The Evaluation of The Prognostic Effect of NT-Pro BNP Levels and Left Ventricular Ejection Fraction in Acute Decompansated Heart Failure During Levosimendan Treatment

İbrahim IZGU, Gulten TACOY, Guliz ERDEM YAZICI, Yusuf TAVİL,
Timur TIMURKAYNAK, Deniz DEMIRKAN
Gazi University Medical School, Cardiology Department, Ankara, Turkey

SUMMARY

Aim: To evaluate the prognostic effect of serum NT-proBNP levels and left ventricular ejection fraction in patients who have acute decompansated heart failure and receive levosimendan treatment.

Method*:* Fourteen patients (10 male (71,4 %), 4 female (28,6%)) with heart failure who have low cardiac output findings and unresponsive to intravenous and vasodilator therapy, functional capacity NHYA class IV were enrolled into the study. Clinical status, systolic (SBP) and diastolic blood (DBP) pressures as hemodynamic parameters, measurements of serum NT-proBNP, BUN, Cre, Na+, K+, AST, ALT, Hb, Htc levels; left ventricular end diastolic (LVEDD) and systolic (LVESD) diameters, end diastolic (LVEDV) and end systolic (LVESV) volumes, cardiac output and ejection fraction (LVEF) by echocardiographic evaluation were obtained before and after levosimendan infusion

Results: Treatment with levosimendan in decompansated heart failure exerts significantly reduction in LVEDD, LVEDV, LVESV, DBP, serum NT-proBNP levels and increase in LVEF ($p<0.05$). A good correlation between the decrease in NT- pro BNP levels and the increase in LVEF was found ($p<0.05$).

Conclusıon: Levosimendan therapy had beneficial effects in patients with decompensated heart failure. The effectiveness of levosimendan therapy may be monitorised with serum NT-proBNP levels and LVEF.

Key words: Heart failure, levosimendan, NT-proBNP, LVEF.

Akut Dekompanze Kalp Yetmezliği varlığında Levosimendan Tedavisi esnasında NT-pro BNP düzeyi ve Sol Ventrikül Ejeksiyon Fraksiyonunun Prognostik Etkisinin Değerlendirilmesi

ÖZET

Amaç: Akut dekompanze kalp yetmezliği nedeniyle levosimendan tedavisi alan hastalarda serum NT-pro BNP düzeyleri ve sol ventrikül ejeksiyon fraksiyonunun prognostik öneminin araştırılması.

Yöntem: NYHA sınıflamasına göre sınıf IV fonksiyonel kapasiteye sahip, intavenöz ve vazodilatör tedaviye cevap vermeyen ve düşük kardiyak debi bulgularına sahip 14 kalp yetmezliği hastası (10 erkek (%71.4), 4 kadın (%28.6) çalışmaya dahil edildi. Klinik durum, hemodinamik parametreler olarak sistolik (SBP) ve diastolik kan basıncı (DBP) değerleri, serum NT-pro BNP, BUN, kreatinin, Na+, K+, AST, ALT, Hb, Htc düzeyleri,

ekokardiyografik olarak sol ventrikül diastol (LVEDD) ve sistol sonu çapları (LVESD) hacimleri, kardiyak debi ve ejeksiyon fraksiyonu (LVEF) parametreleri levosimendan tedavisi öncesi ve sonrasında elde edilerek karşılaştırıldı.

Bulgular: Dekompanze kalp yetmezliği varlığında, levosimendan tedavisi sol ventrikül diastol sonu çapı ve hacmi, sol ventrikül sistol sonu hacmi, diastolik kan basıncı, serum NT-pro BNP düzeylerinde belirgin azalmaya ve sol ventrikül ejeksiyon fraksiyonunda artmaya neden olmuştur ($p< 0.05$). NT-pro BNP düzeyi ile sol ventrikül EF arasında anlamlı ters ilişki varlığı ortaya konmuştur ($p<0.05$).

