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Research Article

The Effect of Positive Inotropic Therapy on Serum Adiponectin Level in Patients with Acute Decompensated Heart Failure

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Abstract

Objectives: Our aim in this study is to investigate the effect of levosimendan and dobutamine treatment on serum adiponectin levels in patients with acute decompensated heart failure (ADHF) who need positive inotropic therapy.

Methods: This study included 44 patients with ADHF who had a functional capacity (FC) of 4 according to NYHA, and had a positive inotropic treatment indication with a left ventricular ejection fraction (LVEF) of less than 35% on echocardiography. LVEF, serum adiponectin level, BNP level, pulmonary artery systolic pressure (PAP) and FC measurment of the patients were taken before the treatment and on the third day of the treatment. The delta (Δ) value, which is the difference between the basal and post-treatment values of these parameters, was calculated.

Results: A decrease in serum adiponectin after treatment was observed in the levosimandan group (p=0.029). In addition, when the rates of change in LVEF (p=0.001), PAP (p=0.005), FC (p=0.041) between both treatment arms were compared, the improvement resulted in favor of levosimendan for these parameters as well.

Conclusion: Adiponectin, which increases proportionally with the severity of HF and is associated with mortality, decreases more with levosimendan treatment than dobutamine.

Keywords: Acute decompensated heart failure, levosimendan, dobutamine, adiponectin

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Chronic heart failure (HF) is a complex syndrome with neuroendocrine, immune and metabolic disorders.[1-3] Low cardiac output is observed in approximately 5-10% of patients with acute decompensated HF (ADHF) upon admission to the hospital, and positive inotropic therapy is recommended for these patients.[4,5] The efficacy of inotropic treatment agents and their effect on mortality are controversial. However, it is known that levosimendan, a new agent, has an effect without increasing intracellular calcium, and in some studies, its effect on mortality has been found to be better than dobutamine.[6,7] Adiponectin is an adipocytokine known for its insulin sensitivity and antiatherogenic activity. Paradoxically, serum levels were found to increase in correlation with serum BNP levels in patients with end-stage heart failure, and the relationship between the increase in serum levels and mortality has been shown in several studies.[8] We aimed to investigate the effects of levosimendan and dobutamine treatment on serum adiponectin, N-terminal brain natriuretic peptid (NT-pro BNP) levels and echocardiographic parameters in patients with ADHF who need positive inotropic therapy.

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Methods

In this study, patients with chronic heart failure, who applied to our clinic between October 2006 and October 2007, had functional capacity IV according to the New York Heart Association (NYHA), LVEF below 35% in echocardiography, hemodynamic instability despite intravenous (IV) vasodilator and IV diuretic therapy, i.e. low cardiac output symptoms and physical examination findings (renal dysfunction, cold extremities, mental status disorder) were included in the study. Levosimendan was started in 22 patients and dobutamine in 22 patients. Dobutamine infusion was given at a dose range of 5-15 µg/kg/min. The dose was adjusted according to the patient's heart rate, hemodynamic response, and systolic blood pressure. Levosimendan was given a 10-minute loading dose of 12-24 µg/kg, followed by infusion therapy at a dose range of 0.05-0.2 µg/kg/min. Dose titration was performed in patients who tolerated the treatment.

Patients with atrial fibrillation in electrocardiography (ECG), peroxe proliferator-activated receptor gamma group drug use, serum creatinine level >2.5 mg/dl, liver dysfunction, systolic blood pressure <85 mmHg, presence of active infection, and a history of myocardial infarction in the last eight weeks were excluded from the study. At the time of admission, physical examination of all patients was performed, and the patients' entry weight, height, body mass index (BMI), blood pressure, arterial, and pulse rate were measured. All patients' 12-lead ECGs were taken. LVEF, serum adiponectin level, BNP level, PAP, FC and weight measurements of the patients were taken before the treatment and on the third day of the treatment. The delta (Δ) value, which is the difference between the basal values of these parameters and the post-treatment values, was calculated. The study was approved by the Local Ethics Committee (Number: B.30.2.DİC.0.01.00.00/14) Consent was obtained from all patients before the study and was conducted according to the principles of the Declaration of Helsinki (as revised in Brasil, 2013).

