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Full Length Research Paper

The effect of levosimendan on BNP and other myocardial injury indicators in chronic atrial fibrillation cases with heart failure

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To compare effects of levosimendan on brain natriuretic factor (BNP) and other myocardial injury indicators in heart failure (HF) patients with chronic atrial fibrillation (AF) versus sinus rhythm (SR). This study was prospective, double blinded and included a total of 62 chronic HF patients in NYHA III -IV classes. Left ventricular ejection fraction ≤35%, and with either SR (n=38) or AF (n=24) received a 12 g/kg dose of levosimendan. Then they were followed up by IV infusions, as tolerated. BNP, cardiac troponin I, creatinine kinase-myocardial band levels were measured. Age mean (67.5 ± 16.5 years), demographic features and medical history were not significantly different between groups. Diastolic blood pressure was lower (p=0.008), whereas blood urea nitrogen was higher (p =0.03) in the AF group. The frequently used concomitant medication in the AF group was amiodarone (p=0.02). Both systolic and diastolic blood pressures were decreased in the SR Group (p=0.009 and 0.006, respectively). Despite the reduction in systolic blood pressure (p=0.04), diastolic blood pressure remained unchanged in the AF group. Levosimendan significantly decreased BNP levels in the SR group (p=0.002). There was symptomatic improvement and decrease in the NYHA classification among patients in both groups, but no significant difference between groups. Levosimendan did not reduce BNP levels in patients with AF patients, which might be considered as an indicator of a limited efficacy of levosimendan on decompensated, acute HF patients with AF, compared to patients with SR.

Key words: Atrial fibrillation, Brain Natriuretic Peptide (BNP), heart failure, levosimendan, myocardial injury.

INTRODUCTION

Heart failure (HF) is among the leading causes of death in developed countries. Nowadays, the prognosis of HF progressively worsens, despite the wide use of angio-tensin-converting enzyme inhibitors (ACEI), aldosterone antagonists and beta blockers. Intravenous inotropic agents are one of the effective treatment options for patients with advanced decompensation and the use of new positive inotropic agents has decreased the incidence of periodic hospitalization (Silva-Cardoso et al., 2009). Currently, levosimendan therapy is widely being used in patients with decompensated HF (New York Heart Association (NYHA) Class III-IV). Levosimendan is a positive inotropic agent with inodilator effects that enhances the susceptibility of myocardial cells to Ca^{2+} without increasing the level of intracellular Ca^{2+} (Mac Gowan, 2005). Both the drug itself and its metabolites have positive inotropic effect in patients with HF (Gross and Fryer, 2000) . In addition, compared to the standard inotropic agents, it is well tolerated and has a side effect profile similar to placebo at the recommended doses (Follath et al., 2002; Moiseyev et al., 2002).

Atrial fibrillation (AF) is one of the most important causes of decompensation in HF. In the presence of AF, the contribution of left atrium to left ventricular filling disappears, and it is also known that it negatively affects

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the reformation of the ventricle in the long term. Previous randomized studies about levosimendan, generally assess patients with sinus rhythm, excluding patients with AF except few studies (e.g. SURVIVE and REVIVE studies (Mebazaa et al., 2007; Packer et al., 2005) in which AF cases were not excluded but not evaluated separately. Therefore, the present study aimed to investigate the effects of levosimendan on cardiac biomarkers, as well as hemodynamic parameters in decompensated HF patients with chronic AF.

METHODS

From 145 patients treated for heart failure in Cardiology Department at Adana Numune Training and Research Hospital between 2007 to 2008, those (n=62; 37 males and 25 females) with decompensated HF in NYHA class III -IV with a left ventricle ejection fraction (EF) ≤35% who had either sinus rhythm (SR) (n=38) or chronic AF (n=24) were included in the study. Decompensated HF was defined as systolic left ventricular (LV) dysfunction and symptoms of NYHA class III or IV HF that caused hospital admission (Nieminen et al., 2005).

Patients with any of the following criteria were excluded: paroxysmal AF, severe cardiac valve diseases, particularly mitral valve insufficiency of >10, thyroid diseases, pericarditis, myocarditis, acute coronary syndrome, cardiogenic shock, borderline renal function (serum creatinine>1.6 mg/dl), cardiac resynchronization, cardiac pacemaker, initial blood pressure < 80 mmHg, and serum potassium levels < 3.5 or > 5.5. The same person who was blinded to whether the patient had AF or SR, evaluated each patient before and after treatment. The present study was performed after the local ethics committee's approval and written consent were obtained from all patients prior to any study-related procedure.