Sonuç: Levosimendan tedavisi dekompanze kalp yetmezlikli hastalarda faydalı etkilere neden olur. Levosimendan tedavisinin faydalı etkileri serum NT-pro BNP düzeyi ve sol ventrikül EF parametreleri ile izlenebilir.

Anahtar kelimeler: Kalp yetmezliği, levosimendan, NT-pro BNP, ejeksiyon fraksiyonu

INTRODUCTION

Acute decompensated heart failure is defined as sudden occurrence of symptoms and findings because of abnormal cardiac function**.** The aims of acute heart failure therapy are to improve hemodynamic parameters, to decrease the hospitalization period and the frequency of hospital admissions. Levosimendan is a calcium sensitizer which has two different mechanisms on the cardiovascular system**.** By sensitizing troponin C to calcium, it increases myocardial contractility without increasing cytosolic calcium concentration, and also leads to vasodilation in systemic, coronary arterial resistance, systemic venous capacitance vessels by opening ATP sensitive potassium channels (1,2)**.**

Measuring BNP and NT-proBNP levels secreted from ventricules, due to the distending ventricules by pressure and volume burden, is a guide for the diagnosis and exclusion of heart failure, and also for monitorizing clinical status. BNP is secreted as an 134 amino asit pre-proBNP; then 26 aminoacite peptid is seperated and the the molecule is divided into 108 aminoacite pro-BNP, 76 aminoacite NT- proBNP and 32 aminoacite active hormon BNP. NT-proBNP is inactive, more specific where BNP is biologically active and more sensitive. So BNP is better for the exclusion of heart failure diagnosis, while NT-proBNP has more positive predictive value (3).

The aim of this study is to evaluate the effect of levosimendan therapy on acute decompensated heart failure by monitorizing the change in serum NT-proBNP levels, effects on systolic and diastolic blood pressure, heart rate, echocardiographic parameters, laboratory findings and clinical status.

MATERIALS AND METHODS

The patients who were hospitalized to Cardiology Clinic with decompansated heart failure and left ventricular systolic dysfunction (ejection fraction ≤35%) demonstrated by echocardiograpic and radionuclid ventriculo-graphy were enrolled into the study. They had symptoms and findings of low cardiac output despite intravenous diuretic, angiotensin converting

enzyme inhibitor (ACEI), digoxin and vasodilator drugs; functional capacity class IV according to New York Heart Association. Exclusion citeria consisted of restrictive and hypertrophic cardiomyopathy, cardiac valve disease with uncorrected stenosis, patients with acute myocarditis or pericarditis, patients with acute myocardial infarction or unstable angina pectoris, cardiac tamponade, cardiogenic shock, systolic blood pressure < 85 mmHg, resting heart beat >120 beat/per minute, incessant ventricular tachycardia or being ressuciated previously because of ventricular fibrilation, second or third degree atrioventricular heart block, severe renal failure (Cr level >2,5 mg/dl), severe hepatic failure.

The clinical characteristics, etiology of heart failure, findings of physical examination and treatment regimen that have been applied were recorded. The side effects during infusion and other clinical findings were determined. Two hours before and after levosimendan infusion, echocardiographic evaluation including M-mode and colour doppler were performed with Vivid 7 (GE, Milwake) echocardiography device in left lateral decubitis position. Left ventricular diameters, left ventricular systolic and diastolic wall thickness with M-mode and left ventricular ejection fraction according to Modified Sympson method were calculated.

