The European Research Journal

http://www.eurj.org

Original Article

e-ISSN: 2149-3189

DOI: 10.18621/eurj.278899

The effect of levosimendan on Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio and QRS interval in heart failure patients

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ABSTRACT

Objectives. Increased Tp-e interval (from the peak-to-the-end of the electrocardiographic T wave) and Tp-e/QT ratio are associated with malignant ventricular arrhythmias. We aimed to evaluate the acute effects of levosimendan on Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio and QRS interval in patients with severe heart failure. ***Methods.*** The study included 85 patients with decompansed heart failure, who were treated with levosimendan in our cardiology department . We evaluated the patients retrospectively. QT and Tp-e interval were assessed in the precordial leads. QRS duration was determined in the single lead which had the longest QRS. Electrocardiographic measurements was performed the basal (just before the levosimendan) and 24th hour after the levosimendan infusion (just after the levosimendan infusion). ***Results.*** No significant differences were found between before and after treatment of levosimendan with respect to Tp-e and QTc interval, QRS duration, Tp-e/QT and Tp-e/QTc ratio (pretreatment versus 24th hour values; p>0.05). Subgroup analysis was performed in the patients with inotropic therapy including dopamine and/or dobutamin (34 patients) and without inotropic therapy (49 patients) during the levosimendan infusion. The analysis showed that pretreatment and 24th hour values of Tp-e interval and Tp-e/QT ratio were significantly higher in the inotropic therapy group; (Pretreatment; Tp-e: 100.12±22.96 milliseconds [ms] versus 89.59±17.67 ms; p=0.03, Tp-e/QT: 0.26±0.05 versus 0.23±0.04; p=0.007, 24th hour: Tp-e: 101.41±27.09 ms versus 88.77±15.89 ms; p=0.009, Tp-e/QT: 0.26±0.07 versus 0.23±0.05; p=0.03). However intra-group changes of these parameters, before and after levosimendan treatment , were not significant (p>0.05). ***Conclusion.*** Our results suggested that, therapeutic doses of levosimendan infusion don't have a significant effect on Tp-e and Tp-e/QT parameters. However inotropic therapy significantly increases these parameters.

Eur Res J 2017;3(3):220-226

Keywords: Levosimendan, arrhythmia, Tp-e interval, QT interval, heart failure

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Received: December 18, 2016; Accepted: March 27, 2017; Published Online: May 24, 2017

Introduction

Ventricular repolarization is commonly assessed using QT interval and T wave measurements. Recent studies indicated that the Tp-e interval, which is the interval from the peak to the end of the electrocardiographic (ECG) T wave, can be used as an index of the total (transmural, apico-basal, global) dispersion of repolarization. Increased Tp-e interval and Tp-e/QT ratio may be associated with malignant ventricular arrhythmias [1, 2].

Levosimendan is an inotropic agent that improves cardiac contractility without increasing myocardial oxygen consumption. Levosimendan binds to the N-terminal domain of troponin C and stabilizes the troponin molecule with subsequent prolongation of its effect on contractile proteins [3]. Levosimendan is a calcium sensitizer that increases the contractile force of the myocardium by enhancing the sensitivity of myofilaments to calcium without increasing intracellular calcium concentration unlike other inotropic agents [4, 5].

Ambulatory electrocardiographic and electrophysiological evaluation did not detect any pro-arrhythmic effect of intravenous levosimendan [6]. But, according to the REVIVE study, the rate of ventricular tachycardia, atrial fibrillation, and ventricular extra-systoles in the levosimendan group were increased compared to placebo [7]. At this present study, we aimed to evaluate the acute effects of levosimendan on Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio and QRS interval in patients with severe heart failure.

Methods

Study population

A total of 85 consecutive patients with decompansed heart failure, who were treated with levosimendan in our cardiology department were enrolled to our study. Patients with presented New York Heart Association Class IV symptoms and left ventricular systolic dysfunction of ischemic or dilated origin were enrolled to the study. The study was approved by the local ethics committee of our Institute.

