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Effect of milrinone on the cardiac function and N−terminal pro−brain natriuretic peptide levels in patients with senile refractory heart failure

Jiao−Na Wei[1]✉, Rui−Hai Yang[2], Yong−Jin Wang[1], Yi Luo[1], Ya−Kun Du[1]

[1.] *Cardiovascular Medicine Department Ward No. 1, Hanzhong People's Hospital in Shaanxi Province, Hanzhong City, Shaanxi Province, 723000*

[2.] *Cardiovascular Research Institute, Hanzhong People's Hospital in Shaanxi Province, Hanzhong City, Shaanxi Province, 723000*

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ABSTRACT

Objective: To study the effect of milrinone on the cardiac function and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in patients with senile refractory heart failure. **Methods:** 90 patients with senile refractory heart failure who were treated in our hospital between August 2013 and August 2016 were collected and divided into control group (n=45) and observation group (n=45) according to the random number table. The control group received regular clinical treatment, and the observation group received regular + milrinone treatment. The cardiac function and serum NT-proBN contents were compared between two groups of patients before and after treatment. **Results:** Before treatment, the differences in ultrasound and serum cardiac function indexes and serum NT-proBN levels were not statistically significant between two groups of patients. After treatment, ultrasound serum cardiac function parameter LVEDD level in observation group was lower than that in control group while CI and SV levels were higher than those in control group; serum cardiac function indexes Cys-C, GDF-15, sST2 and H-FABP contents were lower than those in control group; serum NT-proBNP content was lower than that in control group. **Conclusion:** Milrinone therapy can optimize the cardiac function and reduce the serum NT-proBN levels in patients with senile refractory heart failure.

1. Introduction

Refractory heart failure referes to the condition that patients with heart failure still have significant clinical symptoms after internal optimize treatment, and need long-term repeated hospitalization, and it is the end-stage heart failure state caused by various reasons[1,2]. Bed rest, cardiotonic diuresis, etc., are the normal methods for current refractory heart failure treatment, but their roles are weak in controlling the symptoms in patients with heart failure, and the condition of the majority of patients are still in continuous progress. Milrinone is a phosphodiesterase inhibitor with both positive inotropic and vasodilation effects, it contributes to the disease control of the patients with heart failure, and it is recommended for the treatment of patients with refractory heart failure[3,4]. In the research, adjuvant milrinone therapy was added in treatment of senile patients with refractory heart failure, and the influence on cardiac function and serological index contents was discussed, now reported as follows.

2. Information and methods

2.1 General information

90 patients with senile refractory heart failure who were treated in our hospital between August 2013 and August 2016 were collected as research subjects, and the patients themselves or family members signed informed consent. According to the random number table, the enrolled patients were divided into control group (n=45) and observation group (n=45). Control group included 24 men and 21 women that were 62-78 years old; observation group included 23 men and 22 women that were 61-79 years old. The gender and age distribution of the two groups were not significantly different (P>0.05), and the hospital ethics committee approved the study.

✉Corresponding author: Jiao-Na Wei, Cardiovascular Medicine Department Ward No. 1, Hanzhong People's Hospital in Shaanxi Province, Hanzhong City, Shaanxi Province, 723000.
Tel: 0916-2706900-6530; 13892687655
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2.2 Diagnostic criteria for refractory heart failure

After medical treatment (limited to sodium, water, diuresis cardiotonic) and rest, the symptoms of heart failure were still difficult to get control, and vasodilators, ACE inhibitors and positive inotropic drugs (non-digitalis) were needed to improve the myocardial compliance. The patients were discharged from the hospital again and again/or couldn′t be discharged safety, and auxiliary cardiac device was applied to maintain cardiac function.

2.3 Inclusion and exclusion criteria

Inclusion criteria: (1) in accordance with the diagnostic criteria for refractory heart failure; (2) 60 years old; (3) not treated by the milrinone before. Exclusion criteria: (1) with estimated survival time 3 months; (2) refusing to cooperate with clinical treatment and laboratory examination and with incomplete data; (3) associated with severe lung, liver, kidney and other organ dysfunction.

2.4 Therapy

Control group received clinical conventional therapy for patients with senile refractory heart failure, including ECG monitoring, sedation, furosemide diuresis, and sodium nitroprusside to lower preload and afterload. Observation group of patients, based on regular treatment, received milrinone treatment, specifically as follows: milrinone (Yangtze River Pharmaceutical Group Shanghai Haini Pharmaceutical Co., Ltd., approved by H20123179) 0.5 μg/(kg·min), by intravenous pumping, for continuous treatment for 7 d.