Before and after levosimendan infusion, blood samples were obtained for the levels NT-proBNP, blood count and electrolites, BUN, creatinine, AST, ALT. NT-proBNP levels were measured with Radyoimmunoassay (RIA) method. Electrocardiograms were obtained from all patients. Non-invasive blood pressures, heart rate were monitorized during infusions. Patients were evaluated for symptoms and physical signs**.** Levosimendan infusion was prepared as 0,025 mg/ml infusion solution. After 12 μg/kg loading dose infused within 10 minutes; 0,1 μg/kg/dk maintenance dose within 24 hours was applied. The infusion rate was decreased to 0,05 μg/kg/min if the patient has symptoms or findings as hypotension, lightheadness, palpitation. Standart appropriate treatment with intravenous diuretics, ACE inhibitors and digoxin or the therapies for coexisting diseases such as anticoagulans, antibiotics and antidiabetics were continued during the levosimendan infusion therapy. The patients monitorized for the side effects (headache, hypotension, palpitation, angina, emesis and vomiting) throughout levosimendan infusion.

Statistical analysis:

A commercially available software (SPSS 11.5 for Windows) was used for the statistical analysis. Continuous data were repoted as median (minimum-maximum), while categorical variables were reported as percentage (%). The significance of changes of the values in time were studied with Wilcoxon sign test or Friedman test. The significances of changes of differences or percentages of parameters within groups were tested with Mann-Whitney U test. A p value of less than 0.05 was considered statistically significant..

RESULTS

Fourteen patients (age 68,9±12,1 years, 10 male (71,4 %) 4 female (28,6%)) with acute decompensated heart failure who were hospitalized in cardiology in-patient clinic and had functional capacity NYHA class IV were enrolled into the study. The etiologies of heart failure were ischemic heart disease in 9 patients (64,3%), nonischemic in 5 patients (35,7%) which were idiopathic dilate cardiomyopathy in 4 patients, rheumatic heart valve disease in 1 patient. Nine patients (64,3%) had hypertension and 9 patients (64,3%) had diabetes mellitus.

All patients treated with intravenous diuretics, ACE inhibitors or angiotensin receptor blocker therapy, four patients received oral nitrates, twelve received digoxin and one received beta blockers. Low molecular weight heparin or warfarin therapy were being applied to the patients with atrial fibrillation.

Levosimendan infusions were interrupted in 2 patients (14,3%) before the 24 hours period. One of them had severe headache and the infusion was interrupted at 16th hour and the other infusion was ended at 14th hour because of symptomatic hypotension. No deaths was observed during infusion**.** Improvement of clinical status after levosimendan infusion was observed in 10 patients (71.4%).

Whenever the electrocardiograms of patients were evaluated, it was seen that nine patients (64,3%) had sinus rhythm; five patients (28.6%) had atrial fibrillation.

The median of NT-proBNP levels of all patients before infusion was 12450 (4042-35000) pg/ml, the median of NT-proBNP levels after infusion was 10535 (1220-35000) pg/ml (p=0,004). There was 29% decrease in NT-proBNP levels after levosimendan infusion (Table1).

The decreases in LVEDD (p=0,034), LVEDV (p=0,028), LVESV (p=0,022) and increase in LVEF (p=0,016) after levosimendan infusion were statistically significant. The value of LVCO was unaffected (p=0,109) (Table I, Figure I).

Table 1. Serum NT-proBNP levels, echocardiographic and hemodynamic parameters.

Parameters	Before infusion	After infusion	P
NT-proBNP (pg/mL)	12450 (4042-35000)	10535 (1220-35000)	**0,004**
LV End diastolic diameter (cm)	6,4 (5,3-7,0)	6,25 (5,2-6,8)	**0,034**
LV End diastolic volume (mL)	196 (125-259)	186 (129-240)	**0,028**
LV End systolic volume (mL)	138,5 (93-193)	141,4 (86-180)	**0,022**
LV Stroke volume (mL)	52 (30-82)	57 (30-84)	0,109
LV Ejection fraction (%)	26 (16-34)	29,5 (18-35)	**0,016**
Systolic blood pressure (mmHg)	110 (90-130)	109 (70-140)	0,270
Diastolic blood pressure (mmHg)	67,5 (50-80)	61,5 (50-75)	**0,018**
Heart rate (beat/min)	88 (72-106)	96,5 (80-108)	**0,010**
The values were given as median, minimum-maximum. LV: Left ventricule			

Heart rate was increased (p=0,01), diastolic blood pressure was decreased (p=0,018), systolic blood pressure was unaffected with levosimendan infusion (Table I, Figure II). The parameters of the laboratory findings are shown in Table II.