Exclusion criteria were: acute or chronic infectious or inflammatory diseases; recent myocardial infarction (<8 weeks) or active myocardial ischemia; hypersensitivity to levosimendan or any of its metabolites, severe renal failure (creatinine >2.5 mg/dl), hepatic failure, 2nd or 3rd-degree atrio-ventricular blocks, overt bundle branch blocks, history of ventricular tachycardia or ventricular fibrillation, heart failure due to restrictive or hypertrophic cardiomyopathy or to uncorrected stenotic valvular disease.

Levosimendan was administered as a continuous 24 hour infusion under continuous haemodynamic monitoring. An initial loading dose of levosimendan of 12 µg/kg was infused over 10 min, followed by a continuous infusion of 0.1µg/kg/min for 24 hours. Thirty-four patients with hypotensive were also treated with concomitant inotropic therapy (dopamine and/or dobutamin) during the levosimendan infusion.

Electrocardiography

Resting 12-lead surface ECG was recorded from all the patients before and 24 hours after the start of drugs infusion. The ECG recordings were obtained at a paper speed of 25 mm/sec. and signal size of 1 mV/cm (ECG machine; Cardiofax M, 1350K, Nihon Kohden, Tokyo, Japan).

We evaluated the patients' ECG retrospectively. The 12 lead ECG was scanned at 600 dpi and ECG parameters were measured on a high resolution computer screen by 2 independent observers blinded to all other patient's data and an average of two measurements was accepted as a final result. The QT interval was measured in as many of the 12 leads as possible. Tp-e interval was assessed in the precordial leads. The Tp-e interval was defined as the interval from the peak to the end of T wave. The end of the T wave was defined as the intersection of the tangent to the downslope of the T wave and isoelectric line. The QT interval was measured from the beginning of the QRS complex to the end of the T wave, and corrected for heart rate by using the Bazett's formula, where QTc = QT/√(RR in seconds). QRS duration was determined in the single lead which had the longest QRS. The ECG measurements performed the baseline (just before the levosimendan) and 24th hour after the levosimendan infusion (just after the levosimendan infusion).

Statistical Analysis

Statistical evaluation was performed using the SPSS program (Statistical Package for the Social Sciences version 10.0, SPSS Inc, Chicago, Illinois, USA). Numerical variants were defined as mean ± standart deviation and categorical variables were

defined as percentage. Continuous variables were compared by Student t-test or Mann-Whitney U test, while categorical variables were compared by chi-square or Fisher's exact test when appropriate. Wilcoxon signed ranks test was used to compare continuous variables before and after drug therapy. Differences were considered significant at $p< 0.05$.

Results

Two patients were excluded because their ECG records were not sufficient. Therefore; we analysed 83 patients. Baseline demographic, echocardiographic and biochemical characteristics of the study patients are shown in Table 1. No significant differences were found before and after treatment of levosimendan with respect to Tp-e interval, QTc interval, QRS duration, Tp-e/QT and Tp-e/QTc ratio (pretreatment versus 24th hour values; Tp-e: 93.85±20.53 milliseconds [ms] versus 93.97±21.97 ms, QTc: 465.49±53.38 ms versus 460.82±53.78 ms, QRS duration: 107.10±31.21 ms versus 107.71±30.69 ms, Tp-e/QT: 0.24±0.05 versus 0.24±0.06, Tp-e/QTc: 0.20±0.05 versus 0.20±0.04) (p>0.05) (Table 2).

Subgroup analysis was performed in the patients with inotropic therapy including dopamine and/or dobutamin (34 patients) and without inotropic therapy (49 patients) during the levosimendan infusion. The comparison of both groups for demographic,

Table 1. Baseline demographic, echocardiographic and biochemical characteristics of the study patients

