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Full Length Research paper

The effect of Levoismendan on the D-dimer level in chronic atrial fibrillation cases with cardiac failure

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We determined the short-term effects of Levoismendan, on the D-dimer level in patient's decompensated heart failure (HF) with non valvular atrial fibrillation (NVAF). The study population consisted of 62 chronic HF patients (24 women and 38 men, mean age: 67.5 ± 16.5 years) with New York heart association (NYHA) III-IV and a left ventricular ejection fraction (EF) lower than 35%. Patients were divided into two groups, group I (sinus rhythm, 38 patients) and Group II (chronic NVAF, 24 patients). A loading dose of Levoismendan (12 µg/kg) was administered over 10 min, followed by an infusion (0.1 µg/kg per minute) for 50 min in all patients, the rate was increased to 0.2 µg/kg per minute for an additional 23 h as tolerated. Plasma cardiac D-Dimer levels were measured at pre-treatment period and 5 days after treatment. Demographic variables were similar in both groups. The difference in hemodynamic parameters was not significant with respect to arterial systolic blood pressure and heart rate. However, diastolic blood pressure was significantly low in the NVAF group (p = 0.008). As for biochemical parameters, while there was no difference in baseline creatinine, serum sodium(Na), serum potassium (K), uric acid (UA) and blood urea nitrogen (BUN) value was detected to be higher in the atrial fibrillation (AF) group (p = 0.03). The left ventricular ejection fraction was 26.6 ± 5.5 and 29.2 ± 5.0% in the group with and without NVAF, respectively, no difference was observed (p > 0.05). The D-dimer levels in the NVAF group were upper than sinus rhythm groups (p > 0.05).However, there was no statistically significant difference between the pre-infusion and post-infusion values of d-dimer 1749 vs. 1824 ng/ml, p = 0.69. Furthermore, plasma D-dimer levels increased after Levoismendan infusion, but D-dimer levels showed non significant correlation with atrial fibrillation group. The clinical improvement as reflected in the patients' NYHA classification was found to be higher in the sinus rhythm group than in NVAF group (p = 0.045). No relationship was found between the NYHA class and the D-dimer levels (p > 0.05) both in general and within the treatment groups. The results of our study show that the effect of Levoismendan on both clinical response and thrombogenicity is limited compared to sinus rhythm in decompensated HF patients with NVAF in the acute period. Further studies are required to evaluate the results of this association in the long-term.

Key words: Levoismendan, atrial fibrillation, heart failure, D-dimer

INTRODUCTION

Positive inotropic agents are used in patients with heart failure who do not respond to standard treatment. Levoismendan, an agent that exhibits positive inotropic effect without increasing the intracellular calcium level through its inodilator efficacy, is widely used today in cases with heart failure (HF). The guideline of the European Society of Cardiology suggests Levoismendan for the treatment of acute HF (Nieminen et al., 2005).The initial trials on Levoismendan (Lido, Rusllan) (Follath et al., 2002; Moiseyev et al., 2002) demonstrated that this agent decreased mortality, whereas two recent large randomized trials did not reveal any superiority to Dobutamin or Placebo. The AF rate was very low in the initial trials, but

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quite high in the last two trials (Survive, Revive) (Mebazaa et al., 2007; Packer, 2005).

Atrial fibrillation is the leading parameter for the poor prognosis of HF (Tribouilloy et al., 2010). It exhibits this efficacy particularly by decreasing the ventricular filling in patients with left ventricular dysfunction (Doumas et al., 2010) Atrial fibrillation adversely affects heart failure by leading to contractile dysfunction as a result of myocardial remodelling (Sridhar et al., 2009) At the same time, tendency towards coagulation increases due to left atrial stasis (Watson et al., 2009) Many potential prothrombotic factors exist. One such plasma factor, is the fibrin D-dimer fragment, reflects intravascular turnover of fibrin. D-dimer level provides information on the status of hyper-coagulability (Ohara et al., 2008). The presence of high fibrin D-dimer suggests ongoing fibrin degradation in patients with chronic atrial fibrillation (AF). In recent study it shows that is a drug suppressing D-dimer concentrations in patients with chronic atrial fibrillation (Ezekowitz et al., 2007). This study was designed to investigate the short term effects of Levoismendan on D-dimer among heart failure patients with or without NVAF.