When the change in NT-proBNP levels with respect to the etiologies of heart failure were evaluated, 29,9% decrease in the group with ischemic heart failure, 26,6% decrease in the group with nonischemic heart failure were found. There was no difference between two groups. The increase in ejection fraction of patients whose clinical statuses were improved by levosimendan infusion was statistically significant (p<0,05). There was no difference in alterations of LVEF between the ischemic and nonischemic etiologies of heart failure groups.

Table 2 The change of laboratory findings with levosimendan therapy.

Parameters	Before infusion	After infusion	P
BUN (mg/dL)	30,5(11-58)	34,5 (12-74)	**0,031**
Creatinine (mg/dL)	1,3 (0,8-1,9)	1,35 (0,7-2)	**0,030**
Sodium (mEq/L)	137,0 (125-146)	135,5 (123-147)	0,064
Potassium (mEq/L)	4,4 (2,8-5,0)	4,4 (2,7-5,1)	0,813
AST (U/L)	26 (16-68)	25(12-110)	0,682
ALT (U/L)	21 (10-80)	22,5 (8-147	0,694
Hemoglobine (g/dL)	12,7 (9,6-14,8)	12,3 (9,9-14,5)	**0,049**
Hematocrite (%)	37,4 (27,7-45,3)	36,5 (28,6-44,0)	**0,011**
Leucocytesx10^3(cells/µL)	7.90 (3,96-12,50)	7,29 (4,20-14,10)	0,900
Thrombocytesx10^3(cells/µL)	198 (110-348)	202 (92,6-347)	0,286
The values were given as median, minimum-maximum.			

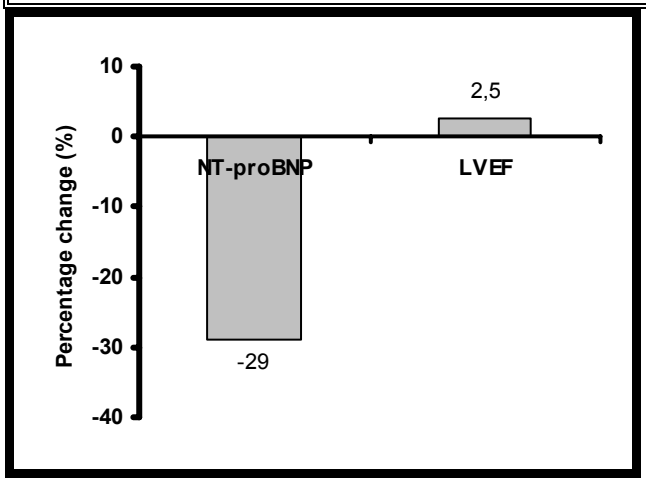

Figure 1: The percentage change of NT-pro-BNP ve left ventricular ejection fraction (LVEF)