Study procedures

Prior to levosimendan treatment, all patients underwent transthoracic echocardiographic examination performed with a Vingmed vivid 7 machine. Echocardiographic techniques and calculations were performed in accordance with the recommendations of The American Society of Echocardiography (Schiller et al., 1989). Left ventricular ejection fraction was calculated by using modified Simpson's method. Pre- and post-treatment arterial blood pressures and pulses were recorded; the mean values were calculated from three measurements both prior to and after the levosimendan treatment in AF patients. Blood samples for evaluation of plasma levels of cardiac markers (BNP, cardiac troponin I (cTnI), creatine kinase-myoglobin (CK-MB), myoglobin), as well as routine biochemical parameters were obtained in recumbent position following 30-min resting period before the levosimendan treatment and at the completion of the infusion.

Venous EDTA-anticoagulated blood (4 ml) was collected and centrifuged within 1 h after sampling (1500 × g, 10 min, 25°C), and plasma was stored at −70°C until analyzed. Samples were measured within 3 months after collection. Plasma BNP concentrations were measured on a diagnostic analyzer (Triage Meter Plus equipment, Germany) with the manufacturer's kit for microparticle enzyme immunoassay for human BNP. The detection limit was 5 pg/ml and the upper reference limit. All patients were monitored for their blood pressures and pulses throughout levosimendan treatment. Meanwhile, treatments for AF and HF were being given according to the clinic's routine practice, and digoxin and/or amiodarone to the AF patients for heart rate control.

Levosimendan treatment

A loading dose of levosimendan (12 g/kg) was administered over 10 min, followed by an infusion (0.1 g/kg per min) for 50 min in all patients; the rate was increased to 0.2 g/kg per min for an additional 23 h as tolerated. The maintenance dose was reduced by half, if there was an arterial blood pressure drop to below 80 mmHg during levosimendan infusion, or intolerance to levosimendan. In 3 patients from SR and 2 from AF groups, the infusion lasted 48 h to apply the targeted amount of levosimendan.

Statistical analysis

The patients were dichotomized as having AF or not (SR). All calculations were performed by using SPSS software package version 16.0. Comparisons for categorical variables were done by Chi-square test. For continuous variables, between groups comparisons were done by unpaired t-test or Mann Whitney U test; and within group comparisons by paired t-test or Wilcoxon Signed Rank test. Data were expressed as mean ± standard deviation, median (min- max) and/or n (%) as appropriate. $P < 0.05$ was considered to be significant.

RESULTS

Pre-treatment characteristics

Mean age in all patients was 67.5 ± 16.5 years, and was not significantly different in AF group than SR patients (67.4 ± 9.2 vs 62.87 ± 11.5 years). There was also no difference between the groups in terms of gender distribution, presence of smoking, alcohol consumption, diabetes and hypertension, etiology of HF (that is ischemic heart disease, hypertension, dilated cardi-omyopathy, alcoholic cardiomyopathy, diabetic cardio-myopathy, unknown), pre-treatment systolic arterial blood pressures and pulses (Table 1) . However, diastolic blood pressure prior to levosimendan was significantly lower in the AF group (p=0.008) (Table 1). Left ventricle EF was 26.6 ± 5.5% in AF group, and 29.2 ± 5.0% in SR group; and the difference was not significant (Table 1). Considering blood biochemistry and cardiac markers, there was no difference between the two groups for initial values except blood urea nitrogen (BUN), that was higher in the AF group (p =0.03) (Table 1).

When the patients were assessed for concomitant medications (ACEIs, angiotensin receptor blockers (ARBs), beta-blockers, diuretics, antiplatellets/ anticoagulants, digoxin and amiodarone) they had been using before levosimendan, there was a significant difference between groups only for amiodarone which was found to be used by significantly more patients in the AF group (p=0.02) (Table 2).

Table 1. Demographics, baseline hemodynamic and laboratory findings of the study groups prior to levosimendan treatment. Data are given as "mean ± SD" or n (%) as appropriate.