Parameters	Value
AGE (year)	66.5±10.6
GENDER (male/female)	63 (75.9%)/20 (24.1%)
BMI (kg/m2)	26.2±4.4
SBP [mm Hg]	
Before*	108.7±18.3
After **	104.1±21.5
DBP [mm Hg]	
Before	63.8±10.8
After	62.3±12.1
Heart rate [bpm]	
Before	85±16.7
After	87±17.2
GFR (mL/min)	67.4±29.1
BNP (pg/ml)	1731.2±1138.6
LVEF [%]	23.09±7.05
LVEDD (mm)	59.4±8.1
LVESD (mm)	47±10.1
IVS (mm)	10±2.09
PW (mm)	9.8±1.6
LA (mm)	47.3±6.1
WBC (10^3 /µL)	10489±3791
HgB (g/dL)	11.2±1.7
PLT (10^3 /µL)	234215±88280
GLUCOSE (mg/dL)	141.9±53.5
UREA (mg/dl)	44.6±22.7
CREATININE (mg/dl)	1.26±0.4
AST (IU/L)	44.4±36.7
ALT (IU/L)	54.8±100
Na (mEq/L)	134.1±14.4
K (mEq/L)	4.2±0.5

*before = pretreatment, ** after = 24th hour of treatment, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, GFR = glomerular filtration rate, BNP = B-type natriuretic peptide, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end diastolic diameter, LVESD = left ventricular end systolic diameter, IVS = Interventricular septum, PW = posterior wall, LA = left atrium; WBC = white blood cell count, HgB = hemoglobin, PLT = platelet count, AST = aspartate aminotransferase, ALT = alanine aminotransferase, Na = sodium, K = potassium

Table 2. QRS duration, QTc interval, Tp-e interval, Tp-e/QT and Tp-e/QTc ratio parameters before (pretreatment) and after treatment (24th hour of treatment) of levosimendan.

	Levosimendan (n=83)		*p* Value
	Before*	After**	
QRS duration (ms)	107.10±31.21	107.71±30.69	0.66
QTc interval (ms)	465.49±53.38	460.82±53.78	0.29
Tp-e (mean) (ms)	93.85±20.53	93.97±21.97	0.95
Tp-e/QT ratio	0.24±0.05	0.24±0.06	0.34
Tp-e/QTc ratio	0.20±0.05	0.20±0.04	0.43

*before = pretreatment; ** after= 24th hour of treatment

echocardiographic and biochemical characteristics are shown in Table 3. The analysis showed that pretreatment and 24th hour values of Tp-e interval and Tp-e/QT ratio were significantly higher in the inotropic therapy group; (pretreatment; Tp-e: 100.12±22.96 ms versus 89.59±17.67 ms; *p*=0.03, Tp-e/QT: 0.26±0.05 versus 0.23±0.04; *p*=0.007, 24th hour: Tp-e:101.41±27.09 ms versus 88.77±15.89 ms; *p*=0.009, Tp-e/QT: 0.26±0.07 versus 0.23±0.05; *p*=0.03) (Table 4). However; the QT and Tp-e parameters did not significantly change with levosimendan infusion in both subgroups (inotropic therapy group and without inotropic therapy group) (p>0.05) (Table 4).

Discussion

The results of this present study revealed that the therapeutic doses of levosimendan infusion did not have a significant effect on QRS duration, QTc interval, Tp-e, Tp-e/QT and Tp-e/QTc ratio parameters. Nevertheless levosimendan and concomitant inotropic therapy significantly increase these parameters that the increasing is related with inotropic (dopamine and dobutamine) therapy.

Arrhythmia is one of the disadvantages and a restriction of usage of positive inotropic drugs. Therefore, it is important to determine the proarhythmic potential of any new inotropic agent intended for treatment of the heart failure. Levosimendan is a novel calcium sensitizer which has inotropic effect by increasing sensitivity of Ca2+ in the contraction site. Levosimendan increases the contractile force of the myocardium by enhancing the sensitivity of myofilaments to calcium without increasing intracellular calcium concentration or intracellular cyclic Adenosine Monophosphate (cAMP) [4, 5].

Tp-e interval was evaluated in different patients' population about its arrhythmias prediction [1, 2, 8]. Recent studies showed that the Tp-e interval can be used as an index of the total (transmural, apico-basal, global) dispersion of repolarization and also, increased Tp-e interval and Tp-e/QT ratio may be associated with malignant ventricular arrhythmias [1, 2]. So, at this present study, we aimed to evaluate the acute effects of levosimendan on Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio, and QRS interval in patients with severe heart failure as a proarhythmic potential effect.