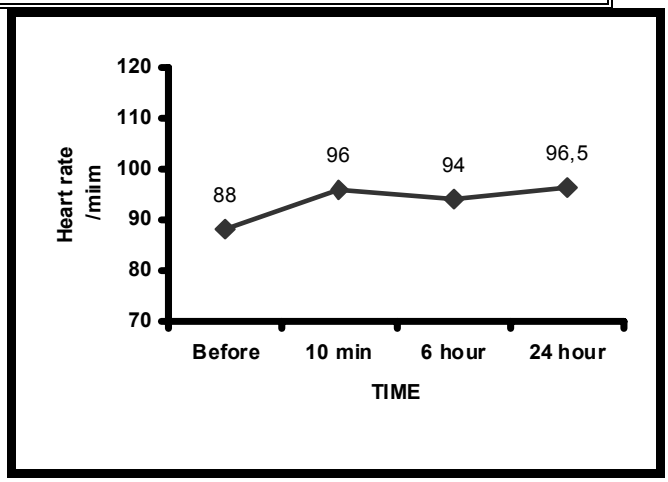

Figure 2: The observation of heart rate during levosimendan infusion

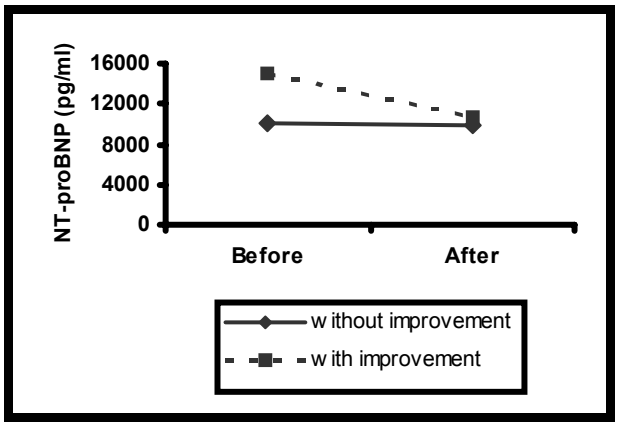

Figure 3. The alteration of NT-pro BNP levels in patients with and without clinical improvement

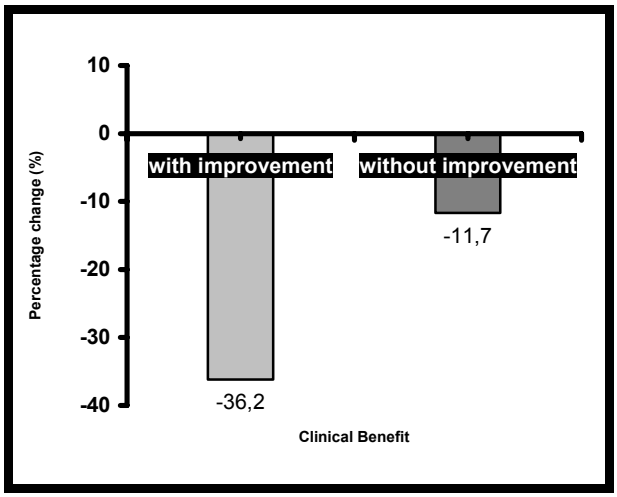

Figure 4. The alteration of NT-pro BNP levels as a percental change in patients with and without clinical improvement.

The decrease of serum NT-proBNP levels in patients whose clinical status improved were 36,2% where it was 11,2% for patients with improvement in clinical status ($p<0,01$) (Figure III and IV). Twelve patients were discharged from the hospital; two patients died because of worsening of heart failure after the end of therapy.

Mortality at 180 day was evaluated in outpatient clinic. At 6th month, no death was observed and beta blocker therapy had been given to all patients without adverse side effects.

DISCUSSION

The short term aims of acute decompensated heart failure therapy are stabilization of the patient, improvement of hemodynamic functions and symptoms. Although there is no enough evidence about the long term benefit of treatment with either diuretics or vasodilators; both of them decrease symptoms. Treatment with inotropic agents can be very helpful in the stabilization of patients and provide serious symptomatic and hemodynamic benefits in the short term. However there are enough evidence about the increase in mortality in long term with the apply of beta agonists and phosphodiesterase inhibitors (4). These limitations reveal the need of new agents that provide symptomatic and hemodynamic improvements without harmfull effects in the long term survival. It has also been shown that the arrangement of heart failure therapy with the guidance of BNP levels decreases the adverse cardiovascular events (5).

In this present study, it has been shown that the infusion of levosimendan therapy decreases the serum NT-proBNP levels. The decrease of NT-proBNP levels in patients with symptomatic improvement was obviously more than the decrease of NT-proBNP levels in patients without symptomatic improvement. In SURVIVE Study, the decrease in BNP levels at 5th day were 46% in levosimendan group and 13% in dobutamin group (6). Serum BNP levels in levosimendan arm were lower than in placebo arm compared to baseline in REVIVE Study (7).