2.5 Observation indexes

Before and after treatment, Doppler diasonograph (Hitachi Co., Ltd, model EUB -8500) was used to detect cardiac function index levels of two groups of patients, including left ventricular end-diastolic diameter (LVEDD), cardiac index (CI) and stroke volume (SV). 2-3 mL fasting cubital venous blood was collected from two groups of patients, anti-coagulated and then centrifuged at low speed to get upper serum, enzyme-linked immunosorbent assay (ELISA) was used to detect the contents of cardiac function indexes cystatin C (Cys-C), growth differentiation factor 15 (GDF-15), soluble ST2 (sST2) and heart type fatty acid binding protein (H-FABP), and ELISA was used to detect serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP).

2.6 Statistical processing

Data were recorded and calculated by specially-assigned person, and statistical software was SPSS 21.0. Measurement data were in terms of mean ± standard deviation, and comparison was by t test. Statistics $P<0.05$ was the standard of statistical significance in differences.

3. Results

3.1 Ultrasound cardiac function indexes

Before and after treatment, comparison of ultrasound cardiac function indexes LVEDD (mm), CI (L/min-1 m-2) and SV (mL) levels between two groups of patients was as follows: before treatment, LVEDD, CI and SV levels were not significantly different between two groups of patients ($P>0.05$); compared with those before treatment, LVEDD levels in both groups decreased significantly while CI and SV levels increased significantly after treatment; compared with those in control group, LVEDD level in observation group decreased significantly while CI and SV levels increased significantly after treatment ($P<0.05$), shown in Table 1.

3.2 Serum cardiac function indexes Cys-C, GDF-15, sST2 and H-FABP contents

Before and after treatment, comparison of serum cardiac function indexes Cys-C (mg/L), GDF-15 (pg/mL), sST2 (pg/mL) and H-FABP (pg/mL) contents between two groups of patients was as follows: before treatment, serum Cys-C, GDF-15, sST2 and H-FABP contents were not significantly different between two groups of patients ($P>0.05$); compared with those before treatment, serum Cys-C, GDF-15, sST2 and H-FABP contents in both groups

Table 1.

Comparison of ultrasound cardiac function indexes LVEDD, CI and SV before and after treatment.

Groups	n	LVEDD		CI		SV	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	45	75.38±9.11	69.72±7.54*	2.11±0.25	2.37±0.28*	40.73±5.18	44.68±5.24*
Observation group	45	75.23±8.96	62.18±7.26*	2.12±0.23	2.89±0.32*	40.69±4.95	51.79±6.08*
T		0.281	8.394	0.175	7.283	0.184	12.482
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

Table 2.

Comparison of serum cardiac function indexes Cys-C, GDF-15, sST2 and H-FABP before and after treatment.

Groups	*n*	Cys-C		GDF-15		sST2		H-FABP	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	45	1.73±0.24	1.25±0.14*	653.28±71.66	371.55±40.94*	6 732.83±794.66	3 842.94±471.88*	45.83±6.19	17.32±2.19*
Observation group	45	1.76±0.28	0.81±0.09*	647.95±72.48	243.84±30.17*	6 694.37±742.18	2 931.26±340.77*	46.79±5.82	8.91±0.95*
T		0.291	6.927	0.573	12.387	0.173	19.387	0.362	11.298
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

decreased significantly after treatment; compared with those in control group, serum Cys-C, GDF-15, sST2 and H-FABP contents in observation group decreased significantly after treatment; ($P<0.05$), shown in Table 2.

3.3 NT-proBNP

Before and after treatment, comparison of serum NT-proBNP contents between two groups of patients was as follows: before treatment, serum NT-proBNP contents were not significantly different between two groups of patients ($P>0.05$); compared with those before treatment, serum NT-proBNP contents in both groups decreased significantly after treatment; compared with that in control group, serum NT-proBNP content in observation group decreased significantly after treatment ($P<0.05$), shown in Table 3.

Table 3.

Comparison of serum NT-proBNP contents before and after treatment (pg/mL).