Measurement of Biochemical Parameters

Venous blood samples were taken in the supine position during admission. Routine biochemical parameters, hemogram were studied immediately from these samples. The blood sample for the NT-Pro BNP level was taken into a biochemistry tube with EDTA and sent to the central laboratory. For the measurement of serum adiponectin, the blood sample taken at the same time was centrifuged at 3.0000 rpm for 10 minutes. The obtained plasma sample was stored at -80 °C until the end of the study to study the adiponectin level. On the 3rd day of the study (post-treatment), the blood sample was taken again for NT-Pro BNP and adiponectin measurements. NT-Pro BNP determination The study was performed on the modular analytical E170 immunoanalyzer with the Elecsys NT-proBNP kit. Adiponectin level was studied by using the R&D systems kit, using the Enzyme-Linked ImmunoSorbent Assay (ELISA) method, in accordance with the literature.

Echocardiographic Examination

Echocardiographic examination was performed with Hewlet-Packard Cardiac Imaging System echocardiography device and 3.5 MHz transducer before inclusion in the study and at the 72nd hour after treatment. Review Considering the criteria recommended by the American Society of Echocardiography, parasternal measurements were taken from the long axis and apical four chambers. Ejection fraction of the left ventricle were measured before and after the treatment, using the modified Simpson method from the apical four chambers.

Statistical Analysis

SPSS Windows 24.0 package program was used to evaluate the data obtained in the study. Frequency and percentage distribution for gender from the demographic features of the patients evaluated in the study; mean and standard deviation values were analyzed for age, weight, BMI, echocardiographic measurements and laboratory measurements. Paired Samples T test was applied to compare the echocardiographic measurements and laboratory measurements of the patients before and after treatment. Independent-Samples t Test was applied to determine the differences of the parameters in terms of "Levosimendan" and "Dobutamine" treatment. In addition, correlation analysis was applied to examine the relationships between the changes in the values of the parameters before and after the treatment. The results were considered significant at 99% ($p<0.01$) and 95% ($p<0.05$) confidence levels.

Results

A total of 44 patients with ADHF were included in the study, half of them were treated with dobutamine and the other half with levosimendan. There was no statistical difference between demographic and laboratory values of both groups before treatment (Table 1). The changes in adiponectin, LVEF, serum log BNP, pulmonary artery systolic pressure (PAP), weight, and FC before and after treatment were analyzed separately for the dobutamine and levosimendan groups. Serum adiponectin (Fig. 1) (20.41±2.93/18.76±2.39 $p<0.001$), BNP (9.38±0.88/8.17±1.31 $p<0.001$), PAP (47.81±12.69/35.59±14.04 $p<0.001$) levels were significantly decreased, while LVEF (23.77±5.22 /29.22±8.26

Table 1. The baseline characteristics, echocardiographic and laboratory results of the groups

Demographic and clinical characteristics	Levosimendan Group (n=22)	Dobutamine Group (n=22)	p
Age, years	67.81±5.47	67.47±13.49	0.908
Weight (kg)	66.77±10.88	65.13±12.72	0.622
Gender, male (%)	11 (50)	8 (36.4)	0.361
BMI (kg/m^2)	24.82±4.53	24.51±4.31	0.897
FC (NYHA)	4	4	
Echocardiographic measurements			
EF (%)	23.77±5.22	25.04±5.43	0.456
IVSDd (mm)	1.10±0.18	1.05±0.15	0.319
LVDd (mm)	6.02±0.44	6.16±0.82	0.448
RVd (mm)	4.69±0.54	4±0.67.52	0.349
LAd (mm)	4.99±0.50	4.93±0.50	0.736
RAd (mm)	5.26±0.74	5.25±1.1	0.920
PAP (mmHg)	47.82±12.70	50.00±11.98	0.497
Laboratory measurements			
Urea, mg/dL	55.72±17.99	50.47±18.54	0.492
Creatinine, mg/dL	1.07±0.25	1.02±0.25	0.445
Sodium, mmol/L	135.63±4.72	133.52±4.33	0.087
Potassium, mmol/L	4.52±0.64	4.20±,84	0.120
Hematocrit (%)	38.13±5.35	36.75±2.83	0.345
NT-pro BNP, pg/ml	16026±10639	17269±23521	0.820
HDL, mg/dL	31.93±8.59	31.91±8.59	0.702
LDL, mg/dL	30.54±12.89	91.39±30.29	0.568
Total cholesterol, mg/dL	153.93±49.27	145.09±38.63	0.623
Triglyceride, mg/dL	119.50±39.59	100.81±34.68	0.218