Avgeropoulou et al. evaluated the effect of dobutamin and levosimendan therapy on NT-proBNP levels in 29 decompansated heart failure patients and found that the decrease of pro-BNP levels in levosimendan group were higher than the decrease of proBNP levels in dobutamin group. They showed that serum IL-6 levels were decreased at the end of levosimendan infusion treatment, however no change was observed at TNF-α levels with both therapy (8).

High BNP levels is accepted as a significant predictor of mortality and morbidity for patients with decompensated heart failure and the drug therapies which cause decrease in BNP levels has important roles in prognosis (4). In our study, the serum NT-proBNP levels of all patients were very high. This reflects that the patients enrolled into the study had severe cardiac decompensation. The amount of decrease caused by levosimendan therapy couldn't be shown exactly because of the absence of a placebo arm in the study. The decrease of BNP levels in decompensated heart failure with other drug therapies particularly with loop diuretics also have been shown before (9). Before and after levosimendan treatment the dosage of other drugs given to the patients was not changed. Therefore the decrease in serum NT-pro BNP levels couldn't be explained with usage of diuretics**.** In this present study, independent from the etiology of the heart failure, the decrease in BNP levels with levosimendan infusion was seen.

In this study, we found that levosimendan therapy increased LVEF values. This increase was more remarkable in patients who showed clinical benefit with levosimendan therapy. There is only one study in the literature which shows the benefit of levosimendan therapy over the LVEF; where 6% increased with levosimendan infusion was seen (p=0,006) (10).

Levosimendan treatment was well tolerated by the patients. RUSSLAN and SURVIVE studies found that side effects with levosimendan therapy frequently occured with higher loading doses. In practical usage, to begin with low doses, not to apply loading dose and to adjust the infusion rate with regard to the patient's symptoms are recommended. In this study, most of patients were received 12 μg/kg within 10 minutes as a loading dosage.

There was no change in systolic blood pressure with levosimendan infusion while average 6 mmHg decrease was seen in diastolic blood pressure. This finding is similar with other previous studies. In some studies, there was no change in systolic blood pressure with respect to loading dose of levosimendan infusion, however in either healthy volunteer (4-17 mmHg) or patients with decompensated heart failure (6-11 mmHg) decreases in diastolic blood pressure were obtained (11). In RUSSLAN Study, with high dose levosimendan therapy, average 7,9 mmHg decrease in systolic blood pressure (p=0,012) and average 8,0 mmHg decrease in diastolic blood pressure (p=0,001) were observed (12). There was average 8,5 beat/ minute increase in heart rate after levosimendan therapy in this study. In healthy volunteers which have normal cardiac functions, the 3,8 beat/ minute increase (6-15%) in heart rate was observed after one dose 2-5 mg levosimendan or after levosimendan infusion for 24 hours**.** In patients with decompensated heart failure, an average 2-6 beat/ minute increase (3-8%) was seen

during levosimendan infusion (43). In LIDO Trial, heart rate increased 5,7 beat/ min with levosimendan and 4,0 beat/ min with dobutamine treatment (53). In RUSSLAN Trial, after 6-h levosimendan infusion, heart rate increased with drug dosage, average 11,4 beat/min rise was seen in high dosage group (12).

Atrial fibrillation, incessant ventricular tachycardia weren't be observed in the patients enrolled into our study. In LIDO Trial, there was difference on the development of atrial fibrillation or ventricular tachycardia (2). In SURVIVE Trial, the incidence of atrial fibrillation was reported as higher in levosimendan arm than dobutamine arm (6). In REVIVE II Trial, the frequencies of atrial fibrillation, ventricular tachycardia and ventricular premature beats with levosimendan treatment was more than the placebo group (6).

