Levosimendan Improves NT-proBNP Levels and Echocardiographic Parameters in Patients with Decompensated Heart Failure Submitted to Optimal Medical Therapy

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ABSTRACT

Introduction: The effect of levosimendan on NT-proBNP levels and echocardiographic parameters in patients with decompensated heart failure receiving optimal medical therapy was evaluated.
Patients and Methods: The study included 30 patients with acute heart failure with New York Heart Association (NYHA) class IV. Although all patients had received standard heart failure therapy, they required support of an inotropic agent. They received bolus and maintenance infusion of levosimendan treatment for 24 hours. Echocardiography was performed before the levosimendan treatment and at the 5th day after the treatment. NT-proBNP levels were taken at 48th hour and 5th day.
Results: Levosimendan treatment (bolus+maintenance infusion) was performed in all patients without any interruption or complication. A significant reduction in NT-proBNP levels was observed at the end of 48th hour and 5th day compared to baseline values ($p<0.001$). After the treatment, a significant improvement was observed in NYHA functional class. Significant improvement was observed in both systolic and diastolic echocardiographic parameters including ejection fraction ($p<0.001$), S' wave ($p=0.03$), E/A ratio ($p<0.01$), deceleration time of E wave ($p<0.01$), TDI S' ($p<0.01$), E' ($p<0.01$), and A' waves ($p<0.01$), and E/E' ratio ($p<0.01$). When the study was grouped into ischemic and nonischemic origin, no significant differences were observed regarding the clinical and echocardiographic parameters. No malignant arrhythmia was observed.
Conclusion: Levosimendan may be safely used in normotensive patients with decompensated heart failure receiving optimal medical therapy. It provides an additional improvement in NT-proBNP levels and echocardiographic parameters.
Key Words: Heart failure; levosimendan; NT-proBNP; echocardiography

Levosimendan Optimal Medikal Tedavi Alan Dekompanse Kalp Yetersizliği Hastalarında NTproBNP Seviyesini ve Ekokardiyografik Parametreleri Düzeltir

ÖZET

Giriş: Optimal medikal tedavi alan dekompanse kalp yetersizliği hastalarında levosimendanın NT-proBNP seviyesi ve ekokardiyografik parametreler üzerindeki etkisi değerlendirilmiştir.
Hastalar ve Yöntem: Çalışmaya "New York Heart Association (NYHA)" Sınıf IV olan 30 akut kalp yetersizliği hastası dahil edildi. Tüm hastalar standart kalp yetersizliği tedavisi almasına rağmen inotrop desteğe ihtiyaç duyuyordu. Hastalara 24 saat boyunca bolus ve idame infüzyon şeklinde levosimendan uygulandı. Levosimendan tedavisi öncesi ve tedavi sonrası 5. gün ekokardiyografi uygulandı. NT-proBNP seviyeleri 48. saat ve 5. gün çalışıldı.
Bulgular: Levosimendan tedavisi (bolus+idame) tüm hastalara kesintisiz ve komplikasyon gelişmeden verilebildi. Bazal bulgulara kıyasla 48. saat ve 5. gün sonunda NT-proBNP seviyelerinde önemli bir azalma sağlandı ($p<0,001$). Tedavi sonrası NYHA fonksiyonel sınıfta anlamlı düzelme izlendi. Ejeksiyon fraksiyonu, E/A oranı, E dalga deselerasyonu, TDI S', E', A' dalgaları ve E/E' oranı gibi sistolik ve diyastolik ekokardiyografik parametrelerde anlamlı düzelme izlendi (sırasıyla $p<0,001$, $p<0,01$, $p<0,01$, $p<0,01$, $p<0,01$, $p<0,01$). Çalışma grubu iskemik ve noniskemik olarak ayrıldığında klinik ve ekokardiyografik parametre açısından anlamlı farklılık izlenmedi. Ölümcül ritim bozukluğu gözlenmedi.
Sonuç: Levosimendan, optimal medikal tedavi altında dekompanse kalp yetersizliği gelişmiş normotansif hastalarda güvenle kullanılabilir. NT-proBNP seviyesi ve ekokardiyografik parametreler üzerinde ilave düzelme sağlar.
Anahtar Kelimeler: Kalp yetersizliği; levosimendan; NT-proBNP; ekokardiyografi

