European Review for Medical and Pharmacological Sciences 2019; 23: 4027-4032

The efficacy of simendan in the treatment of acute heart failure and its impact on NT-proBNP

J. LI[1], X.-Y. WANG[2], Z.-Y. YANG[3], Y. LI[4], F. YANG[5], P. YUAN[1], J. YANG[6]

[1]Department of General Medicine, Affiliated Hospital of Hebei University of Engineering, Handan, Heibei, China
[2]Department of Nephrology, Affiliated Hospital of Hebei University of Engineering, Handan, Heibei, China
[3]Department of Oncology, Handan Central Hospital, Handan, Heibei, China
[4]Department of Cardiology, Affiliated Hospital of Hebei University of Engineering, Handan, Heibei, China
[5]Department of Endocrinology, Handan Central Hospital, Handan, Heibei, China
[6]Department of Endocrinology, Affiliated Hospital of Hebei University of Engineering, Handan, Heibei, China

Abstract. – OBJECTIVE: Simendan is a calcium sensitizer that enhances myocardial contractility but does not affect ventricular diastole. Simendan also has a vasodilatation effect, which causes coronary artery resistance and venous volume blood vessel relax, thereby improving coronary blood supply. This study adopted simendan on the basis of conventional anti-heart failure treatment to explore a new approach for the treatment of heart failure.

PATIENTS AND METHODS: Eighty patients with heart failure were randomly and equally divided into an observation group and control group according to the digital table method. The control group was given a conventional anti-heart failure treatment. The observation group was treated with simendan on the basis of the control group. The left ventricular ejection fraction (LEVF), stroke volume (SV), NT-proBNP, K+, and Ca2+ were measured before and after the treatment. The clinical efficacy and adverse reactions after treatment were compared. The 6-minute walking distance (6MWT) was recorded on the 60th day after treatment.

RESULTS: There were no significant differences in LVEF and SV between the two groups before the treatment. They were significantly increased after treatment and were significantly higher in the observation group than that in the control group ($p < 0.05$). The total effective rate in the observation group (92.50%) was significantly higher than that in the control group (67.50%). There was no statistical difference in the occurrence of adverse reactions between the two groups ($p > 0.05$). The 6MWT in the observation group was 452.63±86.51 meters, which was significantly higher than that in the control group (366.85±70.46 meters) ($p < 0.05$). There was no significant difference in plasma NT-proBNP levels between the two groups ($p > 0.05$). The plasma NT-proBNP level was significantly lower in the observation group than that in the control group after treatment ($p < 0.05$). Serum K+ and Ca2+ were not significantly changed after treatment in the control group ($p > 0.05$). Serum K+, but not Ca2+, was significantly elevated in the observation group.

CONCLUSIONS: Simendan can significantly reduce plasma NT-proBNP level; thus, it is relatively safe and effective for the treatment of acute heart failure (AHF).

Key Words:
Simendan, Acute heart failure, Clinical efficacy, NT-proBNP.

Introduction

In recent years, following the aging of the population, the incidence and mortality of acute heart failure (AHF) has been increased, which has become a serious public health problem[1,2]. The prognosis of patients with heart failure is poor, with the hospital mortality rate of 3%, the 60-day mortality rate of 9.6%, and the 3-year and 5-year mortality rates of 30% and 60%, respectively. Therefore, the treatment of heart failure affects a huge part of the society and brings medical stress[3,4]. The scientists are focused on searching novel drugs for the treatment of AHF. Despite the huge human and financial resources, there are still a few drugs that can reduce the mortality rate of AHF patients.

Simendan is a calcium sensitizer that binds to Cardiac troponin C (cTnC) in a calcium ion con-

Corresponding Author: Jie Yang, MD; email: rtlb5n1b7r3f@sina.com

centration-dependent manner to produce positive inotropic effects, enhance myocardial contractility, without affecting ventricular diastolic. At the same time, it can produce vasodilation by opening the ATP-sensitive K^+ channel (KATP), which makes coronary artery resistance and venous volume vessels vasodilatation, thereby improving coronary blood supply. Moreover, it can also inhibit phosphodiester enzyme[5,6]. In patients with heart failure, the positive inotropic and vasodilating effects of simendan can increase myocardial contractility and reduce the anterior and posterior loads without affecting their diastolic function[7].

This study adopted simendan on the basis of conventional anti-heart failure treatment to explore a new approach for the treatment of heart failure.