PATIENTS AND METHODS

Study population

The effect of Levoismendan was analyzed for two groups of patients whether they had NVAF (24 patients) or sinus rhythm (38 patients).The group with atrial fibrillation was of non-valvular and chronic form. Prior to the procedure, cases with paroxysmal AF, severe valvular disorders, thyroid diseases, pericarditis, myocarditis, a baseline blood pressure ≤ 80 mmHg, a serum potassium level < 3.5 and >5.5 acute coronary syndrome, cardiogenic shock, borderline renal functions (creatinine > 1.8 mg/dl), cardiac re-synchronization, cardiac pacemaker, thrombus in the cardiac cavities, deep vein thrombus with spontaneous echo contrast and suspected pulmonary embolus were excluded from the trial.

Study procedures

Arterial blood pressure and heart rate values of the patients were measured three times before and after treatment with Levoismendan and the mean value were obtained. Blood samples were withdrawn before Levoismendan treatment and at day 5 for cardiac markers and biochemical parameters. Meanwhile, routine treatment for atrial fibrillation and HF was resumed.

Left ventricular ejection fraction was calculated by using modified Simpson's method. All echocardiographic examinations were performed within 2 h before the start of infusion and repeated at the end of 5days.The study was performed using Vingmed vivid 7 equipment echocardiography device (GE Healthcare, Chalfont St. Giles, Bucks, UK). Echocardiographic evaluations were performed according to the criteria of the American Society of Echocardiography (Lang et al., 2005).

For positive inotropic support, Levoismendan (Simdax Abbott Laboratories) infusion was administered to all cases, at the dose of 12 mcg/kg for 10 min for loading and at the dose of 0.1 mcg/kg/min for maintenance. The maintenance dose was reduced by half in cases with arterial systolic pressure decreasing below 80 mmHg during Levoismendan infusion or those who cannot tolerate the dose. All the patients were monitored for pulse and blood pressure before and after treatment. The New York heart association class determined all patients pre and before Levoismendan infusion. In patients with NVAF who had not been treated with anticoagulants previously, we started standard heparin small part patients had taken warfarine (2, 8.3%) Digoxin or amiodaron were administered to the group with fast atrial fibrillation for rate control. In spite of digoxine therapy could not controlled AF rate which is added amiodarone. Fibrin D-dimer was measured before treatment and after treatment. Blood samples were drawn from the antecubital vein anticoagulated with trisodium citrate and centrifuged. Blood samples were stored at -70°C to analysis. Fibrin D-dimer values were investigated by triage meter plus device (made in Germany) this method of coefficient of variation is < 5%. The investigators and attending physicians were blinded to the D-dimer test results. Written consent was obtained from the local ethical committee and the patients before the trial was conducted.

Statistical analysis

All calculations were performed with SPSS 11.5 program (SPSS, Chicago, IL, USA). Categorical variables were tested by Chi-square test. Categorical analyses are expressed as numbers (n) and percentage (%), whereas continuous measurements are given as mean and standard deviation. The effects of Levoismendan on continuous variables were studied by the paired student's t test. Data were expressed as mean ± standard deviation. P value < 0.05 was considered to be significant.

RESULTS

Sixty-two patients (38 males and 24 females) with a mean age of 67.5 ± 16.5, who did not respond to standard treatment of heart failure (NYHA III-IV and ejection fraction < 35%) were included to the study. Five days after the procedure, three patients died, one with NVAF due to cerebrovascular event and two patients in the sinus group due to pulmonary edema. Demographic characteristics were demonstrated in (Table 1). The mean age was observed to be slightly higher in the NVAF group (67.4 ± 9.2 years) compared to the sinus group (62.87 ± 11.5 years) (p = 0.09). There was no difference between two groups with respect to gender distribution, diabetes mellitus, hypertension, smoking and alcohol consumption (p > 0.05).