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INTRODUCTION

Acute heart failure (HF) is an important health problem due to high rates of mortality, with the numbers of patients readmission for acute HF increasing due to ageing populations and improvements in the treatments of coronary heart disease and chronic HF[1]. Intravenous positive inotropic agents play an important role in treating acute decompensation of chronic HF[2,3]. However, classic inotropic drugs are associated with increased myocardial oxygen consumption, major risk of arrhythmias, and reduced short and long-term survival. Therefore, attention has been focused on novel inotropic agents such as levosimendan[4]. Levosimendan is a calcium sensitizer with positive inotropic properties that works on the sensibilization of Ca2+ channels of myocites increasing intracellular Ca2+ concentration[5]. It produces vasodilatation by opening the ATP-sensitive potassium channels in vascular smooth muscle cells and also has phosphodiesterase type III inhibitory properties at high concentrations[6]. The pharmacokinetics of levosimendan are linear and the plasma concentration of the drug increases in a dose proportional manner following single dose i.v. administration and infusion of the drug[7]. It acts for prolonged time, since its two major metabolites OR-1855 and OR-1896 have half-life time of 70-80 hours[8].

Levosimendan induces haemodynamic improvement without an increase in myocardial oxygen consumption[9]. European Society of Cardiology (ESC) Guidelines recommend levosimendan as Class II B (Level of evidence C) with a loading dose (optional) if systolic blood pressure is not too low[10].

There has been a concern about the efficacy and safety of levosimendan in daily practice. In this study we aimed to evaluate the efficacy and safety of levosimendan in patients with decompensated HF submitted to optimal medical therapy.

PATIENTS and METHODS

We evaluated 30 patients with acute New York Heart Association (NYHA) class IV HF. Diagnosis of HF was confirmed by the contribution of physical examination, previous history, but mainly by transthoracic echocardiography and thoracic X-rays. Ejection fraction (EF) less than 40% in echocardiogram was documented in all patients. All patients had received optimal HF therapy (diuretics, oxygen, ACEs or ARBs, digoxin, and beta-blockers in minor doses) and did need support of an inotropic agent. Electrolyte abnormalities were improved during the course of the therapy.

As for the exclusion criteria, patients with an acute coronary syndrome, systolic blood pressure under 100 mmHg resistant to volume administration, left ventricular (LV) dysfunction due to valvular diseases, constrictive pericarditis or pericardial tamponade, restrictive or hypertrophic cardiomyopathy, benign or life-threatening tachyarrhythmias with heart rate over 120/min, and electrolytic abnormalities, and serious comorbid organ failures did not participate. Written informed consent was obtained from the participants and the study was approved by the local Ethics Board.

Study Protocol

All participants took next to their HF medication 12 μg/kg over 10 minutes bolus plus 0.1 μg/kg/min infusion levosimendan treatment for 24 hours.

Echocardiographic Evaluation

Standard echocardiography performed in all patients using General Electric Vivid III with a phases array transducer of 2.5 MHz and TDI technology. Echocardiographic exams were performed by an experienced echocardiographer physician blinded to all data. Recordings were acquired with subjects in the left lateral decubitus during shallow respiration or end expiratory apnea.

Echocardiography was performed at baseline and 5th day after standard levosimendan treatment. LV systolic function was estimated by left ventricular ejection fraction (LVEF) using the biplane modified Simpson's method and the long axis function by TDI S' wave[11].

