Efficacy of levosimendan in patients with chronic heart failure: Does rhythm matter?

Kronik kalp yetersizliği hastalarında levosimendan uygulamasının etkinliği: Ritm önemli mi?

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Abstract

Objective: Levosimendan is a relatively new inotropic agent. Unlike other inotropic agents, Levosimendan does not increase cellular calcium intake, so that, does not cause intracellular calcium overload and related arrhythmias. Atrial fibrillation (AF) was shown to be an independent risk factor for mortality and morbidity in large heart failure (HF) trials. Heart failure induces AF, AF aggravates HF and therefore they generally coexist. We conducted a study to investigate if there is any differential effect of Levosimendan in HF patients with chronic AF and without AF.
Methods: This is a prospective study. Consecutive patients, who were hospitalized because of acutely decompensated HF due to systolic dysfunction and decided Levosimendan administration, were enrolled. Patients were classified into two as those with AF (group A) and those with sinus rhythm (control group, group S). All patients had echocardiography before and after administration. Echocardiographic data were evaluated by ANOVA repeated measurements test.
Results: Baseline left ventricle ejection fraction (LVEF) was poorer in group with AF (mean LVEF for group A: 20.9%, for group S: 26.4%, p=0.04). Baseline diastolic parameters were equally impaired. After infusion, diastolic parameters like velocity of propagation (Vp) and isovolumic relaxation time (IVRT) improved almost to same extent in both groups but deceleration time (DT) did not. IVRT values decreased (p=0.012) both in group S (from 108.6±23.2 msec to 100.4±28.4 msec) and group A (from 117.3±25.1 msec to 92.0±20.9 msec) without a significant difference between groups (p=0.180 for interaction). Another valuable diastolic parameter, Vp was also similarly improved (p<0.01) in both groups to similar extent (for group A, from 35.4±8.8 cm/sec to 41.1±7.7 cm/sec, for group S, from 33.7±7.5 cm/sec to 37.8±7.6 cm/sec; p=0.498 for interaction).
Conclusion: We have shown that in patients with chronic HF and AF, levosimendan improves left ventricular systolic and diastolic functions as good as those with HF and sinus rhythm. We suggest that a positive electrophysiological effect of levosimendan on failing myocardial tissue seems to fill the absence of atrial booster in patients with AF who are on beta-blocker therapy. *(Anadolu Kardiyol Derg 2010; 10: 310-6)*
Key words: Heart failure, levosimendan, atrial fibrillation

Özet

Amaç: Levosimendan, kardiyak kontraktiliteyi arttıran yeni jenerasyon inotropik bir ajandır. Diğer inotropiklerin aksine, levosimendan miyokart hücresinin kalsiyum alımını arttırmadığı için, kalsiyum yüklenmesine ve ilişkili aritmilere sebep olmaz. Atrial fibrilasyonun (AF) kalp yetersizliğinde (KY) mortalite ve morbidite için bağımsız risk faktörü olduğu geniş popülasyonlu çalışmalarla gösterilmiştir. Kalp yetersizliği, AF sıklığını arttırır, AF ise KY'yi kötüleştirir, dolayısı ile genellikle birliktelik gösterirler. Çalışmamızda levosimendan uygulamasının AF ve sinüs ritmindeki hastalarda sistolik-diyastolik fonksiyonlara etkisini karşılaştırdık.
Yöntemler: Çalışma prospektif tipinde dizayn edildi. Akut dekompanse, sistolik disfonksiyona bağlı KY nedeniyle yatırılan ve levosimendan verilmesi planlanan hastalar çalışmaya alındı. Hastalarda AF olup olmamasına göre iki gruba ayrıldılar (grup A ve S). Uygulama öncesi ve sonrası hastaların ekokardiyografik incelemeleri yapıldı. Ekokardiyografik veriler ANOVA tekrarlanan ölçümler testiyle değerlendirildi.
Bulgular: Bazal sol ventrikül ejeksiyon fraksiyonu (SVEF) AF grubunda daha kötüydü (ortalama SVEF, grup A:%20.9, grup S:%26.4, p=0.04). Bazal diyastolik parametreler eşit derecede bozulmuştu, uygulama sonrasında deselerasyon süresi (DT) haricinde, izovolumik kontraksiyon zamanı (IVRT) ve yayılım hızı (Vp) benzer ölçülerde düzelme gösterdi. İnfüzyon sonrası, IVRT değerleri hem grup S'de (108.6±23.2 msn'den 100.4±28.4 msn'ye) hem de grup A'da (117.3±25.1msn'den 92.0±20.9 msn'ye) gruplar arası anlamlı fark olmadan düzelme gösterdi (p=0.012 ve etkileşim için p=0.180). Bir diğer önemli diyastolik parametre olan Vp de iki grupta da benzer (etkileşim için p=0.498) ölçüde düzeldi (grup A için, 35.4±8.8 cm/sn'den 41.1±7.7 grup S için, 33.7±7.5 cm/sn'den 37.8±7.6 cm/sn'ye, p<0.01).

