Value of IGF-I levels in the evaluation of response to treatment with levosimendan in patients with severe heart failure

Ciddi kalp yetersizliği olan hastalarda levosimendan tedavi yanıtını değerlendirmede IGF-I düzeyinin değeri

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ABSTRACT

Objective: Levosimendan treatment has inotropic, anti-stunning, and cardioprotective effects in the setting of acute decompensated heart failure (HF). Among studies conducted on the treatment of heart failure, those based on the growth hormone axis are of particular interest. The aim of this study was to determine the value of baseline insulin-like growth factor 1 (IGF-I) measurements in predicting response to levosimendan treatment.
Methods: The study population included patients on standard heart failure treatment who presented with functional capacity NYHA class 3-4 and left ventricular (LV) ejection fraction less than 35% were enrolled in this prospective, cohort study. Pre- and post-treatment symptoms of patients (72 hours after the completion of levosimendan infusion) and echocardiographic parameters were evaluated and blood samples were collected. Mann-Whitney U, Pearson Chi-square and Wilcoxon Sign Rank tests were used for statistical analysis. Correlations were determined using Spearman correlation analysis.
Results: Thirty patients were enrolled in this study, 83.3% of whom were male and 16.7% were female, with a mean age of 62.6 ±10.1 years. Mean baseline IGF-I level was 106.9±47.0 µg/L. Statistically significant improvements were observed in NYHA class, mean brain natriuretic peptide (BNP) levels, LV ejection fraction and LV end-systolic volume values following treatment with levosimendan (respective pre-treatment and post-treatment values: 3.5±0.5 vs. 2.5±0.7, p<0.001; 1209.8±398.6 pg/ml vs. 704.1±344.6 pg/ml, p<0.001, and 25.7±6.6% vs. 29.0±6.8%, p=0.021, and 164.1±45.7 ml vs. 152.8±50.6 ml, p=0.012). Fourteen patients (46.7%) had low IGF-I levels, taking into consideration variations due to age and gender. Patients with normal baseline IGF-I values showed more significant decreases in BNP levels in response to treatment compared to those with low baseline IGF-I levels (650.5±367.2 pg/ml vs. 340.1±269.0 pg/ml, p=0.014).
Conclusion: Baseline IGF-I levels may be used to predict response to levosimendan treatment in patients hospitalized for decompensated HF. *(Anadolu Kardiyol Derg 2011; 11: 523-9)*
Key words: Heart failure, levosimendan, insulin-like growth factor 1, B type natriuretic peptide

ÖZET

Amaç: Akut dekompanse kalp yetersizliğinde (KY) levosimendan tedavisi pozitif inotropik, "antistunning" ve kardiyoprotektif etkilidir. Kalp yetersizliği tedavisine yönelik yürütülen çalışmalar arasında büyüme hormonuna dayalı olanlar ilgi çekicidir. Levosimendan tedavisinden fayda görmede bazal insülin benzeri büyüme faktörü 1 (IGF-I)'in değerini araştırmak üzere çalışmayı planladık.
Yöntemler: Bu prospektif kohort çalışmaya standart KY tedavisi altında NYHA sınıflamasına göre fonksiyonel kapasitesi 3-4 ve sol ventrikül (SV) ejeksiyon fraksiyonu <%35 olan 30 hasta alındı. Hastaların tedavi öncesi ve sonrası (levosimendan infüzyonu bitiminden 72 saat sonra) semptomları, ekokardiyografik parametreleri değerlendirildi ve kan örnekleri alındı. İstatistiksel analizde Mann-Whitney U, Pearson Chi-square ve Wilcoxon işaret sıralama testleri kullanıldı. Korelasyon Spearman korelasyon analizi ile değerlendirildi.
Bulgular: Hastaların ortalama yaşı 62.6±10.1 yıl idi (minimum 40 maksimum 82). Hastaların %83.3'ü erkek ve %16.7'si kadın idi. Ortalama bazal IGF-I düzeyi 106.9±47.0 µg/L idi (minimum 39, maksimum 258). Hastaların tedavi sonrasında NYHA sınıfı, B-tip natriüretik peptit (BNP) düzeyleri, SV ejeksiyon fraksiyonu ve SV sistol sonu hacim değerlerinde tedavi öncesine göre istatistiksel olarak anlamlı düzelme saptandı (3.5±0.5 ve