BMI: body mass index; EF: ejection fraction; IVSDd: diastolic interventricular septum diameter; LVDd: left ventricular end-diastolic diameter; RVd: right ventricular diameter; LAd: left atrial diameter; RAd: right atrial diameter; PAP: pulmonary artery systolic pressure; FC: functional capacity; NYHA: new york heart association; LDL: low density lipoprotein cholesterol; HDL: high density lipoprotein cholesterol.

p<0.0001) increased in patients receiving levosimendan treatment. Significant improvement was also observed in FC (4.00±0.00/3.00± 0.01 p<0.001) (Table 2). In the dobutamine group, serum adiponectin level (19.38±2.91/18.60 ±3.12 p=0.396) and LVEF (24.14±5.43 /25.21±5.59 p=0.718) did not change after treatment, but significant improvement was observed in PAP, BNP and FC (Table 3). In addition, when compared to dobutamine group of Δ-LVEF, Δ-Log BNP, Δ- Adiponectin, Δ- PAP, Δ-weight, Δ-FC, in patients receiving levosimendan adiponectin (-1.65±0.66 /- 0.71±0.11 p=0.29) PAP (-14.22±12.09/-6.60±9.50 p=0.23) levels decreased more, while LVEF (5.45±5.43/0.17±4.63 p=0.01) further increased. The improvement in FC (-1.00±.00/-0.82±0.38 p=0.41) was again in favor of levosimendan

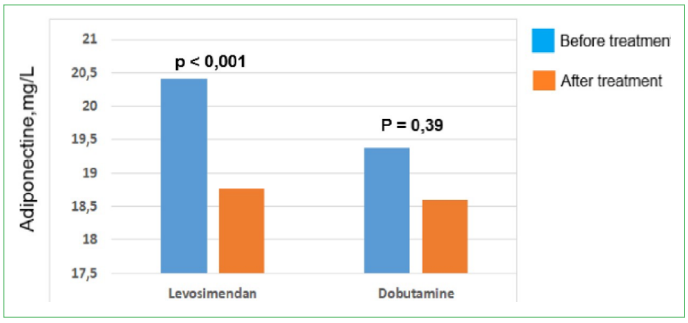

Figure 1. Comparison of before and after treatment values of adiponectin levels in the dobutamine and levosimendan groups.

Table 2. Comparison of before and after treatment parameters in the levosimedan group

Parameters	Before Treatment	After Treatment	p
EF (%)	23.77±5.22	29.22±8.26	<0.001
Log BNP, pg/mL	9.38±0.88	8.17±1.31	<0.001
Adiponectin, mg/L	20.41±2.93	18.76±2.39	<0.001
Weight, kg	66.77±10.88	62.97±10.09	<0.001
PAP, mmHg	47.81±12.69	35.59±14.04	<0.001
FC (NYHA)	4.00±0.00	3.00±0.01	<0.001

EF: ejection fraction; PAP: pulmonary artery systolic pressure; FC: functional capacity; NYHA: new york heart association; log BNP: logarithmic B-type natriuretic peptide.

Table 3. Comparison of before and after treatment parameters in the dobutamine group

Parameters	Before Treatment	After Treatment	p
EF (%)	24.14±5.43	25.21±5.59	0.718
Log BNP, pg/mL	9.51±0.81	8.55±1.08	0.001
Adiponectin, mg/L	19.38±2.91	18.60±3.12	0,396
Weight, kg	64.17±10.88	62.97±10.09	0.004
PAP, mmHg	52.81±12.69	37.59±13.04	0.005
FC (NYHA)	4.00±0.00	3.18±0.08	<0.001

EF: ejection fraction; PAP: pulmonary artery systolic pressure; FC: functional capacity; NYHA: new york heart association; log BNP: logarithmic B-type natriuretic peptide.