The evaluation of other drugs, which were being used by the patients before Levoismendan revealed that amiodaron was used statistically more in the atrial fibrillation group (p = 0.02). Although digoxin was used more in the AF group, this increase did not reach a level of statistical significance (p = 0.06). In addition, use of angiotensin-converting enzyme inhibitors (ACEIs), furosemide, spironolactone, b-blockers, an angiotensin receptor blockers (ARBs), warfarin and ASA showed similarity between the groups (Table 3).

Table 1. Demographic and laboratory findings of groups.

	AF(+) (n=24)	AF(-) (n=38)	P
Age, years	67.4 ± 9.2	62.7 ± 11.5	0.09
Gender, M/F	11/13	26/12	0.1
DM, (%)	9 (37.5)	12 (31.5)	0.5
HT, (%)	7 (29.2)	13 (34.2)	0.8
Smoking, (%)	5 (20.8)	12 (31.6)	0.4
Alcohol, (%)	0 (0.0)	4 (10.5)	0.1
Diastolic BP, mmHg	61.8 ± 16.9	71.5 ± 11.0	0.008*
Heart rate, beat/min	94.5 ± 36.9	88.5 ± 14.0	0.4
EF, (%)	26.6 ± 5.5	29.2 ± 5.0	0.07
BNP	1346.1 ± 161.7	1438.9 ± 324.9	0.8
BUN	72.0 ± 30.9	55.4 ± 26.7	0.03*
Cr	1.4 ± 0.5	1.4 ± 0.6	0.9
Na	142.3 ± 6.0	145.5 ± 6.5	0.4
K	4.8 ± 0.8	4.6 ± 0.6	0.3
UA	7.0 ± 2.1	6.5 ± 1.7	0.4

Results are expressed as mean ± SD DM:Diabetes mellitus, HT: Hipertension, EF: Ejection fraction, BNP:brain natriuretic peptide, cTnI: cardiac troponin I, Myo: myoglobin, BUN: blood urea nitrogen, Cr: serum creatinine, UA: serum uric acid, K: serum potassium, Na: serum sodium.

Table 2. Relationship between pre and post Levoismendan treatment levels of D-dimer and hemodynamics in patients with heart failure.

	AF (+)			AF(-)		
	Pretreat	Posttreat	p	Pretreat	Posttreat	p
TA sys (SD)	110 (23)	101(10)	0.027	118 (27)	108 (22)	0.027*
TA dia (SD)	62 (17)	64 (15)	0.658	71 (12)	65 (10)	0.013*
Heart rate	96 (37)	91 (23)	0.303	89 (14)	88 (16)	0.712
DD (SD)	2014 (321)	2433 (562)	0.314	1592 (225)	1464 (217)	0.489
NYHA	3.56(.50)	3.41 (0.49)	0.244	2.91(0.12)	2.58(0.59)	0.045

TA sys: systolic arterial blood pressure (mmHg), TA dia: diastolic arterial blood pressure (mmHg), Heart rate (per/minute), DD:D-dimer, NYHA ,New York Heart Association.

Comparison of the effect of Levoismendan treatment

After Levoismendan treatment, (Table 2) arterial systolic blood pressure values were significantly reduced compared to baseline in both groups (p = 0.02, Table 3). Diastolic blood pressure remained the same in the atrial fibrillation group (p = 0.65), whereas detected to be significantly low in the patients with sinus rhythm (p = 0.01, Figure 1). The sodium level after Levoismendan infusion was found to be significantly lower (144 vs 140, p = 0.006, troponin (0.17 vs 0.51 ng/ml, p = 0.15), brain natiuretic peptide (235 vs. 281 pg/ml, p=0.33), miyoglobin (167 vs. 170, p=0.91), creatinine phosphokinase MB (4.12 vs. 3.76, p=0.59), urea (61 vs. 62 mg/dl, p=0.78), creatinine (1.35 vs. 1.37 mg/dl, p=0.67), uric acid (6.6 vs 6.7 mg/dl, p=0.65), potassium (4.7 vs. 4.5 mEq/L, p=0.14).

