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Original Research Article

Clinical Effectiveness of Intravenous Levosimendan Therapy in the Treatment of Acute Decompensated Heart Failure and Its Effect on Anti-Inflammatory Cytokines, Pro-Inflammatory Cytokines and NT ProBNP

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ABSTRACT

Aim: Clinical effectiveness of intravenous (IV) Levosimendan therapy in the treatment of acute decompensated heart failure and its effect on anti-inflammatory cytokines; pro-inflammatory cytokines and N-terminal pro-brain natriuretic peptide (NT proBNP) were investigated.
Materials and Methods: 19 patients with diagnosis of acute decompensated heart failure in coronary intensive care unit, who has Class III or Class IV heart failure according to New York Heart Association (NYHA) with a NT proBNP level higher than 500 ng/dl and planned to treat with IV Levosimendan, was included to the study.
Results: Compared to pre-treatment baseline values it was found that left ventricular (LV) ejection fraction, LV stroke volume and anti-inflammatory interleukin-10 (IL-10) measured at 72nd hour were significantly increased; LV end-systolic volume, NT proBNP level and pro-inflammatory cytokines – interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α) were significantly decreased. There was no significant difference in complete blood count and biochemical tests. IV Levosimendan therapy in the treatment of acute decompensated heart failure provided rapid hemodynamic and symptomatic improvement. It was found that it significantly decreases pro-inflammatory cytokines which had a role in the progression of heart failure and significantly increases anti-inflammatory cytokines. Levosimendan treatment significantly decreased serum NT proBNP level which shows correlation with ventricular tension level thereby myocardial oxygen demand.
Conclusion: IV Levosimendan therapy used in the treatment of acute decompensated heart failure is an effective, reliable treatment choice which may provide positive contribution to mortality and morbidity of chronic heart failure.

Keywords: Acute decompensated heart failure, levosimendan, cytokines.

INTRODUCTION

Although there isn't a generally accepted definition of acute heart failure, it may be defined as worsening of chronic heart failure triggered by an acute event or may be defined as new-onset heart failure. According to ACC/AHA Task Force Report, acute heart failure is divided into 3 major clinical groups. These groups are acute cardiac pulmonary edema, cardiogenic shock and decompensation of chronic heart failure respectively. [1]

Acute decompensated heart failure is an important state of emergency. It requires treatment with intravenous drugs by hospitalization in acute phase to ensure improvement in hemodynamic status, regression of pulmonary congestion and improvement of tissue oxygenation. We investigated clinical effectiveness of IV

Levosimendan therapy which recently added to the treatment of acute decompensated heart failure and effect of it on anti-inflammatory cytokines, pro-inflammatory cytokines and N-terminal pro-brain natriuretic peptide (NT proBNP).

MATERIALS AND METHODS

Among patients admitted to the cardiology outpatient clinic of Kahramanmaraş Sütçü İmam University Hospital, 19 patients, whom were hospitalized in coronary intensive care unit as acute decompensate heart failure with functional capacity were Class III or Class IV according to NYHA, serum NT proBNP level were higher than 500 ng/dl, ejection fraction were lower than %35 were included in the study. In our study, 5 ml of 1 vial, contains 2, 5 mg/ml Levosimendan preparation (Simdax®) was used, which is owned by Orion Corporation licensed by ABBOTT Laboratories Imp. and Exp. Corporation, and produced in Espoo, Finland.

Unstable angina pectoris, acute myocardial infarction documented in the last 8 weeks, severe stenotic valvular heart disease, uncontrolled thyroid disease, obstructive cardiomyopathy, pericardial disease, active myocarditis, symptomatic primary pulmonary hypertension, chronic obstructive lung disease requiring long-term treatment with beta-mimetic drugs, ventricular flutter, fibrillation or symptomatic ventricular tachycardia, sudden cardiac death, 2nd and 3rd degree atrioventricular block although there is no implanted pacemaker, heart rate more than 115/min within the following 10 minutes, systolic blood pressure more than 200 mmHg or lower than 85 mmHg in supine position, primary renal or hepatic failure (creatinine >2,0 mg/dl, at least twice of the normal serum levels of aspartate amino transferase and/or alanine amino transferase), long QT interval, presence of acute or chronic inflammation, hypokalemia, pregnancy and being younger than 18 years of age were considered as exclusion criteria. Planned treatment protocol was explained to patients and got written permission. Permission was obtained from local ethics committee.

Patients were monitored after hospitalization in coronary intensive care unit. During the term of study, for all patients hourly based blood pressure and pulse records were taken. Pre-treatment and post-treatment blood pressure and heart rate were recorded.