LV diastolic function was estimated by pulsed wave (PW) Doppler on transmitral flow assessing peak velocities in early (E) and late diastole (A), E/A ratio, deceleration time of E wave (DT) and TDI E' (early) and A' (late) waves. Tissue Doppler velocities were recorded at lateral mitral annulus. The E/E' ratio was calculated and used as an index of LV filling pressures.

NT-proBNP Measurements

For the evaluation of neurohormonal response of the therapy we used measurements of NT-proBNP. Blood samples of 6 mL, included NT-proBNP levels, were taken at the beginning time point of the infusion and at 48th hour and 5th day. Plasma was extracted after centrifugation at 3000 rpm for 5 minutes. NT-proBNP was measured on Elecsys 1010 autoanalyser (Roche Diagnostics, Indianapolis, Indiana) with the use of a commercial kit (Roche Diagnostics) by electrochemiluminescent immunoassay method.

Clinical Status

The well-being status was evaluated by means of clinical examination and subjective confirmation of the patient at 24 hour intervals. Major complications were noted. A continuous

Table 1. Medical therapy at baseline of the study population

Pharmacological agents	n (%)
ACE	20 (67)
ARB	5 (17)
Beta-blocker	22 (73)
Spironolactone	15 (50)
Furosemide	30 (100)
Digoxin	12 (40)
Anticoagulant	26 (87)
Antiaggregant	26 (87)

Data are presented as number (percentage) values
ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker

ECG monitoring during the infusion protocol confirmed the arrhythmias observed.

Statistical Analysis

Statistical analysis was performed using SPSS 16. Quantitative values were expressed as mean ± standard deviation and qualitative values as %. The Kolmogorov Smirnov test was used to test the normality of distribution of continuous variables. The paired t-test or Wilcoxon's paired test was used to compare values before and after drug administration. A p value of <0.05 was considered statistically significant.

Table 2. The echocardiographic and clinical findings and NT-proBNP levels of the study population before and after treatment of levosimendan

	Time 0	5 days	P value
LVEDD (mm)	66±2	65±2	<0.001
LVESD, (mm)	47±3	43±2	<0.001
LVEF, (%)	28±4	35±4	<0.001
E, m/sn	1.02±0.17	1.08±0.19	<0.01
A, m/sn	0.46±0.26	0.48±0.25	<0.01
E/A	2.5±0.9	1.9±0.7	<0.01
E/E'	12.6±3.6	11.5±3.7	<0.01
S'	5.6±0.8	6.5±1.1	0.03
DT, ms	121±16	132±25	<0.01
IVRT, ms	77.3±10	114±11	<0.001
Heart Rate	73±18	79±12	0.08
SBP (mm Hg)	98±6	97±5	0.3
DBP (mmHg)	66±8	65±5	0.1
New York Heart Association	3.5±0.5	3±0.5	<0.001
NT-proBNP, pg/mL	10963±14136	5075±5284	<0.001

Data is expressed as mean ± standard deviation; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; LVEF: Left ventricular ejection fraction; S: Myocardial systolic wave; E: Myocardial early diastolic wave; A: Myocardial atrial diastolic wave; IVRT: Isovolumetric relaxation time; DT: Deceleration time; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

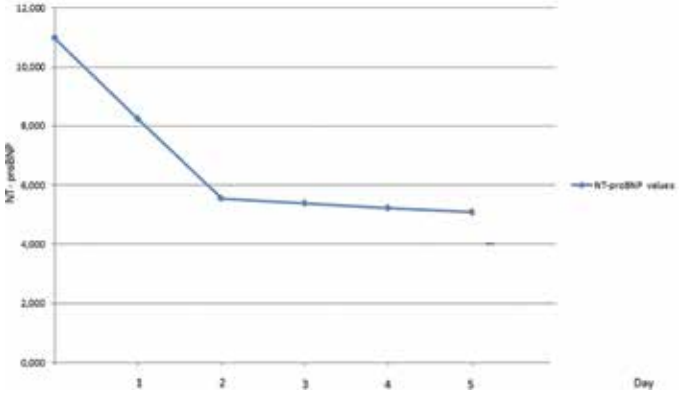

Figure 1. NT-proBNP values during the first five days of levosimendan treatment

RESULTS

The study was comprised of 30 (male:12, female:18) patients. The average age of the study group was 65±10 years (range, 45-84 years). Regarding the etiology of the HF, we observed a population with 40% suffering from coronary artery disease and with 60% from nonischemic dilated cardiomyopathy. The list of medical therapy administered at baseline of the study population was presented in Table 1.