	AF (n=24)	SR (n=38)	P
Demographics			
Age, years	67.4±9.2	62.7±11.5	0.09
Gender, M/F	11/13	26/12	0.1
Presence of cardiovascular risk factor			
Diabetes	9 (37.5)	12 (31.5)	0.5
Hypertension	7 (29.2)	13 (34.2)	0.8
Smoking	5 (20.8)	12 (31.6)	0.4
Alcohol consumption	0 (0.0)	4 (10.5)	0.1
Etiology of heart failure			
Hypertension	8 (33.3)	12 (31.6)	0.8
Ischemic heart disease	1 (4.2)	1 (2.6)	0.9
Dilated cardiomyopathy	2 (8.3)	3 (7.9)	0.9
Alcoholic cardiomyopathy	4 (16.7)	4 (10.5)	0.5
Diabetic cardiomyopathy	5 (20.8)	12 (31.6)	0.6
Unknown	4 (16.7)	6 (15.8)	0.7
Hemodynamic parameters and echocardiography findings			
Systolic BP, mmHg	110.3±22.3	118.9±27.2	0.2
Diastolic BP, mmHg	61.8±16.9	71.5±11.0	0.008
Pulse, bpm	94.5±36.9	88.5±14.0	0.4
EF, %	26.6±5.5	29.2±5.0	0.07
Serum biochemistry			
BUN, mg/dl	72.0±30.9	55.4±26.7	0.03
Serum creatinine, mg/dl	1.4±0.5	1.4±0.6	0.9
Serum sodium, mEq/L	142.3±6.0	145.5±6.5	0.4
Serum potassium, mEq/L	4.8±0.8	4.6±0.6	0.3
Serum uric acid, mg/dl	7.0±2.1	6.5±1.7	0.4
Cardiac markers in blood			
BNP, pg/ml	1346.1±161.7	1438.9±324.9	0.8
CK-MB, ng/ml	3.4±1.9	5.0±0.8	0.3
cTnI, ng/ml	0.18±0.30	0.21±0.52	0.8
Myoglobin, ng/ml	177.5±139.9	151.5±132.3	0.5

AF: atrial fibrillation; BP: blood pressure; BUN: blood urine nitrogen; BNP: brain natriuretic peptide; CK-MB: creatine kinase-myoglobin band; cTNI: cardiac troponin I; EF: ejection fraction; SR: sinus rhythm;

Effect of levosimendan on hemodynamics and cardiac markers

Compared to baseline, both systolic and diastolic blood pressures significantly decreased after levosimendan therapy in SR Group (p=0.009 and 0.006, respectively) (Table 3). However, diastolic blood pressure remained unchanged in AF group, while there was a significant reduction in systolic blood pressure (p=0.04). Heart rates were not affected by levosimendan in both groups (Table 3). After levosimendan therapy, BNP levels in SR group significantly decreased (pre-treatment: 1438.9 ± 324.9 pg/ml, post-treatment: 894.0 ± 140 pg/ml; p=0.002), whereas it did not change in the AF group (Table 3).

Table 2. Distribution of patients according to the concomitant medication at baseline.

Drugs	AF (n=24) n (%)	SR (n=38) n (%)	p
ACEI	15(62.5)	25 (65.8)	0.8
Aldosteron antagonist	17(70.8)	24 (63.2)	0.6
Allopurinol	3 (12.5)	3 (7.9)	0.7
Amiodarone	12 (50)	7 (18.4)	0.01
ARB	5 (20.8)	4 (10.5)	0.3
ASA	13(54.2)	24 (63.2)	0.6
Beta blocker	7 (29.2)	16 (42.1)	0.4
Digoxin	18 (75)	18 (47.4)	0.04
Furosemid	17(70.8)	26 (68.4)	1.0
Heparin (standard)	10(41.7)	21 (55.3)	0.4
Warfarin	2(8.3)	3 (7.9)	1.0

ACEI: Angiotensin converting enzyme inhibitor; AF: atrial fibrillation; ASA: Acetyl salicylic acid; ARB: Angiotensin receptor blocker; SR: sinus rhythm.

There was also no significant change in other cardiac markers in response to levosimendan in both groups (Table 3). The NYHA class of the patients shifted to lower classes in both groups with levosimendan treatment representing symptomatic improvement, but there was no significant difference between groups in this regard (Table 4).

Safety

A total of 3 patients died approximately 2 days after the initiation of levosimendan treatment; two of pulmonary edema in SR group and one of cerebrovascular accident in AF group. No other adverse events were observed.