Left ventricular systolic functions were assessed with transthoracic echocardiography technique before and during 72nd hour of treatment of the treatment with Levosimendan. Echocardiographic measurements were performed by Acuson-Aspen® (Acuson Computer Sonography, Mountain, California) brand device with 3.5 MHz probe for all patients. Echocardiographic examinations were performed through views of standard parasternal long axis, parasternal short axis, apical two chambers, apical four chambers and apical five chambers. Left ventricular (LV) end-diastolic diameter, end-systolic diameter, posterior wall thickness, interventricular septum thickness, ejection fraction, fractional shortening, left atrium (LA) and aortic root measures were determined by M-mode of echo which is defined as American Echocardiography Association. [2] Also ejection fraction and stroke volume were calculated by Simpson's method through views of apical two chambers and apical four chambers. [3]

Before and during 72nd hour of Levosimendan treatment, complete blood count, glucose, BUN, creatinine, AST, ALT, Na and K levels were measured. NT proBNP levels were measured by using Biosite® Triage Meter Plus from the blood samples without further processes which were taken into EDTA containing tubes before and during 72nd hour of the Levosimendan treatment.

Before the treatment and during 72nd hour of treatment QT interval was measured

by using Bazett's formula through 12-lead ECG recording. [4] The blood samples taken from patients before the treatment and during 72nd hour of treatment were kept at room temperature till it was coagulated. Then blood serum was obtained by centrifuging in 2000 cycles/min through 10 minutes. This blood serum was stored at -70°C and dissolved immediately prior to analysis. Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-10 (IL-10) and tumor necrosis factor-alpha (TNF-α) were measured by ELISA method (BioSource Europe S.A., 8 B-1400 Nivelles Belgium).

Study Protocol

After patients received 12 µg/kg/min loading dose within 10 minutes, infusion was continued with 0.05 µg/kg/min speed. As from 60th minutes, infusion was continued with 0.01 µg/kg/min speed for 24 hours.

Statistical analysis

Clinical and laboratory data of the patients were divided into two groups as before and after therapy. Demographic, clinical and laboratory values which were obtained from both groups were expressed as mean ± SD. Wilcoxon Test was used for comparison of these values between groups. All statistical analyzes were performed using SPSS 15.0, p value less than 0.05 was considered as statistically significant.

RESULTS

The mean age of patients included in the study was 66±8.5 years. Eight of 19 patients included in the study were male and 11 of them were female. According to NYHA criteria 4 patients had functional capacity of Class IV while 15 patients had Class III symptoms. As a result of transthoracic echocardiography carried out before treatment, left ventricular ejection fraction was found %26±5 and stroke volume was found 46±10 ml. In blood analysis carried out before treatment, NT proBNP level was 1271±878 ng/dl on average. It was found that 12 of patients had Diabetes mellitus or glucose tolerance disorders, 8 of patients had hypertension, 2 of patients had dyslipidemia, 4 of patients had history of myocardial infarction. In electrocardiography taken before starting the treatment; sinus rhythm was observed in 13 patients, atrial fibrillation was observed in 5 patients, and ventricular pace-maker rhythm was observed in 1 patient. The demographic characteristics of the patients were summarized in Table 1.

Table 1: Sociodemographic characteristics of patients

Variable	Total
Age	66±8.5
Gender, Male / Female	8/11
NHYA, Class III	15/19
NHYA, Class IV	4/19
Ejection Fraction (%)	26±5
Stroke Volume (ml)	46±10
NT proBNP (ng/dl)	1271±878
Diabetes Mellitus or Glucose Tolerance Disorders	12/19
Hypertension	8/19
Dyslipidemia	2/19
Myocardial infarction history	4/19
Sinus Rhythm	13/19
Chronic Atrial Fibrillation	5/19
Permanent Pacemaker	1/19

Prior to initiation of Levosimendan infusion treatment and after treatment systolic-diastolic blood pressure and heart rate of 19 patients were compared. It was found that systolic blood pressure (p=0.000) and diastolic blood pressure (p=0.001) were significantly reduced. There was no significant change in heart rate (p=1.0) (Table 2).

In spite of there was no significant change in measurements with M-mode of transthoracic echocardiography prior to initiation of Levosimendan infusion treatment and during 72nd hour of treatment which were left ventricular end-diastolic volume, interventricular septum thickness, left ventricle posterior wall thickness, diameter of aorta and left atrium; we found that reduction in left ventricular end-systolic diameter was statistically significant (p=0.001). In measurements of four chambers which were carried out by transthoracic echocardiography with Simpson method while there was no significant change in end-diastolic volume (p=0.6), there was a significant decrease in end-systolic volume (p=0.0001) and a

significant increase in stroke volume (p=0.0002) and ejection fraction (p=0.0001) (Table 3).