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Sonuç: Çalışmamızda, levosimendanın AF'li ve sinüs ritmindeki hastalarda sistolik ve diyastolik fonksiyonlarda benzer derecelerde düzelme sağladığını saptadık. Bunun nedeninin, levosimendan'ın beta-bloker tedavisi alan hastalarda, hasar görmüş miyokart üzerinde yaptığı olumlu etkiye bağlı olabileceğini düşünüyoruz. *(Anadolu Kardiyol Derg 2010; 10: 310-6)*
Anahtar kelimeler: Kalp yetersizliği, levosimendan, atrial fibrilasyon

Introduction

Levosimendan is a recently introduced inotropic agent, which improves cardiac contractility without increasing myocardial oxygen consumption. Unlike other inotropic agents, levosimendan does not increase cellular calcium intake, so that, does not cause intracellular calcium overload and related arrhythmias (1). Levosimendan binds to N-terminal domain of troponin C and stabilizes the troponin molecule with subsequent prolongation of its effect on contractile proteins (2). Studies show 24-h infusion of levosimendan in patients with severe left ventricular dysfunction improves cardiac functions and relieves symptoms, also causes reductions in short-term morbidity and mortality (3, 4). Levosimendan has electrophysiological effects on myocardium; the drug shortens sinus cycle length and sinus node recovery time, as well as atrioventricular nodal conduction interval and refractory periods (5).

Atrial fibrillation (AF) is a chaotic supraventricular tachyarrhythmia, which causes deterioration of mechanical function. On the electrocardiogram, presentation of rapid oscillations or fibrillatory waves that vary in amplitude, shape and timing are typical. Uncoordinated atrial activations cause an irregular ventricular response (6). The estimated prevalence of AF is 0.4% to 1% in the general population (7), increasing with age to 8% in those older than 80 years (8). It was shown to be an independent risk factor for mortality and morbidity in large heart failure trials (9, 10). Heart failure (HF) induces AF, AF aggravates HF, therefore they generally coexist (11). Atrial fibrillation impairs both systolic and diastolic functions.

Levosimendan was shown to increase incidence of AF in patients with acute decompensated HF (4), whereas starting the levosimendan treatment before cardiac surgery was associated with a higher initial postoperative stroke volume and a lower incidence of postoperative AF (12). In a randomized study (13), it was alleged that left atrial functions respond better to levosimendan than to dobutamine in decompensated HF. Authors suggested that left atrial functions were mainly dependent on left ventricular (LV) diastolic properties and dobutamine exacerbated diastolic dysfunction. In the light of these conflicting results, one could have an idea that patients who were on sinus rhythm would respond better to levosimendan. To our knowledge, available data about levosimendan and AF relationship remains insufficient and conflicting.

Therefore, we aimed to study the effects of levosimendan on left ventricular volumes, global contractility and diastolic function, as well pulmonary artery pressures in patients with heart failure with and without AF.