Levosimendan treatment (bolus+infusion) was performed in all study patients without any interruption. No significant hypotension was reported. Five patients received potassium treatment due to hypokalemia during the course of HF treatment. Diuretic doses were adjusted due to volume overload and clinical status.

The echocardiographic parameters and clinical findings of the study population before and after levosimendan treatment were presented in Table 2. A significant reduction of pro-BNP levels was observed at the end of 48th hour and 5 days compared to baseline values (Table 2, Figure 1). After the administration of levosimendan, the study group showed a significant improvement in NYHA functional class. Significant improvement was observed in both systolic and diastolic parameters (Table 2). When the study was grouped into ischemic & nonischemic origin, no significant differences were observed regarding the clinical and echocardiographic parameters.

Adverse Events

There were not patients who had to discontinue the study due to hypotension or other minor complications. Within a period of a month, one patient was presented with acute renal exacerbation, and three others needed to be rehospitalised for exacerbated HF. Infrequent ventricular extrasystole was observed in 2 patients; no malignant arrythmia was detected. No mortalities were reported.

DISCUSSION

In this study, we evaluated the efficacy and safety of levosimendan in patients with acute decompensated HF who are receiving optimal medical therapy. We analysed changes in clinical and echocardiographic parameters and showed that levosimendan therapy leaded to an essential improvement in clinical NYHA class, pro-BNP blood levels and echocardiogaphic characteristics of ventricular function after 5 days of administration without complications. We believe that levosimendan can be successfully administered in decompensated HF in daily practice when eligible patients are carefully selected and strict clinical follow-up is maintained during the course of treatment.

Despite all the advances in the management of heart disease, HF is still associated with high mortality rates[12]. LV pump function plays a central role as a cause of dyspnea and fatigue, poor peripheral perfusion, and end-organ dysfunction[13]. Although neurohormonal antagonists have improved the prognosis of the patients with HF, inotropic agents are needed

for improving cardiac output and peripheral perfusion, levosimendan is one of these inotropic agents that has been extensively studied recently.

Levosimendan increases cardiac output and decreases pulmonary capillary wedge pressure. In contrast to other conventional positive inotropic drugs, levosimendan does not increase oxygen demand of the myocardium and no negative effects on diastolic functions. The site of action of levosimendan is beyond the beta adrenergic receptor and is independent of the occupancy of the beta adrenergic receptors. Thus, there is potential benefit of combined therapy with beta-blockers and levosimendan when compared to dobutamin[14]. Accordingly, some recent trials presented beneficial hemodynamic effects of levosimendan in comparison to dobutamine in patients with acute decompensated HF treated with beta-blockers[15-17]. We, in this study, successfully used levosimendan in decompensated HF patients treated concomitantly with beta-blocker drugs.

Natriuretic peptides are useful markers in the diagnosis of HF and in evaluation of the course of HF treatment. Levosimendan has been shown to reduce levels of BNP compared with dobutamine in acute decompansated HF[2,18]. In our study, pro-BNP levels were significantly decreased at 48th hour and 5th day after levosimendan therapy, underscoring the favorable effects of levosimendan in acute HF. The decrease of pro-BNP levels is associated with an improvement in echocardiographic parameters. We used TDI and M-mode analysis to evaluate LV longitudinal systolic and diastolic functions. Because of the high vulnerability of longitudinal subendocardial fibers to several injury mechanisms, assessment of the longitudinal component of LV shortening is an important parameter for the early detection of LV contractile impairment[19]. In the study, after levosimendan treatment we obtained an improvement of LVEF and a reduction of E/E' ratio.