As a result of blood tests done prior to initiation of Levosimendan infusion treatment and during 72nd hour of treatment, while there was no significant change in hemoglobin, hematocrit, glucose, BUN, Cr, AST, ALT, Na, K levels; there was a significant decrease in IL-1, IL-6, TNF- α, NT proBNP values and a significant increase in IIL-10 level (Table 4).

QTc interval was compared with electrocardiography which was performed before Levosimendan treatment and after treatment. There was no significant change in applied doses (Table 5).

Table 2: Vital signs of patients before and after treatment

Variable	N	Before Treatment	After Treatment	P Value
Systolic Blood Pressure (mmHg)	19	136.21±22.8	113.90±18.36	0.000
Diastolic Blood Pressure (mmHg)	19	85.63±12.54	67.73±10.76	0.001
Pulse (Rate/min)	19	85.73±15.08	86.36±14.84	1.00

Table 3: Transthoracic echocardiography findings before starting the treatment with Levosimendan and during 72nd hour of treatment

Variable	n	Before Treatment	72nd hour of Treatment	P value
Left ventricular end-diastolic volume measurement	19	6.35±0.85	6.31±0.82	0.84
Left ventricular end-systolic volume measurement	19	5.51±0.78	5.34±0.90	0.001
Interventricular septum measurement	19	0.99±0.15	1.01±0.21	0.84
Left ventricle posterior wall measurement	19	0.89±0.13	0.88±0.11	0.55
Aorta	19	3.17±0.40	3.24±3.17	0.21
Left atrium	19	4.53±0.62	4.48±0.69	0.85
End-diastolic volume (By Simpson Method) (ml)	19	174.60±36.49	173.68±36.94	0.60
End-systolic volume (By Simpson Method) (ml)	19	128.85±30.35	119.21±28.37	0.0001
Stroke volume (By Simpson Method) (ml)	19	45.76±10.22	54.44±11.38	0.0002
Left Ventricular Ejection Fraction (%)	19	26.00±5.04	31.63±4.42	0.0001

Table 4: Complete blood count, cytokine and biochemical values before starting the treatment with Levosimendan and during 72nd hour of treatment

Variable	N	Before Treatment	72nd hour of Treatment	P value
Hemoglobin	19	12.15±1.42	12.54±1.58	0.08
Hematocrit	19	37.15±4.50	37.80±4.80	0.40
Glucose	19	134.10±59.24	127.15±61.77	0.68
BUN	19	24.63±9.15	23.26±10.40	0.37
Cr	19	1.11±0.30	1.06±0.41	0.08
AST	19	24.94±9.50	24.00±7.49	0.52
ALT	19	40.15±15.72	40.63±14.32	0.95
Sodium	19	140.10±2.55	138.68±3.77	0.40
Potassium	19	4.52±0.42	4.41±0.25	0.30
Il-1	19	4.53±3.34	2.85±0.34	0.002
IL-6	19	41.71±42.33	15.41±21.56	0.001
IL-10	19	8.15±5.09	13.44±8.04	0.02
TNF-α	19	14.47±7.68	5.80±5.99	0.001
NT proBNP	19	1271.31±877.93	338.36±224.80	0.000

Table 5: QTc interval taken by electrocardiography before starting the treatment with Levosimendan and during 72nd hour of treatment

Variable	N	Before Treatment	72nd hour of Treatment	P value
QTc interval	19	430.57±52.42	437.31±49.06	0.34

Table 6: Side effects seen during Levosimendan therapy and following 48 hours

Side effect	Total	Ratio
Headache	3/19	%15.8
Nausea	1/19	%5.3
Hypotension	3/19	%15.8
Requirement of Inotropic Drug	1/19	%5.3
Supraventricular Tachycardia	3/19	%15.8

During the first three hours of initiation of Levosimendan infusion within 24 hours, 3 patients suffered from headache. The pain was not severe so as to require termination of treatment. One patient had nausea which was not accompanied by vomiting. During the treatment 3 patients had hypotension. After one hour break in the treatment, although blood pressure of 2 patients got normal values, dopamine infusion was started as positive inotropic support for one patient. After 4 hours of

dopamine infusion, there was no need to keep dopamine infusion then the treatment was started again. During the treatment 3 patients whom had atrial fibrillation showed an increase of ventricular response time (Table 6).