Patients and Methods

General Information

Eighty patients with heart failure who were admitted to the Affiliated Hospital of Hebei University of Engineering (Handan, Heibei, China) from February 2015 to December 2017 were enrolled, including 42 males and 38 females, with an average age of 65.84 ± 8.95 (ranges: 50-82) years. All patients met the diagnostic criteria according to the "Guidelines for the Diagnosis and Treatment of Acute Heart Failure" developed by the Chinese Medical Association. The cardiac function was graded III to IV, and LVEF ≤ 40%. Patients with congenital heart disease, severe liver and kidney dysfunction, severe ventricular arrhythmia, severe heart valve disease, cardiogenic shock, hypovolemia, and inability to use vasodilators were excluded. Patients were equally and randomly divided into an observation group and control group by random number table method. There were 22 males and 18 females with an average age of 65.26 ± 9.38 years old in the observation group. There were 20 males and 20 females with an average age of 66.07 ± 9.12 years in the control group. There were no significant differences in the general data between the two groups ($p > 0.05$). The study was approved by the Affiliated Hospital of Hebei University of Engineering (Handan, heibei, China) Ethics Committee and all patients signed the informed consent.

Methods

The control group received conventional anti-heart failure treatment, including statins, diuretics, vasodilators, beta-blockers, and angiotensin receptor blockers when necessary. The patients with poor blood pressure control were added with dihydropyridine-based calcium ion antagonists, and adequate anti-infection, salt limitation and other measures to correct the predisposing factors of heart failure. The observation group was added with simendan (specification: 5 ml: 12.5 mg, batch number: 150114, manufacturer: Chengdu Shengnuo Bio-Pharmaceutical Co., Ltd.) on the basis of the control group. The initial loading dose was 12 μg/kg, pumping time > 10 min. If the patient did not suffer from adverse conditions, the dose was adjusted to 0.1 μg·min-1·kg-1 and continued intravenous pumping for 24 h.

Observation Index

The patient's vital signs (breathing, blood pressure, pulse, heart rate) (UMEC7 ECG monitor, Shenzhen Mindray), 24 h urine volume, dyspnea, lung voice, and double lower extremity edema were closely monitored. The left ventricular ejection fraction (LEVF), stroke volume (SV), NT-proBNP, K^+, and Ca^{2+} (BS-800 automatic biochemical analyzer, Shenzhen Mindray, Shenzhen, China) were measured before the treatment and after 24 h of treatment.

Efficacy Evaluation

(1) Significant effective: after treatment, the clinical symptoms and signs of the patient disappeared, the heart function returned to normal or increased by 2 grades or more than before treatment; (2) effective: after treatment, the patient's clinical symptoms and signs improved significantly, and the heart function was better than before treatment for 1~2 grades; (3) invalid: after treatment, the patient's clinical symptoms and signs did not change significantly, even the condition was aggravated, and the cardiac function did not improve significantly. Total effective rate = (significant effective number of cases + effective number of cases)/total number of cases × 100%. The prevalence of adverse reactions in the two groups was recorded and compared.

6MWT

All patients were tested at the same time after 60 days of treatment. The patient's 6MWT was recorded with a timer.

Statistical Analysis

All data analyses were performed on SPSS 17.0 software (SPSS Inc., SPSS Statistics for Windows, Chicago, IL, USA). The measurement data

Table I. Comparison of cardiac function indexes between the two groups before and after treatment.

	LVEF (%)		SV (mL)	
	Before treatment	After treatment	Before treatment	After treatment
Observation group	29.12±7.04	37.84±5.93	63.91±3.85	74.82±4.13
Control	28.76±6.58	33.42±6.61	64.14±4.02	68.73±3.69
t	0.236	3.148	0.261	6.955
p	0.814	0.002	0.795	< 0.001

were presented as mean ± standard deviation and compared by the Student's *t*-test. The enumeration data were compared by the Chi-square test. $p < 0.05$ was considered as statistical difference.

Results

Comparison of Cardiac Function Indexes Between the Two Groups Before and After Treatment

There were no significant differences in LVEF and SV between the two groups ($p > 0.05$). After treatment, LVEF and SV were significantly higher than those before the treatment, and they were significantly higher in the observation group than that in the control group ($p < 0.05$) (Table I).

Comparison of Treatment Effects Between the Two Groups

In the observation group, 23 cases were significantly effective, and 14 cases were effective with the total effective rate of 92.50%. In the control group, 11 cases were significantly effective, and 16 cases were effective with the total effective rate of 67.50%. The effective rate in the observation group was significantly higher than that in the control group ($p < 0.05$) (Table II).