However, levosimendan has a peripheral vasodilatory effect as well as inotropy[20]. This is important as most of the patients have a borderline preserved systolic pressure and levosimendan could induce hypotension and hypoperfusion[21]. In the present study all selected patients were initially normotensive and the levosimendan treatment was well tolerated.

Arrhythmia is another potential nightmare during the course of levosimendan treatment. In the present study, probably keeping electrolyte balance within normal limits prevented the development of lethal arrhythmias. In our recently published study, therapeutic doses of levosimendan did not have a significant effect on QT parameters the predictors of arrhythmias, in patients with decompensated HF when compared with dobutamine infusion[22].

Considering the current literature, patients that are expected to benefit more by levosimendan administration are acute decompensated heart failure (ADHF) patients with NYHA class III/IV, ischemic etiology of HF (hibernating or stunning myocardium), SBP>100 mmHg, reduction of NT-proBNP>30% from baseline after 48 h, and concomitant treatment with beta-blocker[23-26]. Our findings are in concordance with this previous reports except that the etiology (ischemic & nonischemic) did not effect the success of the treatment.

Use of inotropes in acute HF is generally restricted to patients with hypotension, hypoperfusion, or shock in the most recent ESC Guidelines from 2012 because of safety concerns. The guidelines note that the efficacy and safety of levosimendan are still uncertain, though they suggest a potential pharmacologic rationale for intravenous levosimendan (or a phosphodiesterase inhibitor) to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypoperfusion[10]. In this study levosimendan provided additional benefit without any complications in normotensive patients submitted to optimal medical therapy.

Clinical Implications

Our experience show that levosimendan provides an essential improvement of cardiac systolic and diastolic functions early after administration. Careful selection of patients that are expected to be more benefited by levosimendan administration may result in improvement of clinical and echocardiographic parameters.

Limitations

Our study included some limitations. It was an observational study without control group. The sample size of the study was relatively small due to high cost of levosimendan. Also all patients did not get the same medical therapy excluding the diuretics. Furthermore, invasive hemodynamic monitoring was not performed. New onset of atrial flutter, atrial fibrillation or ventricular tachycardia were not detected; however, it should be noted that since no Holter recording was made during the study, this may not be entirely accurate.

Levosimendan may be safely used in normotensive patients with decompensated HF already submitted to optimal medical therapy. It provides an additional improvement in NT-proBNP levels and both systolic and diastolic echocardiographic parameters.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

REFERENCES

1. Krum H, Liew D. New and emerging drug therapies for the management of acute heart failure. Intern Med J 2003;33:515-20.
2. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, Thakkar R, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA 2007;297:1883-91.
3. Fotbolcu H, Duman D. A promising new inotrope: levosimendan. Anadolu Kardiyol Derg 2010;10:176-82.
4. De Luca L, Mebazaa A, Filippatos G, Parissis JT, Böhm M, Voors AA, et al. Overview of emerging pharmacologic agents for acute heart failure syndromes. Eur J Heart Fail 2008;10:201-13.
5. Hasenfuss G, Pieske B, Castell M, Kretschmann B, Maier LS, Just H. Influence of the novel inotropic agent levosimendan on isometric tension and calcium cycling in failing human myocardium. Circulation 1998;98:2141-7.
6. Yildiz O. Vasodilating mechanisms of levosimendan: involvement of Kþ channels. J Pharmacol Sci 2007;104:1-5.
7. Lilleberg J, Sundberg S, Häyhä M, Akkila J, Nieminen MS. Haemodynamic dose-efficacy of levosimendan in healthy volunteers. Eur J Clin Pharmacol 1994;47:267-74.