(Table 4). Correlation analysis was performed to determine the relationship between Δ-adiponectin and Δ-LVEF, Δ-log BNP value and BMI in the post-treatment levosimandan group. While no significant correlation was found between adiponectin level and LVEF, a significant moderately correlation between adiponectin and BMI (r:-0.60 ; p=0.000), a significant positive and significant moderately relationship between log BNP (r:0.522; p=0.000) were determined. In addition, it was observed that there was a weakly significant negative correlation (r:-0.353; p=0.017) between Δ-Log BNP and BMI difference values (Table 5).

Table 4. Comparison of difference values of LVEF, log BNP, adiponectin, PAP, weight, PK before and after treatment in terms of levosimendan and doputamine groups

Parameters	Levosimedan Group	Dobutamine Group	p
Δ EF (%)	5.45±5.43	0.17±4.63	0.001
Δ Log BNP, pg/mL	-0.52±0.36	-0.35±0.43	0.159
Δ Adiponectin, mg/L	-1.65±0.66	-0.71±0.11	0.029
Δ Weight, kg	-3.77±4.13	-2.82±4.11	0.446
Δ PAP, mmHg	-14.22±12.09	-6.60±9.50	0.023
Δ FC (NYHA)	-1.00±.00	-0.82±0.38	0.041

EF: ejection fraction; PAP: pulmonary artery systolic pressure; FC: functional capacity; NYHA: new york heart association; log BNP: logarithmic B-type natriuretic peptide.

Discussion

We evaluated the effect of dobutamine and levosimendan treatment on serum adiponectin, NT-pro BNP level, LVEF, PAP and functional capacity in patients with ADHF who needed positive inotropic therapy. In addition, the effects of levosimendan and dobutamine treatment on these parameters were also evaluated comparatively.Nakamura Tomohiro et al.[9] revealed that the serum adiponectin levels in patients admitted to the hospital due to HF were higher than the serum adiponectin levels in healthy individuals, and this level increased proportionally with the FC of the patients. In the same study, they also showed that adiponectin level decreased in correlation with BNP level after treatment (including patients receiving positive inotropic support therapy) in patients with FC III-IV according to NYHA. In parallel with these findings, Sokhanvar S. et al.[10] also demonstrated a linear relationship between the severity of HF and serum adiponectin level in a study they conducted. However, according to our literature, there is no study directly investigating the effect of positive inotropic therapy on serum adiponectin levels. In our study, we have shown that dobutamine treatment had no effect on adiponectin levels, but there was a significant decrease in adiponectin levels after treatment in patients receiving levosimendan. In addition to the decrease in adiponectin levels, it was shown that the improvement in FC, PAP and LVEF was more significant in patients treated with levosiman than in patients treated with dobutamine. A significant decrease in BNP levels was observed in both patient groups. However, the rate of decrease was more pronounced in patients who received levosimendan treatment. These results of our study are in line with the results of the study of Nakamura Tomohiro et al.[9] There may be several reasons for the change in these parameters to favor levosiman. First of all, levosimandan exerts its positive inotropic effect without increasing myocardial oxygen demand and without impairing ventricular relaxation. On the other hand, it exerts a vasodilator effect through the ATP-sensitive potassium channel, thus causing a decrease

Table 5. Correlation analysis between the delta values of various variables and the delta values of EF, Adiponectin and logBNP

Variables	Δ-EF		Δ-Adiponectin		Δ-logBNP	
	r	P	r	P	r	P
Δ-BMI	0.16	0.919	-0.601	<0.001	-0.353	0.017
Δ-EF		-0.03	0.983	-0.113	0.459	
Δ-Adiponectin	-0.03	0.983		-0.522	<0.001	
Δ-log BNP	-0.113	0.459	0.522	<0.001		

BNP: brain natriuretic peptide; BMI, body mass index; EF: ejection fraction; Delta (Δ) values were obtained by subtracting 72th hours values from the baseline values. Pearson and Spearman correlation coefficients were calculated to investigate the relationships between the selected variables.