Arrhythmic potential of the levosimendan has been previously studied in the several major trials and small-sized studies [9, 10]. The Levosimendan Infusion versus Dobutamine (LIDO) study and the Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarct (RUSSLAN) are the major trials evaluating levosimendan. The RUSSLAN study was a double-blind, placebo-controlled trial conducted in 504 patients who had recently experienced an acute myocardial infarction and the patients were allocated to placebo or one of four dose regimens of levosimendan. At the end of the study, the frequency of atrial and ventricular arrythmias were similar to placebo in all of the four levosimendan regimens and also, the risk of arrhythmic events showed no dose-relation [9]. In LIDO study, 203 patients with severe heart failure randomly received a 24 h infusion with either levosimendan or dobutamine. At dobutamine group, there was a higher rate rhythm disorders [11]. Flevari *et al.* [12] examined effects of short-term levosimendan infusion on ventricular arrhythmias. Forty-five patients with heart failure were randomized to levosimendan or placebo group. 24-hour Holter

Table 3. The comparison of both groups for demographic, echocardiographic and biochemical characteristics

	Levosimendan and Inotropic Therapy (n=34)	Levosimendan (n=49)	*p Value*
Age (year)	67.09±10.8	66.2±10.6	0.72
BMI (kg/m2)	25.4±4.2	26.9±4.5	0.37
SBP [mm Hg]			
Before*	105.6±16.5	110.8±19.3	0.21
After**	106.8±13.5	102.3±25.5	0.37
DBP [mm Hg]			
Before	63.7±11.5	63.9±10.5	0.93
After	63.4±9.4	61.6±13.7	0.52
Heart rate [bpm]			
Before	91.2±16	81±16	0.007
After	95.2±18	82.3±14	0.001
Causes of HF (ischemic /nonischemic)	29/5	39/10	0.50
GFR (mL/min)	62.9±28.8	70.7±29.6	0.45
BNP (pg/ml)	1802.5±590.1	1695.6±1372.4	0.88
LVEF [%]	22.5±5.7	23.5±7.9	0.51
LVEDD (mm)	59.4±7.5	59.3±8.5	0.98
LVESD (mm)	47±9.9	46.9±10.3	0.96
IVS (mm)	10.1±2.2	9.9±1.9	0.64
PW (mm)	9.8±1.5	9.8±1.7	0.94
LA (mm)	47.1±5.9	47.4±6.3	0.81
WBC (10^3 /μL)	10497±3884	10483±3765	0.98
HgB (g/dL)	11±1.3	11.3±1.9	0.56
PLT (10^3 /μL)	232382±84068	235487±91927	0.87
Glucose (mg/dL)	151.5±61.5	133.8±44.9	0.16
Urea (mg/dl)	48.6±23	41.9±22.3	0.19
Creatinine (mg/dl)	1.34±0.46	1.21±0.44	0.18
AST (IU/L)	50.8±50.7	39.9±21.7	0.18
ALT (IU/L)	72.9±148.7	41.9±36.4	0.16
Na (mEq/L)	137.1±6.2	132.1±17.9	0.12
K (mEq/L)	4.1±0.4	4.2±0.6	0.40
Ca (mEq/L)	8.6±0.9	8.9±0.7	0.23
Mg (mEq/L)	2±0.4	2.2±0.2	0.15

*before = pretreatment, ** after = 24th hour of treatment, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, GFR = glomerular filtration rate, BNP = B-type natriuretic peptide, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end diastolic diameter, LVESD = left ventricular end systolic diameter, IVS = interventricular septum, PW = posterior wall, LA = left atrium; WBC = white blood cell count, HgB = hemoglobin, PLT = platelet count, AST = aspartate aminotransferase, ALT = alanine aminotransferase, Na = sodium, K = potassium, Ca = calcium, Mg = magnesium

recording was performed to assess changes in ventricular arrhythmogenesis, 24-hour heart rate variability indexes, QTc, QT variability, and QT/RR slope. Episodes of non-sustained ventricular tachycardia were found increased with levosimendan group (21.9±9.6 versus 3.0±1.2, $p<0.05$) [12]. Lilleberg *et al.* [13] assessed levosimendan to generate cardiac arrhythmias by analysing ECG recordings from clinical studies on intravenously administered levosimendan in heart failure patients. Their database consisted of continuous 1□day recordings, of which 366 were during levosimendan and 142 during placebo comparison. At the end, there was no difference appeared between levosimendan and control groups in the occurrence of atrial fibrillation (12% versus 13%), SVT (28% versus 30%), or VT