DISCUSSION

Acute decompensated heart failure is an important state that it requires treatment immediately after hospitalization to ensure stabilization in hemodynamic status, regression of pulmonary congestion and improvement of tissue oxygenation. The aim of short-term treatment is to ensure symptomatically improvement and stabilization of hemodynamic status. Long-term treatment intends to halt the disease progression and to have positively impact on mortality and morbidity. The drugs that used for acute decompensated heart failure treatment are diuretics, vasodilators and positive inotropic drugs. In spite of diuretic and vasodilator drugs provide symptomatic relief in short-term therapy, their effect on long-term mortality and morbidity is very slight. Drugs such as beta adrenergic agonists and phosphodiesterase inhibitors which are used to benefit their positive inotropic effects until today have been found to have negative effects on mortality and morbidity in long-term treatment despite they provide symptomatic relief and hemodynamic stabilization in short-term therapy. This negative effect is thought to be due to increase in myocardial oxygen consumption and susceptibility to arrhythmias because of increasing intracellular calcium and cAMP levels. OPTİME CHF study showed no decreasement of mortality in the group of patients whom treated with intravenous milrinone compared to placebo, and hypotension was more. [5] In the FIRST study monthly mortality ratio was found higher in NYHA Class III-IV patients treated with continuous dobutamine infusion than placebo. [6] In randomized trials comparing Levosimendan and dobutamine it was found that mortality and morbidity were higher in dobutamine taking patients. [7,8] In the SURVIVE study which is the most extensive study comparing mortality of Levosimendan with dobutamine, although it was not statistically significant, mortality was lower. [9] Therefore, studies have gained acceleration to investigate a drug which provides positive inotropic effect without increasing mortality and morbidity besides contributes positive effects.

In this study the clinical effectiveness of Levosimendan, which shows positive inotropic effect by increasing troponin-C sensitivity without increasing intercellular calcium level and peripheral vasodilatation by activating ATP-dependent K channels and which is used in the treatment of acute decompensated heart failure and effect of it on anti-inflammatory cytokines, pro-inflammatory cytokines and NT proBNP were investigated.

Extensive studies which investigated the clinical efficacy and reliability of Levosimendan showed that it increases cardiac output therewithal decreases systemic vascular resistance. It is reported that Levosimendan makes this effect by activating ATP-dependent K channels. In our study we observed that systolic and diastolic blood pressure which was measured immediately after Levosimendan infusion stopped were significantly lower than values which were measured before the treatment and there was no significant change in heart rate. Levosimendan reduces the oxygen needs of myocardium by reducing the workload of heart at failure.

It was found that ejection fraction was significantly increased immediately after termination of Levosimendan infusion at 6^{th}, 24^{th} and 48^{th} hours compared to pre-treatment values with in performed echocardiography. [7,8,10,11] In our study we investigated the situation of this effect at 72^{nd} hour by performing transthoracic echocardiography at pre-treatment and 72^{nd} hour of treatment. In our study, comparison of the 72^{nd} hour to pre-treatment

transthoracic echocardiographic values, we determined that end-systolic diameter which reflects left ventricular systolic function was decreased; stroke volume and ejection fraction was increased significantly. This effect that lasted from 72nd hour of Levosimendan infusion to 48th hour of end of infusion is probably due to OR-1896 metabolite which has approximately 80 hours half-life. [12]

Before the treatment and during 72nd hour of treatment we recorded electrocardiographic measurements of all patients. From these records QT interval was measured by using Bazett's formula. [4] In the study of Kivikko et al, patients were randomized into two groups, through 7 days Levosimendan infusion was done at a rate of 0.05 µgr/kg/min for one group and 0.1 µgr/kg/min for other group, it was found that QTc interval was significantly longer in the group whom received high doses. [12] In dose determination study of Nieminen et al it was shown that at high doses such as 0.4 µgr/kg/min and 0.6 µgr/kg/min QT interval corrected with heart rate prolonged correlatively with dose. [8] In our study the rate of 0.1 µgr/kg/min infusion dose throughout 24 hours appeared to have no significant change in QT interval. Although dosage of optimal therapy has no prolonging effect on QT interval, we concluded to be used carefully in patients whom had long QT interval.