DISCUSSION

HF causes peripheral hypoperfusion and pulmonary congestion, as a result of decreased cardiac flow rate. The aim of the treatment in HF is to lessen the symptoms of patients by providing hemodynamic stabilization. For that purpose, positive inotropic agents are being used together with diuretics and vasodilator therapies. Beta adrenergic agonists and phosphodiesterase inhibitors, which are positive inotropic agents, are used in the treatment of advanced decompensated HF, cause myocardial ischemia and cardiac arrhythmia, although they provide rapid hemodynamic improvement (Chatterjee et al., 1994) . The first randomized medium scaled studies regarding levosimendan have shown that, its use in decompensated HF, is more beneficial in terms of both reliability and efficacy than other positive inotropic agents (Follath et al., 2002; Moiseyev et al., 2002). However, this benefit of levosimendan has not been confirmed for the first 6 months of treatment in the later conducted large scaled studies (Chatterjee et al., 1994). In the SURVIVE study, it was found that levosimendan had no superiority over dobutamine, while in the REVIVE study, it had no superiority over placebo (Mebazaa et al., 2007; Packer, 2005). It is possible to monitor the efficacy of agents used in HF cases via clinical, echo-cardiographic and cardiac biomarkers. In our study, the BNP level was measured as a marker in assessing the effect of levosimendan on myocardial functions.

Nowadays, BNP level is routinely being used for diagnosing HF. It provides beneficial information concerning acute phase alterations in cardiac hem-odynamic state (Gardner et al., 2003); it is released by ventricular myocardium as a response to overloading (both for afterload and preload (Nakagawa et al., 1995); and it is accepted as a good indicator for the left ventricular function (McLean et al., 2005) . Additionally, BNP has been found to be important in terms of diagnosis and follow up in patients with both left ventricular dysfunction and HF (Ewald et al., 2008). Besides having a good correlation with EF, pulmonary artery pressure and functional capacity in cases with acute HF (Cowley et al., 2004; McLean at al., 2003), it has been pointed out that BNP is also beneficial in the follow- up of the response to treatment (Gardner et al., 2003). AF is the leading cause in worsening of HF prognosis. It is responsible for decreasing ventricular loading, particularly in patients with impaired left ventricular function. The control of either the rate or the rhythm of AF is a significant contribution to the treatment of HF. The efficacy of levosimendan in HF patients with AF has been minimally investigated until now. In the RUSSLAN study, the number of participants with AF was quite low in both placebo (2.9%), and levosimendan (6.8%) groups, and the AF patients with rapid ventricular response were excluded (Moiseyev et al., 2002). In the LIDO study, the number of AF cases was not reported (Follath et al., 2002). The SURVIVE study, one of the two largest trials of recent days, described a markedly high proportion of AF patients, with a rate of 49% in levosimendan group and 46% in dobutamin group; however, a separate statistical analysis was not done in this subset of patients (Mebazaa et al., 2007). The REVIVE II study focused on addition of levosimendan to standard therapies, and it contributed to the clinical improvement (Packer, 2005). Therefore, in randomized large scaled studies, the effect of levosimendan in HF patients with chronic AF has not been thoroughly studied. Recent studies have suggested that myocardial injury is an important contributor to the mechanism of acutely decompensated HF, and that current therapies should focus on preserving the myocyte, as well as on improving hemodynamic functions (Abraham et al., 2005; Sato et

Table 3. Pre- and post-levosimendan treatment levels of hemodynamic parameters and blood cardiac biomarker levels. Data are given as "mean±SD" and [median (min-max)].

	AF (n=24)			SR (n=38)		
	Pre-treatment	**Post-treatment**	**p**	**Pre-treatment**	**Post-treatment**	**p**
Systolic BP, mmHg	110.3±22.3	101.5±10.2	0.04	118.9±27.2	108.7±21.8	0.009
Diastolic BP, mmHg	61.8±16.9	63.8±14.5	0.6	71.5±11.0	65.8±10.4	0.006
Pulse, bpm	94.5±36.9	90.1±23.2	0.4	88.5±14.0	87.0±16.6	0.5
BNP, pg/ml	1346.1±161.7 [1070 (100-3760)]	1117.7±128.8 [714 (85.5-4000)]	0.2	1438.9±324.9 [981.9 (132-5000)]	894.0±145.0 [705 (84.4-3278)]	0.002
CK-MB, ng/ml	3.4±1.9 [3.3 (0.5-7.3)]	4.0±5.4 [1.8 (0.3-20.1)]	0.6	5.0±0.8 [2.7 (0.4-22.5)]	7.4±1.2 [2.0 (0.3-46.7)]	0.3
cTnI, ng/ml	0.18±0.30 [0.05 (0.0-0.50)]	0.46±1.1 [0.06 (0.0-5.3)]	0.2	0.21±0.52 [0.05 (0.0-2.54)]	0.18±0.36 [0.05 (0.0-13.9)]	0.5
Myoglobin, ng/ml	177.5±139.9 [115 (32.9-486)]	231.7±165.3 [110 (23-1000)]	0.3	151.5±132.3 [104 (22.2-500)]	129.6±172.3 [80 (26.2-1000)]	0.3

AF: atrial fibrillation; BP: blood pressure; BUN: blood urine nitrogen; BNP: brain natriuretic peptide; CK-MB: creatine kinase-myoglobin band; cTNI: cardiac troponin I; EF: ejection fraction; SR: sinus rhythm.