The effect of Levoismendan treatment on the plasma D-dimer levels

The baseline D-dimer levels of each group are shown in (Table 2).The D-dimer levels in the NVAF group were upper than sinus rhythm groups (p > 0.05). However, there was no statistically significant difference between the pre-infusion and post-infusion values of d-dimer (1749 vs. 1824 ng/ml, p = 0.69 and Table 2, Figure 2). Furthermore, plasma D-dimer levels increased after Levoismendan infusion, but d-dimer levels showed non significant correlation with atrial fibrillation group). The

Table 3. Distribution of drugs used by patients with heart failure according to the groups.

Drugs (%)	AF (+)	AF(-)	P
ACE-I*	15 (62.5)	25 (69.4)	0.5
Furosemid	17 (70.8)	26 (72.2)	1
Beta blocker	7 (29.2)	16 (44.4)	0.2
Digoxin	18 (75)	18 (50)	0.06
Aldosteron ant	17 (70.8)	24 (66.7)	0.7
Amiodaron	12 (50)	7 (19.4)	0.02
Nitrat	9 (37.5)	17 (47.2)	0.5
ARB**	5 (20.8)	4 (11.1)	0.4
Statin	1 (4.2)	2 (5.6)	1
Heparin	10 (41.7)	21 (58.3)	0.2
Allopurinol	3 (12.5)	3 (8.3)	0.6
ASA***	13 (54.2)	24 (66.7)	0.4
Warfarin	2 (8.3)	3 (8.3)	1

ACE-I* = Angiotensin converting enzyme inhibitors, ARB** = Angiotensin receptor blocker, ASA*** = Acetyl Salicylic Acid.

clinical improvement as reflected in the patients' NYHA classification was found to be higher in the sinus rhythm group than in NVAF group ($p = 0.045$; Table 2).No relationship was found between the NYHA class and the D-dimer levels ($p > 0.05$) both in general and within the treatment groups.

DISCUSSION

Levoismendan increases myocardial performance during systole without increasing the cardiac rhythm and myocardial oxygen consumption (Haikala et al., 1995).This effect was detected to decrease the left and right cardiac filling pressure and the systemic arterial pressure in cases with decompensated HF (Sundberg et al., 1995). Previous studies have shown that atrial fibrillation have abnormalities in prothrombotic or hypercoagulable state that may contribute to this risk of thromboembolism (Kumagai et al., 1990; Gustafsson et al., 1990).

This study was designed to detect whether there was a change in thrombolytic activity after Levoismendan therapy in cases with heart failure ((NYHA II-IV) with atrial fibrillation. D-dimer levels provide information not only on activation of fibrinolysis but also on the status of hypercoagulability. D-dimer level was suggested to be an important indicator of mortality and prognosis (Marcucci et al., 2006; Habara et al., 2007). D-dimer level is reported to be high also in AF cases without heart failure (Mahé et al., 2004). Another trial detected that it was an independent cardiovascular risk factor in heart failure cases with an ejection fraction (EF) below 40%, it may provide additional prognostic information in patients with heart failure (Alehagen et al., 2004). Coagulation and fibrinolytic activity is increased along with the accumulation of the risk factors of thromboembolism in NVAF patients (Ohara et al., 2008). D-dimer level was clinically useful to guide the management of patients with NVAF, especially for those complicated with congestive heart failure (Habara et al., 2008). In the this study we analyzed D-dimer levels as a screening index of a hyperclotting state of atrial fibrillation and using Levoismendan in advance heart failure. Patients with AF have increased thrombogenesis compared with patients in sinus rhythm. Recent studies have shown that compared with patients in sinus rhythm, patients with AF have abnormalities that contribute to hypercoagulable state. The abnormalities in fibrin D-dimer in patients with AF have been found to be independent of underlying origin or structural heart disease (Lip et al., 1995).This study demonstrated high plasma levels of fibrin D-dimer, patients with chronic AF. Our findings of high D-dimer in AF are consistent with previous reports (Kumagai et al., 1990; Gustafsson et al., 1990). After Levoismendan treatment decreased d-dimer levels on sinus rhythm but it was not a significant reduction, however it was detected to improved in NHYA functional class on sinus rhythm compared to the AF group. In our study, changing D-dimer levels was fewer in AF group compared to the sinus rhythm. But no difference were observed between before and after using of Levoismendan of both groups on D-Dimer levels.