Methods

Patients

Seventy consecutive patients, who were hospitalized because of acutely decompensated HF with low LVEF, and decided to be administered levosimendan up on judgment of their primary physician, were enrolled into our study after obtaining informed consent within a six-month period (see flow chart). This is a prospective study, patient's primary physician decided to administer levosimendan in a whole study group, and then patients were referred to our study. Patients with left ventricular ejection fraction (LVEF) > 40% (n=3), patients with a recent acute coronary syndrome (within 2 months, n=3), patients with severe impairment of renal function with glomerular filtration rate <30 ml/min (n=2), patients with severely impaired hepatic function (alanine aminotransferase>5 times upper limit of normal), patients with hyperthyroidism and patients with resting heart rate of more than 120 beats/min (n=5, 2 with sinus rhythm, 3 with AF) were excluded from the study. The study was approved by institutional Ethics Committee and written informed consent was obtained before randomization.

The study protocol

The indication for inotropic therapy among patients with low ejection fraction was persisting signs of hypoperfusion despite traditional therapy. All patients had echocardiography, performed by an experienced echocardiographer, who was unaware of study plan, before and after administration. Patients were hospitalized in coronary care unit and monitored by means of electrocardiography, 24-hour urine output, blood pressure. Also, all patients' biochemical work up was done before and after the levosimendan administration. Patients received a loading dose of levosimendan (3-6 µg/kg), then infusion continued 0.1 µg/kg per minute for 50 minutes; the rate was increased to 0.2 µg/kg per minute for an additional 23 hours as tolerated.

Echocardiography

Patients' echocardiographic examination was performed with available ultrasound equipment (GE-Vivid 4 with a 3.5 MHz transducer, Wisconsin, USA) at baseline and 24 hours after the administration. All measurements were performed in conformity with guidelines of American Society of Echocardiography (14, 15, 16). LVEF was measured by the Simpson's rule (14) and systolic pulmonary artery pressure (SPAP) along with respiratory collapse of inferior vena cava for determination of right atrial pressure was calculated as shown previously (15). The isovolumic relax-

ation time (IVRT) is defined as the time interval between aortic valve closure and mitral valve opening, during which LV pressure falls without a change in volume (16). Another important measure of LV diastolic function is the deceleration time of the early filling velocity. The deceleration time (DT) was determined by the slope of the peak left ventricular filling velocity (16). Finally, intraventricular flow propagation was obtained by positioning the scan line across the mitral valve in parallel with LV inflow. The slope (cm/s) of flow propagation of the initial velocity was recorded as Vp (16). LV end-systolic and end-diastolic volumes, mitral early inflow velocity (E) were also recorded and E/ Vp ratio was calculated. All values were the average of 10 measurements for each parameter to get reliable results. All echocardiographic data (before and after levosimendan) were stored on disks, which were only labeled by capital letters randomly without any identification of the patients. Data were analyzed offline by a single experienced reader, totally blinded to records and the study plan. Measurements were then matched accordingly for the analysis. Ten patients in each group were randomly chosen for separate analysis. It was found that intraobserver variability was 7% for systolic parameters and 5% for diastolic parameters.

During infusions, no nephrotoxic agent was allowed (e.g, nonsteroidal anti-inflammatory agents, nesiritide is not available in the country), also no increase in the dose of continuing loop diuretics (only furosemide is available in the country) and no change in the intravenous fluid administration, unless patient had hypotension, were allowed. Other drug therapy and judgment for discharge, determined by status of the patients, were left up on discretion of the primary physicians, who were totally blinded to study outcomes including clinical parameters.

Statistical analysis

Parametric data were expressed as mean (Standard deviation), and categorical data as percentages. SPSS 13.0 (SPSS, Inc., Chicago, Illinois, USA) was used to perform statistical procedures. Baseline continuous clinical variables were compared using t test to independent samples and Mann-Whitney U test, and Chi-square test was used for comparison of categorical variables. Echocardiographic parameters were evaluated by ANOVA repeated measurements test. Temporal change of parametric data except echocardiographic data were evaluated by Wilcoxon signed rank test. A p value $\leq$0.05 was accepted significant.