The studies have shown that immune system is continuously active in patients with heart failure. The production of inflammatory mediators from the myocardium with failure has increased independently from the etiology. The elevation in levels of circulating inflammatory cytokines (TNF-α, IL-1β, IL-6) and chemokines (MCP-1, IL-8) reflects this status. [13-17] IL-1, IL-6 and TNF-α are the most important proinflammatory cytokines which play a role in progression of heart failure. [18] Members of the family of IL-6 and TNF-α can make structural changes such as interstitial fibrosis and hypertrophy of myocytes in the myocardium in failure. [18,19] IL-1: There is a general belief that IL-1 together with TNF-α are the prototype of proinflammatory cytokines. In patients with idiopathic dilated cardiomyopathy, it was found that IL-1 level increases and suppresses the myocardial contractility. This effect shows a synergy with TNF-α. Also it was shown that it has apoptotic, hypertrophic and arrhythmogenic effects on myocardium. [18] IL-6: Circulating IL-6 level has been found to be high in heart failure. On one hand it was showed that IL-6 has effects such as myocyte hypertrophy ad myocardial dysfunction. Because TNF-α has a directly effect on release of IL-6, there is a linear correlation in between them. [20] TNF-α: First discovered in 1975 and was called as cachectin. In 1990, Levine and colleagues have found that TNF-α is higher than normal in patients with heart failure. [13] TNF-α is a proinflammatory cytokine. It has effects such as negative inotropic, enhancing endothelial dysfunction, increasing free oxygen radicals. [18,19] IL-10: It is the most important anti-inflammatory cytokine. It suppresses the production of IL-1, IL-6 and TNF-α. Also it suppresses macrophage derived nitric oxide and production of free oxygen radicals. Circulating IL-10 concentrations of patients with heart failure may be increased or decreased compared to healthy individuals. [21] In the randomized, placebo-controlled trial of Parissis et al., circulating proinflammatory cytokines had been found to be significantly lower levels during 72nd hour of Levosimendan therapy. This prolonged effect was evaluated as an indicator of activity of active metabolite OR-1896. [22] In our study, proinflammatory cytokines IL-1, IL-6 and TNF-α levels were found to decrease significantly during 72nd hour treatment compared with baseline values before treatment. We observed that IL-10 level which reduces IL-1, IL-6 and TNF-α blood levels and has anti-inflammatory effect was significantly higher

during 72nd hour treatment compared with baseline values before treatment. These results support evidence for long-term positive effects of Levosimendan therapy for apoptosis of myocytes and positive impact on left ventricular remodeling beside hemodynamic improvement in short-term therapy.

As a compensatory mechanism BNP is secreted in heart failure because of ventricular tension, pressure and volume load. [23,24] Heart failure which caused by left ventricular systolic function disorder, there are correlations between BNP levels and hemodynamic parameters such as pulmonary capillary wedge pressure, ejection fraction. [25] Blood levels of BNP or NT proBNP are used as an indicator in assessing diagnosis of heart failure, determination of disease severity and response of treatment. [26,27] In our study we found that NT proBNP level was significantly lower during 72nd hour treatment compared with values before treatment (p=0.000). There was no significant difference between complete blood count and biochemical parameters during 72nd hour treatment compared with values before treatment.

In LIDO and RUSSLAN studies, the most common side effect was headache which was seen in %7.4 of patients. Then the second common reported side effect was hypotension which was seen in %6.5 of patients. In our study 3 patients had headaches within first 24 hours. One patient had nausea which was not accompanied by vomiting. Within the first 24 hours of the treatment 3 patients had hypotension. The blood pressure of 2 patients got normal values after pause in infusion and then infusion was continued. Despite pausing infusion, the blood pressure of one patient could not have controlled. Then dopamine infusion was started at a rate of 5mg/kg/min. After controlling the blood pressure of patient, Levosimendan infusion was stared again and infusion time is completed to 24 hours. During the infusion, one patient had developed an asymptomatic, short-term supraventricular tachycardia without hemodynamic disorder and it was not severe enough to affect the treatment course. As a result of these observations we concluded that Levosimendan has an acceptable limit for side effect profile.

CONCLUSION

IV Levosimendan therapy in the treatment of acute decompensated heart failure provided rapid hemodynamic and symptomatic improvement. Levosimendan therapy was well tolerated by patients. It was found that it significantly decreases pro-inflammatory cytokines which had a role in the progression of heart failure and significantly increases anti-inflammatory cytokines. Levosimendan treatment significantly decreased serum NT proBNP level which shows correlation with ventricular tension level thereby myocardial oxygen demand. In conclusion with these effects; IV Levosimendan therapy used in the treatment of acute decompensated heart failure is an effective, reliable treatment choice which may provide positive contribution to mortality and morbidity of chronic heart failure.

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