Table 4. Subgroup analysis and comparative effects of levosimendan according to inotropic therapy on QT, QTc, Tp-e,Tp-e/QT and Tp-e/QTc ratio parameters.

	Levosimendan and Inotropic Therapy (n=34)	**Levosimendan (n=49)**	***p* Value**
QT interval (ms)			
Before*	385.29±54.72	389.38±57.35	0.74
After **	373.82±51.22	380.20±55.65	0.59
p	0.08	0.14	
QTc interval (ms)			
Before	474.44±59.58	459.82±48.35	0.22
After	476.44±61.48	449.98±45.27	0.02
p	0.60	0.33	
Tp-e (mean) (ms)			
Before	100±22.96	89.59±17.67	0.02
After	101.47±27.09	88.77±15.89	0.009
p	0.98	0.91	
Tp-e/QT ratio			
Before	0.26±0.05	0.23±0.04	0.007
After	0.26±0.06	0.23±0.04	0.03
p	0.44	0.51	
Tp-e/QTc ratio			
Before	0.21±0.04	0.19±0.04	0.06
After	0.21±0.04	0.19±0.03	0.11
p	0.95	0.28	

*before = pretreatment, ** after = 24th hour of treatment

(41% versus 44% of all recordings; all p>0.05) and also the frequency of VT was similar (0.55±3.89 vs 0.20±1.08 episodes/h; *p*>0.05) [13].

In the light of these aforementioned studies, we assessed the short-term effects of levosimendan therapy on QRS duration QTc interval, Tp-e, Tp-e/QT and Tp-e/QTc ratio parameters in surface ECG in 83 patients who had severely depressed left ventricle functions. The analysis showed that levosimendan did not have a significant effect on QRS duration, QTc interval, Tp-e, Tp-e/QT and Tp-e/QTc ratio parameters. So, our analysis supports the previous studies' results that short□term levosimendan therapy of heart failure had no tendency to increase cardiac arrhythmias [14, 15]. We performed subgroup analysis to the patients with inotropic therapy (dopamine and/or dobutamin) during the levosimendan infusion (34 patients) and without inotropic therapy (49 patients). We found that pretreatment and 24th hour values of Tp-e interval and Tp-e/QT ratio were significantly higher in the inotropic therapy group. On the other hand, levosimendan and concomitant inotropic therapy may significantly affect these parameters but actually these alterations were related with the inotropic therapy. Because; the QT and Tp-e parameters did not significantly change with levosimendan infusion in the inotropic and without inotropic treatment group. Paksoy *et al.* [16] investigated the effect of intravenous levosimendan and dobutamine on QT parameters and found that levosimendan and dobutamine did not have a significant effect on QT parameters (16). In our study group we used dopamine/dobutamine and levosimendan concomitant at inotropic therapy. However, Paksoy *et al.* [16] used dobutamine and levosimendan in two different groups separately. QT

prolongation is usually associated with cardiac ischemia. QT is not affected by inotropic therapy unless patients have cardiac ischemia. There was no ischemic event in our study patients. This point could explain our results.

The Limitations of the Study

This study has a number of limitations. Small number of patients, non randomized, retrospective analysis are the major limitations. However our analysis is the first study which evaluate the Tp-e and Tp-e/QT parameters in patients with levosimendan treatment. When viewed from this aspect this study could flash on novel investigations.

Conclusions

In conclusion, our study supported that short□term therapeutic doses of levosimendan infusion for heart failure had no tendency to increase cardiac arrhythmias according to Tp-e and Tp-e/QT parameters. However levosimendan and concomitant inotropic therapy may have arrhythmia potential, that is related with inotropic therapy.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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