8. Takahashi R, Talukder MA, Endoh M. Inotropic effects of OR-1896, an active metabolite of levosimendan, on canine ventricular myocardium. Eur J Pharmacol 2000;400:103-12.
9. Ukkonen H, Saraste M, Akkila J, Knuuti J, Karanko M, Iida H, et al. Myocardial efficiency during levosimendan infusion in congestive heart failure. Clin Pharmacol Ther 2000;68:522-31.
10. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803-69.
11. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107-33.
12. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22:6A-13A.
13. Stevenson LW. Are hemodynamic goals viable in tailoring heart failure therapy? Hemodynamic goals are relevant. Circulation 2006;113:1020-7.
14. Zafrir B, Amir O. Beta blocker therapy, decompensated heart failure, and inotropic interactions: current perspectives. Isr Med Assoc J 2012;14:184-9.
15. Mebazaa A, Nieminen MS, Filippatos GS, Cleland JG, Salon JE, Thakkar R, et al. Levosimendan vs. dobutamine: outcomes for acute heart failure patients on β-blockers in SURVIVE. Eur J Heart Fail 2009;11: 304-11.
16. Kirlidis TT, Skoularigis KT, Karayiannis G, Karayiannis G, Tsaknakis TK, Triposkiadis F. The influence of β-blockade on the hemodynamic effects of levosimendan in elderly (≥70 years) patients with acutely decompensated systolic heart failure. Int J Clin Pharmacol Ther 2009;47:454-9.
17. Duygu H, Turk U, Ozdogan O, Akyuz S, Kirilmaz B, Alioglu E, et al. Levosimendan versus dobutamine in heart failure patients treated chronically with carvedilol. Cardiovasc Ther 2008;26:182-8.
18. Bergh CH, Andersson B, Dahlström U, Forfang K, Kivikko M, Sarapohja T, et al. Intravenous levosimendan vs. dobutamine in acute decompensated heart failure patients on beta-blockers. Eur J Heart Fail 2010;12:404-10.
19. Marwick TH. Clinical applications of tissue Doppler imaging: A promise fulfilled. Heart 2003;89:1377-8.
20. Põder P, Eha J, Sundberg S, Antila S, Heinpalu M, Loogna I, et al. Pharmacodynamics and pharmacokinetics of oral levosimendan and its metabolites in patients with severe congestive heart failure: a dosing interval study. J Clin Pharmacol 2004;44:1143-50.
21. Aidonidis G, Kanonidis I, Koutsimanis V, Neumann T, Erbel R, Sakadamis G. Efficiency and safety of prolonged levosimendan infusion in patients with acute heart failure. Cardiol Res Pract 2011;2011:342302.
22. Paksoy F, Ulaş T, Tursun I, Dal MS, Oztekin E, Borlu F. (The effect of levosimendan and dobutamine treatment on QT dispersion in patients with decompensated heart failure: a prospective study). Anadolu Kardiyol Derg 2012;12:16-22.
23. Parissis JT, Rafouli-Stergiou P, Paraskevaidis I, Mebazaa A. Levosimendan: from basic science to clinical practice. Heart Fail Rev 2009;14:265-75.
24. Cavusoglu Y. The use of levosimendan in comparison and in combination with dobutamine in the treatment of decompensated heart failure. Expert Opin Pharmacother 2007;8:665-77.
25. Cohen-Solal A, Logeart D, Huang B, Cai D, Nieminen MS, Mebazaa A. Lowered B-type natriuretic peptide in response to levosimendan or dobutamine treatment is associated with improved survival in patients with severe acutely decompensated heart failure. J Am Coll Cardiol 2009;53:2343-8.
26. Parissis J, Farmakis D, Bistola V, Adamopoulos S, Kremastinos DT. Levosimendan for the treatment of acute heart failure syndromes: time to identify subpopulations of responding patients. Am J Cardiol 2007;99:146-7.