Groups	*n*	Before treatment	After treatment
Control group	45	2 834.91±308.62	1 712.35±192.88*
Observation group	45	2 893.66±312.74	853.26±91.83*
T		0.271	20.398
P		>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

4. Discussion

Refractory heart failure is the end stage of coronary heart disease, dilated cardiomyopathy, valvular heart disease and other organic heart diseases, it is also one of the main causes of death of patients in cardiology department, and the pathogenesis includes the following: (1) pulmonary congestion and systemic congestion lower cardiac output; (2) the pulmonary capillary pressure is elevated after prolonged pulmonary congestion[5,6]. Reducing cardiac preload and afterload, and increasing myocardial contractility is the fundamental means for current refractory heart failure treatment, the therapeutic dose of digitalis positive inotropic drugs is close to toxic dose and thepositive inotropic action is not strong, so it is not suitable for treatment of patients with refractory heart failure, and milrinone, as a phosphodiesterase inhibitor, is with both positive inotropic and vasodilation effects, and is considered to be the ideal drug for refractory heart failure treatment[7]. In order to define the clinical value of milrinone, the changes in cardiac function as well as serum levels of NT-proBNP and other indexes in patients before and after adjuvant milrinone treatment were detected in the study in order to define the reliability and feasibility of the treatment.

There is severe cardiac dysfunction in patients with refractory heart failure, mainly including the reduced cardiac pumping function and congestion. Doppler ultrasound is the most common noninvasive way to judge patients' cardiac function, and the levels of cardiac function parameters in two groups before and after treatment were compared in the study at first[8,9]. LVEDD is the main indicator to evaluate the left cardiac diastolic function, and the ventricular end-diastolic blood deposits with the weakening of cardiac pumping function, so the diameter increases[10]. CI is the quotient of cardiac pumping volume and surface area, the value keeps dynamic constant in people with different body types under physiological conditions, and the pumped blood volume drops when the cardiac pumping function decreases, which leads to the reduction of CI value[11]. The trend of SV is highly consistent with that of CI and is also a sensitive indicator to reflect cardiac pump function. It was found in the study that LVEDD levels in both groups of patients after treatment decreased than those before treatment while and CI and SV levels increased than those before treatment; further compared with control group, the observation group of patients were with lower level of LVEDD, and higher levels of CI and SV after treatment, which shows from the perspective of ultrasound that adjuvant milrinone therapy can effectively optimize the cardiac function in patients with refractory heart failure. Milrinone can inhibit phosphodiesterase and make the concentration of cAMP and calcium ions in myocardial cells increase, it enhances the myocardial contractility and increases cardiac output, and this is the internal cause of these changes in ultrasound cardiac function indexes in the study.

During the evolution of refractory heart failure, the serum levels of various factors have changed, and the degree of change is the indirect indicator of the cardiac function state. Cys-C levels are closely associated with the development of cardiovascular disease, and the high blood Cys-C disease is a significant factor causing continuous decline of heart function in patients[12]. GDF-15 is associated with ventricular remodeling, which can promote myocardial fibroblast growth and collagen deposition[13]. sST2 belongs to interleukin 1 receptor family, its secretion increases when myocardial cell

capacity/pressure load changes, and it can block the endogenous myocardial protective effect of IL-33/ST2L, and cause continuous ventricular dysfunction. H-FAB is a new type of myocardial injury marker, which is released in blood early after myocardial injury, and the H-FAB content continues to rise with disease progression[14,15]. In the study, serum levels of these cardiac function indexes were compared between two groups of patients before and after treatment, and it was found that compared with those before treatment, serum Cys-C, GDF-15, sST2 and H-FABP contents in both groups of patients were lower after treatment; further compared with control group, the observation group of patients were with lower serum Cys-C, GDF-15, sST2 and H-FABP contents after treatment, confirming that adjuvant milrinone therapy can effectively optimize the serum cardiac function index contents in patients with senile refractory heart failure, and it is also the important serological factor of ultrasound cardiac function index improvement in patients.

NT-proBNP is the inactive N-terminal fragment split by BNP prohormone, its serum content can accurately reflect the BNP release newly released in a short period of time, and the sensitivity is high to determine the severity of heart failure[16]. Myocardial ischemia causes weakened myocardial contractility, increased ventricular wall tension and increased NT-proBNP release, and studies have confirmed that plasma NT-proBNP drops accordingly when the myocardial ischemia is improved. NT-proBNP is considered to be one of the most reliable indicators to reflect the illness changes in patients with senile refractory heart failure, so serum NT-proBNP contents were compared between two groups of patients before and after treatment in the study, and it was found that compared with those before treatment, serum NT-proBNP contents were lower in both groups of patients after treatment; further compared with control group, the observation group of patients were with lower serum content of NT-proBNP after treatment, further explaining that adjuvant milrinone therapy can effectively improve the condition of patients with senile refractory heart failure.

Milrinone therapy can improve the cardiac function and reduce the serum NT-proBNP content in patients with senile refractory heart failure, it helps to improve the overall clinical curative effect and it is worthy of popularization and application in clinical practice in the future.