The lack of long-term results in D-dimer levels may in part a reflection of the AF compared with that of the sinus rhythm. We did not relate d-dimer levels to underlying clinical risk factors (age, hypertension and diabetes mellitus) or assessments of left ventricular function, because previous trials have indicated that there was no significant relationship between D-dimer and medical history or other cardiac disfunction in patients with AF (Kumagai et al., 1990; Lip et al., 1995). D-dimer levels are reported to increase with age (Hager and Platt, 1995). However, D-dimer levels in patients with chronic AF remain in the same range over time irrespective of age. Thus, D-dimers appear to be a useful parameter for assessing the degree of hypercoagulability of patients whatever their age (Mahé et al., 2002). D-dimer levels that may also increase as a result of other conditions such as in renal and liver failure, infection, neoplastic disease,acute coronary syndromes and the presence of this co-morbidit conditions should exclude. We could not detect any relation to AF, hyperclotting state change of D-dimer levels after using Levoismendan in HF .we do not perform other risk factor measurement (left atrial and ventricular size).This probably is due to our inability to study.

Anticoagulation therapy with warfarin has been shown to significantly reduce plasma fibrin D-dimer levels in AF (Lip et al., 1996). However, D-dimer level in combination with clinical risk factors could effectively predict subsequent thromboembolic events in patients with NVAF