Table 4. Pre- and post-levosimendan treatment NYHA classes of patients with sinus rhythm (SR) and atrial fibrillation (AF). Data are given as n (%).

NYHA class	**AF (n=24)**		**SR (n=38)**	
	Pre-treatment	**Post-treatment**	**Pre-treatment**	**Post-treatment**
II	----	5 (20.8)	----	18 (47.4)
III	10 (41.7)	16 (66.7)	22 (57.9)	18 (47.4)
IV	14 (58.3)	3 (12.5)	16 (42.1)	2 (5.3)
Pre- and post-treatment difference*				
No change	8 (33.3)		7 (18.4)	
1 class lower shift	16 (66.7)		31 (81.6)	

*p=0.229; both groups (AF, SR), pre and post treatment difference have expressed as p value (AF group no change 8 (33.3),SR 7 (18.4) and 1 class lower shift : AF group 16 (66.7), SR 31 (81.6) is not significant (p=0.229).

al., 2006). Compared to sinus rhythm, AF is known to be associated with a higher extent of myocardial damage, since preserved atrial contraction or a regular rhythm, or both, are critical to maintain cardiac output and exercise performance (Pardaens et al., 1997). Myocardial cell necrosis increases in cases with HF depending on the grade of HF. The high level of troponin, which is the most sensitive biomarker of myocardial damage, observed in HF is associated with undesirable outcomes (Yilmaz et al., 2006; Ishii et al., 2002). Some studies suggest that, myocyte destruction occurs in response to increased ventricular pressure or volume in cases with HF (Chen et al., 1999; Stanton et al., 2005). In another trial, the high cTnI level was associated with poor prognosis (Pagel et al., 1996). If levosimendan is injurious to the myocyte, the levels of myocardial markers of injury during treatment of acutely decompensated HF are expected to increase. It has also been stated that cardiac biomarkers, which are indicators of myocardial damage, might be high in the presence of AF (Yilmaz et al., 2006).

However, in the present study, no significant differences were observed between the two groups in terms of basal levels of cTnI, CK-MB and myoglobulin levels; and also in post-treatment levels that should be re-evaluated upon long term levosimendan administration. On the other hand, levosimendan significantly decreased BNP

levels in SR patients while no change was seen in AF group that may be translated as a reduced efficacy in this subgroup of patients. Since basal BNP levels were not significantly different between SR and AF patients, the presence of AF is not likely to affect BNP levels.

Furthermore, pre-treatment pulses and EF values were also similar in two groups. This might be related to the structural remodelling (Thijssen et al., 2000) that causes impaired atrial contractility and electrical changes (Van Wagoner and Nerbonne, 2000) in AF, which would possibly result in reduced response to levosimendan treatment. In addition, the use of amiodarone was significantly higher in AF group compared to sinus group. It is known that amiodarone, a class 3 anti-arrhythmic, has a negative inotropic effect. This might be another factor for the lower response to levosimendan in the AF group.

The severity of HF and the presence of functional mitral regurgitation, may contribute to difference in BNF response between SR and AF patient; however, the distribution of patients according to NYHA classes at baseline and shift to better classes in response to levosimendan, did not significantly differ between groups and patients with severe mitral regurgitation were not included in the study.

Conclusion

The results of our study showed that, short-term use of levosimendan did not reduce cTnI, CK-MB and myoglobulin levels, although a clinical benefit was observed (that is shift to better NYHA classes) in advanced HF cases. On the other hand, a significant reduction could be seen in BNP levels in patients with SR, but not in AF patients. The relation of levosimendan therapy to higher levels of BNP in patients with chronic AF when compared to patients with SR, may indicate the influence of AF itself on the increase obtained in BNP levels. Further studies are needed to evaluate the long term effects of levosimendan in this respect, particularly on NT-proBNP levels, since it is slightly superior in terms of diagnostic and prognostic factors, than BNP (Masson et al., 2006).

LIMITATIONS OF THE STUDY

The small number of patients, particularly in the AF group; difference in amiodarone use between groups and lack of the measurements of left atrial dimensions are the major limitations of our study. In addition, higher mean BUN level in AF group, might indicate relatively worse renal functions that might have some implication on BNP levels, although serum creatinine >1.6 mg/dl were not included in the study.

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