References

[1] Costache II, Costea CF, Danciu M, Costan VV, Aursulesei V, Dumitrescu GF, et al. Amyloidosis - a rare cause of refractory heart failure in a young female. *Rom J Morphol Embryol* 2017; **58**(1): 201-206.

[2] Rigamonti F, Montecucco F, Liberale L. Advanced refractory heart failure: conservative or interventional approach. *Eur J Clin Invest* 2017; **47**(2): 193-194.

[3] Koster G, Bekema HJ, Wetterslev J, Gluud C, Keus F, van der Horst IC. Milrinone for cardiac dysfunction in critically ill adult patients: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. *Intensive Care Med* 2016; **42**(9): 1322-1335.

[4] Kaye DM, Nanayakkara S, Vizi D, Byrne M, Mariani JA. Effects of milrinone on rest and exercise hemodynamics in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2016; **67**(21): 2554-2556.

[5] Miller EO, Malhotra S, Schwartz RG. Quantitative radionuclide assessment of cardiac dyssynchrony: breakthrough in patient selection for cardiac resynchronization therapy for refractory heart failure. *J Nucl Med* 2016; **57**(12): 1840-1842.

[6] Nakamura M, Sunagawa O, Hokama R, Tsuchiya H, Miyara T, Taba Y, et al. A case of refractory heart failure in becker muscular dystrophy improved with corticosteroid therapy. *Int Heart J* 2016; **57**(5): 640-644.

[7] Mrozek S, Srairi M, Marhar F, Delmas C, Gaussiat F, Abaziou T, et al. Successful treatment of inverted Takotsubo cardiomyopathy after severe traumatic brain injury with milrinone after dobutamine failure. *Heart Lung* 2016; **45**(5): 406-408.

[8] Nakano SJ, Nelson P, Sucharov CC, Miyamoto SD. Myocardial response to milrinone in single right ventricle heart disease. *J Pediatr* 2016; **174**: 199-203.

[9] Axelsson B, Haggmark S, Svenmarker S, Johansson G, Gupta A, Tyden H, et al. Effects of combined milrinone and levosimendan treatment on systolic and diastolic function during postischemic myocardial dysfunction in a porcine model. *J Cardiovasc Pharmacol Ther* 2016; **21**(5): 495-503.

[10]Wang Xiaolin, Zhou Yuanli, Sun Wei, Li Li. Efficacy observation of tolvaptan combined with levosimendan in the treatment of severe decompensated heart failure. *China Pharm* 2016; **27**(8): 1074-1077.

[11]Muser D, Nucifora G, Gianfagna E, Pavoni D, Rebellato L, Facchin D, et al. Clinical spectrum of isolated left ventricular noncompaction: thromboembolic events, malignant left ventricular arrhythmias, and refractory heart failure. *J Am Coll Cardiol* 2014; **63**(16): e39.

[12]Shigeru M, Fujiwara S, Takamine S, Yoshida A, Kawai H, Shiotani H, et al. Predicting the response to cardiac resynchronization therapy using 99mTc-tetrofosmin myocardial scintigraphy in patients with drug-refractory heart failure: additional value of the washout of 99mTc-tetrofosmin. *Nucl Med Commun* 2014; **35**(9): 939-946.

[13]Cui Yuan, Jin Fengbiao, Sun Lixian, Ding Zhenjiang, Zhang Aiwen, Ju Mingfei, et al. Value of GDF-15, sST2 and BNP in evaluating cardiac function of patients with chronic heart failure. *Shandong Med J* 2016; **56**(17): 1-4.

[14]Zoair A, Mawlana W, Abo-Elenin A, Korrat M. Serum level of heart-type fatty acid binding protein (h-fabp) before and after treatment of congestive heart failure in children. *Pediatr Cardiol* 2015; **36**(8): 1722-1727.

[15]Mishra RK, Judson G, Christenson RH, DeFilippi C, Wu AHB, Whooley MA. The association of five-year changes in the levels of n-terminal fragment of the prohormone brain-type natriuretic peptide (nt-probnp) with subsequent heart failure and death in patients with stable coronary artery disease: the heart and soul study. *Cardiology* 2017; **137**(4): 201-206.

[16]Huang Wei-sheng, Du Yan-li, Zhang Xian-yuan, Zhang Ai-dong, Luo Sen-hua. The diagnostic value of plasma NT-pro-BNP and CRP combined detection of myocardial infarction in the elderly patients with chronic heart failure. *J Hainan Med Univ* 2015; **21**(4): 467-470.