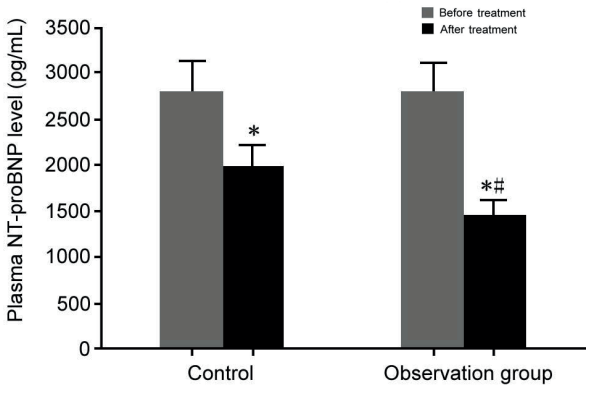

Figure 1. Comparison of plasma NT-proBNP level between the two groups.

Comparison of Adverse Reactions Between the Two Groups

In the observation group, 1 patient developed hypotension, 2 patients suffered from hypokalemia with the occurrence of adverse reactions of 7.50%. In the control group, 1 patient developed tachycardia, 1 patient developed palpitations, 3 patients developed nausea and vomiting with the occurrence of adverse reaction of 12.5%. There was no statistical difference between the two groups ($p > 0.05$). The adverse reactions of the two groups were significantly improved after symptomatic treatment.

Comparison of 6MWT Between Two Groups

The 6-minute walking distance was 452.63±86.51 m in the observation group and 366.85±70.46 m in the control group. The observation group was significantly higher than the control group ($p < 0.05$) (Table III).

Comparison of Plasma NT-proBNP Level Between the Two Groups

There was no statistical difference in plasma NT-proBNP levels between the two groups before the treatment ($p > 0.05$). The levels of plasma NT-proBNP in the two groups after treatment were significantly lower than those before treatment ($p < 0.05$). Its level in the observation group was significantly lower than that in the control group after treatment. ($p < 0.05$) (Figure 1).

Comparison of Serum K+ and Ca^{2+} of the Two Groups

There were no significant differences in serum K^+ and Ca^{2+} levels between the two groups before treatment ($p > 0.05$). Serum K^+ and Ca^{2+} were not significantly changed after treatment in the control group ($p > 0.05$). Serum K^+, but not Ca^{2+}, was

Table II. Comparison of treatment effects between the two groups (n,%).

	Significant effective	Effective	Invalid	Total effective rate
Observation group	23 (57.50%)	14 (35.00%)	3 (7.50%)	37 (92.50%)
Control	11 (27.50%)	16 (40.00%)	13 (32.50%)	27 (67.50%)
χ^2	7.813			
p	0.005			

Table III. 6MWT comparison.

	6MWT (m)	*t*	*p*
Observation group	452.63±86.51	4.863	<0.001
Control	366.85±70.46		

significantly elevated in the observation group (Table IV).

Discussion

AHF is a systolic and diastolic dysfunction caused by a variety of reasons, resulting in a blood supply that does not meet the metabolic requirements, and produces a series of clinical signs and symptoms[8,9]. The incidence of AHF is mostly in the elderly, and the prognosis is poor, with up to 3% of the mortality rate during hospitalization[10]. Clinically, positive inotropic drugs, such as cardiotonic, beta-agonists, and phosphodiesterase inhibitors, are widely used in the treatment of AHF. They can directly or indirectly enhance muscle strength and vasodilating effects by increasing the concentration of cyclic adenosine monophosphate (cAMP) in the myocardium. However, these drugs may elevate the myocardial oxygen consumption and induce arrhythmia, thus increasing the long-term mortality rate[11]. Therefore, the identification of a new drug with definite curative effect and small adverse reactions is urgently required in clinic.