Results

There were 35 patients with sinus rhythm (Group S), and 22 patients with AF (Group A) included in the analysis. Baseline demographics and clinical characteristics were similar in both groups (Table 1). Twenty seven male and eight female patients (mean age: 65.2±11.2 years) formed group S, while, other twenty one male and one female patients (mean age: 64.7±9.6 years) formed group A. All patients in both groups were on angiotensin converting enzyme inhibitor therapy of efficient doses and beta-blocker therapy of varying doses before levosimendan infusion. Beta-blocker was carvedilol in 6/22 of Group A and 10/35 of Group S; and metoprolol succinate in 16/22 of Group A, and 25/35 of Group S (p=1.00). Digoxin was more prevalent in patients with AF (Table 1). Functional class in both groups before infusions was NYHA Class IV.

Group A had significantly poorer systolic function and lower (p=0.04) LVEF than group S (Table 2). However, after levosimendan infusion, both groups LVEF values were improved (p<0.01 for both groups and p=0.427 for interaction). In addition, IVRT values decreased significantly (p=0.012) both in group S and group A without a significant difference between groups (p=0.180 for interaction). Another valuable diastolic parameter, Vp was also improved (p<0.01) in both groups to similar extent (p=0.498 for interaction). On the other hand, no significant improvement was detected in DT, which is a less valuable marker for diastolic functions than Vp and IVRT, before and after infusion in both groups (Table 2).

Laboratory values after levosimendan infusion did not show significant differences between groups except serum potassium (Table 3).

Table 1. Baseline clinical characteristics

Variables	Atrial fibrillation (n=22)	Sinus rhythm (n=35)	p*
Age, years	64.7±9.6	65.2±11.2	0.867
Male gender, %(n)	95.5 (21/22)	77.1 (27/35)	0.020
Diabetes, %(n)	45.5 (10/22)	45.7 (16/35)	1.000
Hypertension, %(n)	59.1 (13/22)	54.3 (19/35)	0.935
Beta blocker, %(n)	100 (22/22)	100 (35/35)	1.000
ACEI or ARB, %(n)	100 (22/22)	100 (35/35)	1.000
Digoxin, %(n)	63.6 (14/22)	17.1 (6/35)	0.001
Spironolactone, %(n)	100 (22/22)	100 (35/35)	1.000
Furosemide, %(n)	100 (22/22)	100 (35/35)	1.000
Median furosemide dose, mg/day	80 (40-80)	80 (20-80)	1.000

Parametric data are expressed as mean (standard deviation) and median (min-max) values, categorical data as percentages and proportions
*-t test for independent samples, Mann Whitney U and Chi -square tests
ACEI - angiotensin converting enzyme inhibitor, ARB - angiotensin receptor blocker

Table 2. Echocardiographic variables before and after levosimendan treatment

Variables	Atrial fibrillation (n=22)	Sinus rhythm (n=35)	p for factor	F
LVEF before,%	20.9±6.5	26.4±6.3	0.427	0.641
LVEF after,%	26.9± 7.3	31.1±8.4		
p for pairs	<0.01			
F	43.810			
DT before, msec	189.9±78.8	238.8±114.7	0.272	1.241
DT after, msec	203.1±103.5	212.2±87.0		
p for pairs	0.710			
F	0.140			
IVRT before, msec	117.3±25.1	108.6±23.2	0.180	1.891
IVRT after, msec	92.0±20.9	100.4±28.4		
p for pairs	0.012			
F	7.190			
Vp before, cm/sec	35.4±8.8	33.7±7.5	0.498	0.467
Vp after, cm/sec	41.1±7.7	37.8±7.6		
p for pairs	<0.01			
F	18.052			
LVEDV before, cm^3	244.3 ±121.2	169.1±53.5	0.866	0.029
LVEDV after, cm^3	245.8 ±139.7	168.4± 44.5		
p for pairs	0.951			
F	0.004			
LVESV before, cm^3	197.1±108.6	126.4±42.4	0.438	0.611
LVESV after, cm^3	183.7±112.4	121.3± 42.8		
p for pairs	0.090			
F	2.983			
E before, m/sec	1.05±0.30	0.82±0.34	0.458	0.561
E after, m/sec	1.05±0.32	0.75± 0.33		
p for pairs	0.375			
F	0.802			
E/Vp ratio before	0.029±0.00	0.025±0.01	0.648	0.212
E/ Vp ratio after	0.025±0.01	0.020± 0.07		
p for pairs	0.006			
F	8.389			