In our study serum BUN and creatinine levels were increased. In LIDO Trial, with respect to dobutamine, serum creatinine levels were decreased after levosimendan infusion. This decrease was reported as a result of hemodilution because of vasodilation. This conclusion isn't compatible with our study. This disconcordance may be resulted from the intensive diuretic usage with levosimendan infusion. In this present study, there was no change in platelet and leucocyte levels while decrease in hemoglobin and hematocrite levels was observed. This results are similar with LIDO Trial (2). There was no significant difference in serum potassium, sodium and transaminase levels with levosimendan infusion in our study.

The most important limitation of the study is small patient number. However being an only one-centered study and the strict enrollment criterias for patients such as advanced stage and unresponsiveness to standart therapy, the expected number of patients couldn't be reached. Another limitation of the study which was absence of a placebo and/or other therapy strategy was also because of low patient number and absence of longer time period for detection of serum NT-proBNP measurements and evaluation of the prognosis of patients. In this study, after levosimendan infusion, there was a significant decrease in serum NT-proBNP levels. The decrease in serum NT-proBNP concentrations was concordant with clinical improvements. The measurement may be helpful in determining the benefit of levosimendan therapy. Especially in centers where invasive monitorization is not available or for patients whom it is not suitable, NT-proBNP levels can be used for this aim.

Correspondence: *Gülten Taçoy*
Gazi University Medical School
Cardiology Department
Besevler 06500 Ankara TURKEY
Phone:+90 312 2025633
+90 312 2025629
Fax:+90 312 2129012
e-mail:gtacoy@gmail.com

REFERENCES

1. Kopustinskiene DM, Pollesello P, Saris N: EL Levosimendan is a mitochondrial KATP channel opener. Eur J Pharmacol 428 (3): 311-4, 2001.
2. Follath F, Cleland JGF, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet. 360 (9328): 196-202, 2002.
3. Gardner RS, Özapl F, Murday AJ et al. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. Eur Heart J 24:1735-1743, 2003.
4. Greenberg B, Borghi C, Perrone S: Pharmacotherapeutic approaches for decompensated heart failure: a role for the calcium sentitiser, levosimendan? Eur J Heart Fail. 5(1):13-21, 2003.
5. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM: Treatment of heart failure guided by plasma NTproBNP concentrations. Lancet 355(9210):1126-30, 2000.
6. Mebazaa A: The SURVIVE-W Trial: Comparison of Dobutamine and Levosimendan on Survival in Acute Decompensated Heart Failure. American Heart Association Scientific Sessions; Dallas, 2005.
7. Packer M. REVIVE II: Multicenter Placebo-Controlled Trial of Levosimendan on Clinical Status in Acutely Decompensated Heart Failure. American Heart Association Scientific Sessions; Dallas, 2005.
8. Avgeropoulou C, Andreadou I, Markantonis-Kyroudis S, Demopoulou M, Missovoulos P, Androulakis A, Kallikazaros I: The Ca^{+2} sensitizer Levosimendan improves oxidative damage, BNP and pro-inflammatory cytokine levels in patients with advanced decompensated heart failure in comparison to dobutamine. Eur J Heart Fail. 7(5):882-7, 2005.
9. de Lemos JA, McGuire DK, Drazner MH: B-type natriuretic peptide in cardiovascular disease. Lancet. 362(9380):316–22, 2003.
10. McLean AS, Huang SJ, Tang B and Nalos M: Levosimendan benefits critically ill patients with decompensated heart failure assessed with plasma B-type natriuretic peptide (BNP) and LVEF. Critical Care. 7 (Suppl 2)**:**P056, 2003.
11. Innes CA, Wagstaff AJ: Levosimendan. A review of its use in the management of acute decompensated heart failure. Drugs. 63(23): 2651-2671, 2003.
12. Moiseyev VS, Poder P, Andrejevs N, et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction: a randomized, placebo-controlled, double-blind study (RUSSLAN). Eur Heart J. 23 (18): 1422-32, 2002.