Simendan is a new type of positive inotropic drug, which has been also recommended for AHF treatment[12]. Simendan is a novel Ca^{2+} sensitizer with a dual mechanism of calcium sensitization and potassium ion channel opening[12]. Pharmacological studies revealed that simendan can bind to cTnC, enhance the sensitivity of cTnC to Ca^{2+}, increase myocardial contractility, but not elevate myocardial oxygen consumption, or induce arrhythmia. In addition, simendan also has the capacity of dilating the coronary arteries and peripheral blood vessels, improving the hemodynamic status, correcting heart failure, and alleviating the symptoms and signs of heart failure in patients[13]. Kivikko et al[14] investigated 1327 cases of Finnish AHF patients and found that simendan can effectively reduce the mortality rate of AHF patients compared to the traditional drug dobutamine. Altenberger et al[15] also reported the good therapeutic effect of simendan on AHF and its improvement on cardiac function indicators. This study found that the cardiac function indicators of LVEF and SV in patients treated with simendan were significantly higher than those in the control group after treatment, suggesting that simendan is superior to traditional drugs in improving cardiac function in patients with AHF. It was observed that the effective rate of the patients treated with simendan was as high as 92.5%, while the effective rate of traditional drug therapy was only 67.5%, suggesting that simendan exhibited a better curative effect on AHF. Moreover, it was revealed that it did not increase the occurrence of adverse reactions compared with traditional drugs. 6MWT also suggested that simendan treatment had a better prognosis than traditional drugs. The above re-

Table IV. Comparison of serum K^+ and Ca^{2+} of the two groups.

	K^+		Ca^{2+}	
	Before treatment	After treatment	After treatment	Before treatment
Observation group	4.03±0.52	4.57±0.48	2.18±0.15	2.19±0.13
Control	4.05±0.51	4.14±0.53	2.13±0.18	2.20±0.19
t	0.134	3.803	1.350	0.275
p	0.863	<0.001	0.181	0.784

sults indicated that simendan is safe and effective in the treatment of AHF, which is consistent with the other reports[13,16].

NT-proBNP is an inactive N-terminal fragment produced by the pro-protein (BNP) after division. It is a neuroendocrine hormone secreted by the left ventricle when the pressure load and volume load on the cardiomyocytes increase (are increased). It exhibited high sensitivity to evaluate the motor coordination of the ventricular wall segment and systolic and diastolic dysfunction[17-21]. With the deepening of research, more and more results confirmed that NT-proBNP has the advantages of the long half-life and high concentration in blood, which is suitable as a marker for diagnosing heart failure[22-24]. This study also found that plasma NT-PROBNP level was significantly lower in the simendan-treated group than that in the control group, confirming that simendan can effectively reduce plasma NT-PROBNP level.

Conclusions

We found that simendan can significantly reduce plasma NT-proBNP level, thus it is relatively safe and effective for the treatment of AHF.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

This work was supported by the Hebei Health Planning Commission (No. 20180795).

References

1) Long B, Koyfman A, Chin EJ. Misconceptions in acute heart failure diagnosis and management in the emergency department. Am J Emerg Med 2018; 36: 1666-1673.
2) Cheema B, Ambrosy AP, Kaplan RM, Senni M, Fonarow GC, Chioncel O, Butler J, Gheorghiade M. Lessons learned in acute heart failure. Eur J Heart Fail 2018; 20: 630-641.
3) Rayner-Hartley E, Virani S, Toma M. Update on the management of acute heart failure. Curr Opin Cardiol 2018; 33: 225-231.
4) Kurmani S, Squire I. Acute heart failure: definition, classification and epidemiology. Curr Heart Fail Rep 2017; 14: 385-392.
5) Faisal SA, Apatov DA, Ramakrishna H, Weiner MM. Levosimendan in cardiac surgery: evaluating the evidence. J Cardiothorac Vasc Anesth 2019; 33: 1146-1158.
6) Hansen MS, Andersen A, Nielsen-Kudsk JE. Levosimendan in pulmonary hypertension and right heart failure. Pulm Circ 2018; 8: 2045894018790905.
7) Nieminen MS, Buerke M, Cohen-Solal A, Costa S, Edes I, Erlikh A, Franco F, Gibson C, Gorjup V, Guarracino F, Gustafsson F, Harjola VP, Husebye T, Karason K, Katsytadze I, Kaul S, Kivikko M, Marenzi G, Masip J, Matskeplishvili S, Mebazaa A, Moller JE, Nessler J, Nessler B, Ntalianis A, Oliva F, Pichler-Cetin E, Poder P, Recio-Mayoral A, Rex S, Rokyta R, Strasser RH, Zima E, Pollesello P. The role of levosimendan in acute heart failure complicating acute coronary syndrome: a review and expert consensus opinion. Int J Cardiol 2016; 218: 150-157.
8) Tanaka TD, Sawano M, Ramani R, Friedman M, Kohsaka S. Acute heart failure management in the USA and Japan: overview of practice patterns and review of evidence. ESC Heart Fail 2018; 5: 931-947.
9) Pineton de Chambrun M, Bréchot N, Combes A. Mechanical circulatory devices in acute heart failure. Curr Opin Crit Care 2018; 24: 286-291.
10) Michaud AM, Parker SIA, Ganshorn H, Ezekowitz JA, McRae AD. Prediction of early adverse events in emergency department patients with acute heart failure: a systematic review. Can J Cardiol 2018; 34: 168-179.
11) Teneggi V, Sivakumar N, Chen D, Matter A. Drugs' development in acute heart failure: what went wrong? Heart Fail Rev 2018; 23: 667-691.
12) Farmakis D, Alvarez J, Gal TB, Brito D, Fedele F, Fonseca C, Gordon AC, Gotsman I, Grossini E, Guarracino F, Harjola VP, Hellman Y, Heunks L, Ivancan V, Karavidas A, Kivikko M, Lomivorotov V, Longrois D, Masip J, Metra M, Morelli A, Nikolaou M, Papp Z, Parkhomenko A, Poelzl G, Pollesello P, Ravn HB, Rex S, Riha H, Ricksten SE, Schwinger RHG, Vrtovec B, Yilmaz MB, Zielinska M, Parissis J. Levosimendan beyond inotropy and acute heart failure: evidence of pleiotropic effects on the heart and other organs: an expert panel position paper. Int J Cardiol 2016; 222: 303-312.
13) Zhou S, Zhang L, Li J. Effect of levosimendan in patients with acute decompensated heart failure: a meta-analysis. Herz 2018 Apr 10. doi: 10.1007/s00059-018-4693-3. [Epub ahead of print].
14) Kivikko M, Pollesello P, Tarvasmaki T, Sarapohja T, Nieminen MS, Harjola VP. Effect of baseline characteristics on mortality in the survive trial on the effect of levosimendan vs dobutamine in acute heart failure: sub-analysis of the Finnish patients. Int J Cardiol 2016; 215: 26-31.
15) Altenberger J, Gustafsson F, Harjola VP, Karason K, Kindgen-Milles D, Kivikko M, Malfatto G, Papp Z, Parissis J, Pollesello P, Polzl G, Tschope C. Levosimendan in acute and advanced heart failure: an appraisal of the clinical database and evaluation of its therapeutic applications. J Cardiovasc Pharmacol 2018; 71: 129-136.