Data are represented as mean± standard derivation
ANOVA for repeated measurements factorial design test. "p for factor" value represents the interaction between levosimendan administration and the rhythm factor
DT - deceleration time, E - mitral early inflow velocity, IVRT - isovolumic relaxation time, LVEDV - left ventricular end-diastolic volume, LVEF - left ventricular ejection fraction, LVESV - left ventricular end-systolic volume, Vp - ventricular propagation velocity

In terms of side effects, only four of our patients (two in group A, two in group S) experienced mild and asymptomatic hypotension, which was temporary and restored by fluid administration. No patient complained of any type of headache.

Discussion

One of the most life quality-ruining features of HF is AF; studies revealed that AF coexists in up to 30% of these patients (17, 18). Irregular contractions and rapid fastening heart beats cause decrease in left ventricular contractility and filling and impaired relaxation (19-22). Intrinsic contractility of left atrium plays a major role in left ventricular diastolic filling (23). Atrial fibrillation causes loss of atrial contraction therefore atrial contribution to left ventricle filling decreases (24).

In our study, two groups' diastolic functions were equally impaired at the baseline, the two diastolic parameters in both groups (IVRT and Vp) significantly improved after levosimendan

Table 3. Laboratory values before and after levosimendan treatment

Variables	Atrial fibrillation (n=22)	Sinus rhythm (n=35)	p
Serum potassium before, mEq/L	4.4±0.6	4.6±0.6	0.421
Serum potassium after, mEq/L	4.1±0.5	4.6±0.6	0.007
Serum sodium before, mEq/L	135.1±4.7	136.8±4.8	0.240
Serum sodium after, mEq/L	134.4±5.8	135.0±6.2	0.745
Serum creatinine before, mgr/dl	1.10±0.18	1.73±2.76	0.203
Serum creatinine after, mgr/dl	1.11±0.34	1.82±2.58	0.150
Blood urea nitrogen before, mgr/dl	26.8±10.3	28.0±15.9	0.749
Blood urea nitrogen after, mgr/dl	28.1±8.7	32.2±20.6	0.353
Hemoglobin before, gr/dl	13.0±1.6	12.1±1.9	0.160
Hemoglobin after, gr/dl	12.8±1.4	12.1±1.9	0.182

Data were expressed as mean ± standard derivation
t test for independent samples and Wilcoxon signed rank test

infusion (Table 2). Both groups were similar in terms of DT values at baseline and after infusion. Group S showed significant improvement in DT (Table 2), however, DT values ranged widely so that results were not found to be reliable. It has been shown that Vp is relatively independent of loading conditions, so, we thought that it might be more appropriate to consider Vp compared to DT (24). Hence, it would not be inappropriate to state that levosimendan is as effective in improving diastolic functions in patients with AF as in those with sinus rhythm.

In our study, we also appraised a newer parameter, E/Vp, indicating LV diastolic functions and filling pressures. The ratio of E to Vp was shown to be an informative parameter in patients especially with low ejection fraction and comparable with E/E' ratio and Vp alone (25- 29). Before and after infusion E to Vp ratio was not significantly different between the two groups, levosimendan improved E/Vp almost similarly in both groups (Table 2). Before and after infusion values of LV diastolic and systolic volumes decreased in both groups, without statistical importance, however, LVEF was found to increase to similar extent, after levosimendan administration.