in cardiac preload and afterload, which leads to a decrease in LV filling pressure. In addition, levosimendan, unlike dobutamine, causes an increase in diastolic coronary blood flow through the ATP-sensitive potassium channel.[11] In our study, correlation analysis was performed to determine the relationship between adiponectin level and LVEF, BMI, and log BNP values. As a result, it was shown that there was a negative correlation between adiponectin level and BMI, while there was a positive correlation with log BNP value. In addition, it was observed that there was no relationship between LVEF and adiponectin level. The relationship between adiponectin level and log BNP and BMI values in our study is similar with the relationship obtained from the results of the study conducted by Caroline Kistrop et al.[12] In other words, the increase in adiponectin and BNP levels in thin individuals with severe heart failure was again higher than in overweight individuals with severe heart failure.

In a study by Haugen et al.[13], they revealed that the mortality rate of patients with serum adiponectin level below 11.6 mg/L in their 50-month follow-up period was significantly lower than patients with serum adiponectin level above 19.8 mg/L. Furthermore, they showed that there was a negative correlation between BMI value and mortality rate. In the study of T. Szabó et al.[14], they proved that the relationship between BMI value and adiponectin level is stronger especially in cachectic HF patients than in non-casectic HF patients. They interpreted that this situation could not only be explained by decreased adipose tissue, but could be the result of a global catabaolic process. In severe heart failure, there are several mechanisms suggested for the increase in serum adiponectin level in parallel with the BNP level and inversely correlated with the BMI ratio. It has been shown that there is glycerol mobilization in human subcutaneous adipose tissue after intravenous infusion of BNP.[14] Serum adiponectin level is found to be low in individuals with increased body fat.[15] As a result of these effects, it is thought that increased BNP level leads to lipid mobilization, which indirectly leads to an increase in adiponectin synthesis.[16]

In our study, it was observed that the BNP levels of the patients at 72 hours after the treatment decreased significantly in both the levosimendan group and the dobutamine group. However, the decrease was more pronounced in the levosimendan group. This result is similar to the results of the SURVIVE[17] study. In this study, it was shown that the decrease in BNP at the 24th hour of the treatment was more pronounced in the levosimendan group than in the dobutamine group. Although this difference was not statistically significant in our study, the decrease in BNP was higher in the group receiving levosimendan treatment.While no effect of dobutamine treatment on LVEF was observed, we determined that LVEF in the levosimendan group increased significantly after treatment compared to before treatment. The average half-life of the OR-1896 molecule, which is the active metabolite of levosimendan, is around 80 hours, and the effect of this drug has a long-lasting effect of 10 to 14 days.[18] This may explain the higher increase in LVEF in the levosimendan group on the 3rd day of the study. Parallel results with these findings were also demonstrated in the LIDO study.[8] In addition, in parallel with the results of our study, a negative correlation was shown between BMI and BNP in the study of Caroline Kistrop et al.[12] Natriuretic Clearance Receptor is involved in the clearance of peripheral natriuretics and has been isolated in adipose tissue. Levels of this receptor are increased in obese patients. Therefore, lower BNP levels are observed in obese patients with heart failure compared to normal individuals. [19] This relationship was also demonstrated in our study. It is also known that inflammatory markers increase in heart failure, and it is suggested that adiponectin has the opposite effect of TNF-α, and that adiponectin level increases in response to increased TNF-α in heart failure.[9]

Conclusion

Serum adiponectin level increases in patients with ADHF, and this increase is correlated with the severity of heart failure. Also, serum adiponectin level is associated with mortality in heart failure patients. İn this study, it was shown that levosimandan treatment decreased serum adiponectin level in ADHF patients, but dobutamine treatment did not affect serum adiponectin level.

Disclosures

Ethics Committee Approval: Ethics committee pproval was received for this study from Dicle University Faculty of Medicine (Document no.0588/ UN2.F1/ETIK/2018).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.K.; Design – M.K.; Supervision – N.T.; Resources – M.K.; Materials – M.K.; Data Collection and/or Processing – M.K.; Analysis and/or Interpretation – M.K., N.T.; Literature Search – M.K.; Writing Manuscript – M.K.

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