iNOS cells have strong toxicity and will accelerate the damage of myocardial cell function, leading to a vicious cycle (15,16). On the other hand, IL-6 can cause excessive synthesis and release of oxygen-free radicals in neutrophils *in vivo*, further damaging myocardial cells (17). Recently, many studies have shown that Cys-C is related to the occurrence and severity of chronic heart failure, which can inhibit cysteine protease in the human body,

so it is often used to evaluate whether renal damage occurs, and it is also positively correlated to the death rate of heart failure (18). The main role of milrinone is positive inotropic effect, to inhibit the phosphodiesterase *in vivo*, increase the cyclic adenosine monophosphate (cAMP) in myocardial cells and reduce the myocardial tension, thereby reducing the cardiac preload and afterload. On the other hand, milrinone can also result in influx of calcium ions and increased myocardial contractility, and improve the cardiac function (19).

In the present study it was found that after the application of milrinone in patients with chronic heart failure, the serum IL-6, TNF-α and Cys-C levels were significantly decreased, and milrinone could effectively increase the overall effective rate of treatment, and improve CO, SV and LVEF, compared with conventional anti-heart failure therapy, and the differences were statistically significant ($p<0.05$), indicating that the short-term application of appropriate dose of milrinone in the treatment of chronic heart failure can regulate the levels of IL-6, TNF-α and Cys-C in patients, effectively improve the cardiac function and reduce the mortality rate. Although other studies have shown that milrinone does not improve the long-term mortality rate of patients with chronic heart failure (20), more data show that the application of milrinone can increase the therapeutic effect, in consistency with the results in this study. However, whether the application of milrinone can reduce the levels of inflammatory factors and Cys-C in patients for a long time and improve the cardiac function needs studies with larger number of samples.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

TS designed the study and wrote the manuscript; YZ and RT contributed significantly to the analysis and manuscript preparation; HZ was involved in the conception of the study; QW analyzed the patient data; YY and TL performed the analysis with constructive discussions. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Shouguang People's Hospital (Weifang, China) and informed consents were signed by the patients or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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