16) Pollesello P, Parissis J, Kivikko M, Harjola VP. Levosimendan meta-analyses: is there a pattern in the effect on mortality? Int J Cardiol 2016; 209: 77-83.
17) McCullough PA, Kluger AY. Interpreting the wide range of nt-probnp concentrations in clinical decision making. J Am Coll Cardiol 2018; 71: 1201-1203.
18) Scrutinio D, Passantino A, Guida P, Ammirati E, Oliva F, Sarzi Braga S, La Rovere MT, Lagioia R, Frigerio M, Di Somma S. Relationship among body mass index, nt-probnp, and mortality in decompensated chronic heart failure. Heart Lung 2017; 46: 172-177.
19) Grande D, Leone M, Rizzo C, Terlizzese P, Parisi G, Gioia MI, Leopizzi T, Segreto A, Guida P, Romito R, Ciccone MM, Serio FD, Iacoviello M. A multiparametric approach based on nt-probnp, st2, and galectin3 for stratifying one year prognosis of chronic heart failure outpatients. J Cardiovasc Dev Dis 2017; 4. pii: E0009.
20) Taylor CJ, Roalfe AK, Iles R, Hobbs FD. The potential role of nt-probnp in screening for and predicting prognosis in heart failure: a survival analysis. BMJ Open 2014; 4: e004675.
21) Sargento L, Longo S, Lousada N, Palma Dos Reis R. Serial measurements of the nt-probnp during the dry state in patients with systolic heart failure are predictors of the long-term prognosis. Biomarkers 2014; 19: 302-313.
22) Onur S, Niklowitz P, Jacobs G, Lieb W, Menke T, Doring F. Association between serum level of ubiquinol and nt-probnp, a marker for chronic heart failure, in healthy elderly subjects. Biofactors 2015; 41: 35-43.
23) Park HS, Kim H, Sohn JH, Shin HW, Cho YK, Yoon HJ, Nam CW, Hur SH, Kim YN, Kim KB, Park HJ. Combination of uric acid and nt-probnp: a more useful prognostic marker for short-term clinical outcomes in patients with acute heart failure. Korean J Intern Med 2010; 25: 253-259.
24) Wieshammer S, Dreyhaupt J, Basler B, Marsovszky E. Nt-probnp for pulmonologists: not only a rule-out test for systolic heart failure but also a global marker of heart disease. Respiration 2009; 77: 370-380.