Levosimendan is known for its unique arrhythmia-safe effects on myocardial tissue. However, available data in literature for AF and levosimendan relationship is insufficient and conflicting. In a large, randomized and prospective trial, AF incidence was tending to increase with levosimendan administration (4). However, contrary evidence continues to accumulate. In a review by Lilleberg et al. (30) electrocardiogram recordings of HF patients who received levosimendan in ten clinical trials were assessed for any supraventricular or ventricular arrhythmias. Short-term levosimendan therapy did not show tendency for increasing arrhythmias compared to placebo. Authors concluded that levosimendan has an electrophysiologically neutral effect. Recently, in a trial with relatively small patient population (12), authors sought to evaluate the effects of two different administration modalities of levosimendan (started before heart surgery or started at the end of surgery) compared with a standard treatment with milrinone started at the end of operation in patients with preoperative low LVEF (<30%). Starting levosimendan therapy before cardiac surgery was associated with a higher initial postoperative stroke volume and a lower incidence of postoperative AF. Some other authors suggested that beneficial effects of levosimendan in this occasion was related to its anti-inflammatory properties, such as reducing inflammatory cytokines like interleukin-6 and tumor necrosis factor alpha (31). This hypothesis based on anti-inflammatory effect provides a potential underlying mechanism for paroxysmal AF. However, it is still unclear if levosimendan improves LV systolic and diastolic functions in patients with chronic AF as much as in patients with sinus rhythm. We believe that the answer lies not only in the anti-inflammatory properties, but also in the electrophysiological properties of levosimendan.

It is foreknown that levosimendan enhances the sensitivity of myofilaments to calcium by stabilizing the conformational change of troponin C, thus increasing contractile force (1, 2). At high concentrations, the drug inhibits phosphodiesterase type III in vitro, but enhances neither myosin adenosine triphosphatase (ATPase) activity nor intracellular levels of cyclic adenosine monophosphate (AMP) at useful therapeutic concentrations (32, 33). Also, a modest increase in intracellular calcium transient is attributed to selective phosphodiesterase inhibition (34). In a study conducted on healthy individuals, short-term intravenous administration of levosimendan exerted recognizable electrophysiological effects. It shortened sinus cycle length and sinus node recovery time, as well as atrioventricular nodal conduction interval and refractory periods, indicating that levosimendan enhances impulse formation and conduction and accelerates the recovery of excitability in the slow-response tissue. Both atrial and ventricular effective refractory periods were shortened, indicating that the recovery of excitability is enhanced also in the working myocardial tissue (5). In the light of these findings, we can argue about the advantage of atrial booster

effect in patients who are in sinus rhythm over the other group. All patients in our study were on beta-blocker therapy, so we may allege that at least ventricular conduction and sinus node excitations were under control. Besides, these electrophysiological findings were of healthy individuals, that is why we think it would be inappropriate to expect same responses from harmed myocardium of heart failure. An example for this issue could be that the author of aforementioned study (5) suggested that ventricular action potential duration was slightly prolonged. However, in a review (35), it was suggested that levosimendan reduced ischemia-induced ventricular fibrillation in animal models and did not provoke after depolarizations. Authors claimed that, theoretically, levosimendan might reverse the lengthening of action potentials during ischemia by stimulating ATP-dependent potassium current (35). It seems that there is a probability of levosimendan to control rate of inordinate atrial oscillations in a damaged atria while ventricular rate is under control with beta-blocker and/or digoxin therapy. This effect may improve ventricle filling in the absence of atrial booster in AF patients who are on beta-blocker therapy. As mentioned above, our data indicates that levosimendan improves diastolic filling pattern in both sinus rhythm and AF (Table 2).

Study limitations

Main limitations of this study are study design and relatively small patient population. However, our results should be considered as preliminary data. For reaching more certain conclusions, prospective and randomized (double blinded) studies enrolling larger number of patients are needed, since patients with AF are relatively underrepresented in trials with levosimendan. Longer follow up period is essential for reaching substantial data about long term left ventricle functions, morbidity and mortality.

Conclusion

Considering the potential life threatening increase in heart rate following traditional inotropes, and relative safety and efficacy of levosimendan in patients on beta-blocker therapy (4), patients with AF and HF, who are usually treated with combination of digoxin and beta-blocker, seem to be the most suitable candidates for levosimendan if an inotrope is required. It seems that levosimendan improves left ventricular hemodynamics significantly among patients with HF and AF, particularly with the background beta- blocker therapy, and this therapy is efficient as in patients with HF and sinus rhythm.

Conflict of interest: None declared.

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