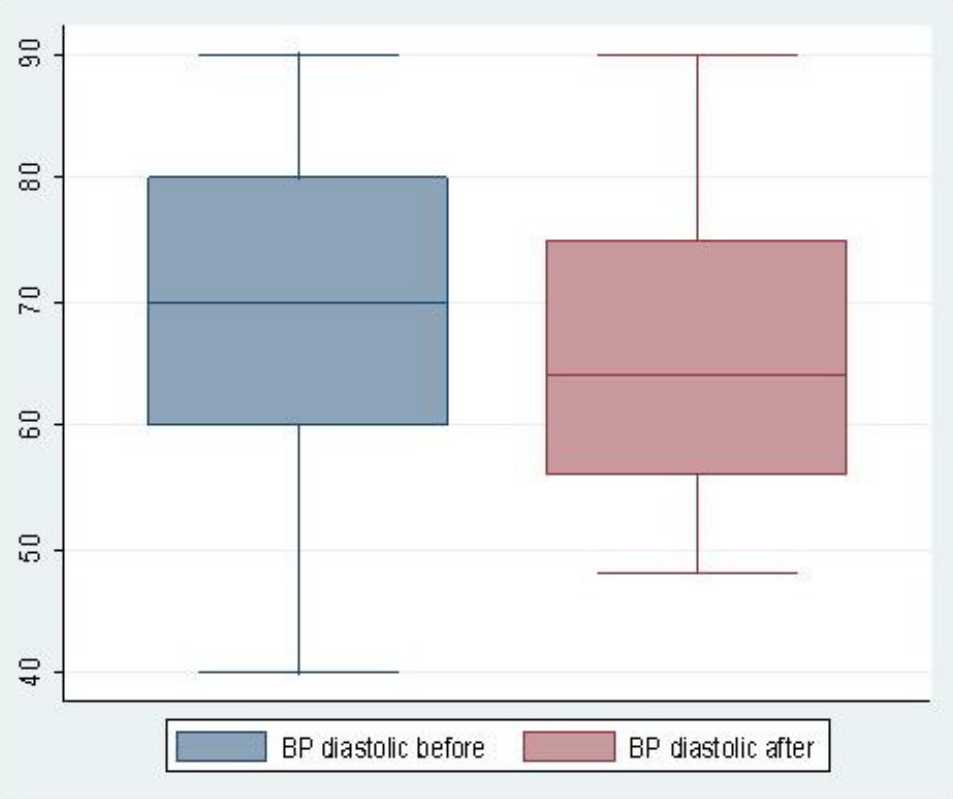

Figure 1. Blood pressure before and after Levoismendan among the patients with no AF.

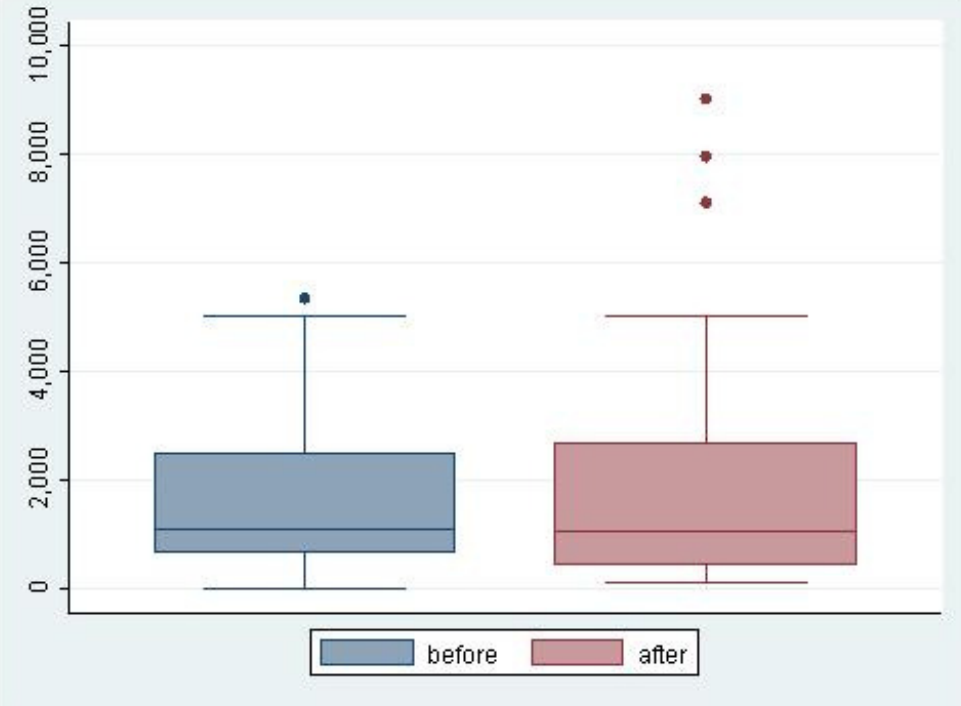

Figure 2. D-Dimer leves before and after Levoismendan among the patients with AF and no AF.

even when treated with warfarin (Nozawa et al., 2006). In our study, the effect of long-term outcomes after Levoismendan treatment on thrombogenicity and mortality in heart failure cases with atrial fibrillation was not evaluated.

Further studies are required to evaluate the results of this association in the long-term.

Conclusion

The present results confirmed that high levels of fibrin D-dimer levels were present in patients with AF compared with sinus rhythm. The results of our study show that the effect of Levoismendan on clinical response is limited compared to sinus rhythm in decompensated HF patients with AF in the acute period, but in this study no significant correlations between Levoismendan and plasma concentrations of D-dimer.

STUDY LIMITATIONS

This study is limited by the relatively short follow-up period D-dimer levels in patients given Levoismendan. In addition, the small number of patients entering AF group, we did not relate abnormalities of thrombogenesis risk to detailed other echocardiography measurements (left atrial size, ventricular size). The problem of this study is the fact that it is not randomized.

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