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2.5±0.7, p<0.001; 1209.8±398.6 pg/ml ve 704.1±344.6 pg/ml, p<0.001, 25.7±6.6% ve 29.0±6.8%, p=0.021, ve 164.1±45.7 ml ve 152.8±50.6 ml, p=0.012). Hastaların 14'ünde (%46.7) IGF-I düzeyleri yaş ve cinsiyete göre normal değerlerden düşük saptandı. Bazal IGF-I düzeyi normal olan hastalarda IGF-I düzeyleri düşük olan hastalara göre daha fazla BNP düşüşü olmaktaydı (650.5±367.2 pg/ml ve 340.1±269.0 pg/ml, p=0.014).
Sonuç: Dekompanse KY ile hastaneye yatan hastaların levosimendan tedavisine verecekleri yanıtı öngörmede bazal IGF-I düzeyleri yol gösterici olabilir. *(Anadolu Kardiyol Derg 2011; 11: 523-9)*
Anahtar kelimeler: Kalp yetersizliği, levosimendan, insülin benzeri büyüme faktörü 1, B tip natriüretik peptit

Introduction

In recent years we have witnessed a significant increase in the prevalence of cardiovascular diseases, mainly due to a worldwide rise in the elderly population. Improved survival rates for heart patients attributed to the availability of developed treatment options have led to a hike in the incidence of heart failure (HF). Despite all the advances in the management of heart disease, HF is still associated with high mortality rates (1), while at the same time placing a heavy burden on healthcare expenditures due to escalating hospitalization and treatment costs.

Levosimendan, a novel phosphodiesterase inhibitor, has positive inotropic and anti-stunning effects mediated by calcium sensitization of contractile proteins, while also exerting vasodilatory and anti-ischemic effects mediated by the opening of adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels in vascular smooth-muscle cells (2-5). It has been shown to prevent or limit myocyte apoptosis via the activation of mitoKATP channels, a potentially protective mechanism that could be exploited for the management of acute HF (6, 7).

Among the studies conducted on HF treatments, those based on growth hormone (GH) are of particular interest (8-10). Investigations on this subject have focused on two different aspects; some have evaluated the benefit of GH as a treatment option for HF while others have attempted to examine the prognostic correlation between the GH/ insulin-like growth factor 1 (IGF-I) axis and HF, the results of which remain a cause of controversy.

Prevention of cardiomyocyte loss through suppression of cell death pathways has been proposed as a treatment strategy for the prevention of progression of HF. On the other hand, IGF-I has been shown to decrease cardiomyocyte apoptosis in animal models (11-13).

A possible relationship between serum IGF-I levels and HF has been proposed based on the results of several studies which reported on an increased risk of congestive HF associated with diminished growth hormone and IGF-I expression in patients with hypopituitarism (14). Further clinical studies on patients with HF have demonstrated a significant correlation between decreases in IGF-I levels and severity of ventricular systolic dysfunction (15, 16). Not only have recent trials demonstrated an association between GH deficiency and cardiac abnormalities, but improvements in cardiac function have also been reported with short-term GH therapy (8, 10). In another study, GH replacement therapy has been shown to improve exercise capacity, vascular reactivity, left ventricular function, and indices of quality of life in patients with congestive HF (9).

The aim of this study was to evaluate the response to treatment with levosimendan in HF patients, with reference to changes in baseline IGF-I levels.

Methods

Study design and patients

This prospective cohort study was undertaken at Ankara Numune Teaching and Research Hospital with approval of the local Ethics Committee. Written informed consent was obtained for all participants.

Patients followed-up at the department of Cardiology with a diagnosis of congestive HF between June 2008 and June 2009 were screened, and those on standard HF treatment with a functional capacity of 3-4 based on NYHA classification and with a left ventricular ejection fraction (LVEF) of <35% were approached for inclusion in the study. Patients with atrial fibrillation, hypotension (systolic blood pressure <85 mmHg), tachycardia (resting heart rate >115 beat/min), aortic or mitral stenosis, hypertrophic or restrictive cardiomyopathy, 2nd or 3rd degree AV block, severe liver (AST/ALT values twice the normal values or higher) and renal failure (creatinine >2.5 mg/dl), recent (<8 weeks) myocardial infarction, pacemaker, sustained or non-sustained ventricular tachycardia were excluded. Similarly, patients with known hypopituitarism (any hormone axis) were also excluded. Prior to enrollment, all patients were screened for the presence of a pituitary disorder by measuring serum levels of anterior hypophyseal hormones. The presence of a doubtful result was considered a cause for exclusion, without the need for further dynamic tests.

A standard insulin tolerance test was not attempted to confirm a diagnosis of GH deficiency in patients with low IGF-I levels, as it was deemed too risky, particularly for the elderly and in HF patients.

Baseline evaluation

A detailed medical history, including medications, was obtained for each patient followed by a careful physical examination during which heart rate and resting blood pressure were recorded. Functional class was determined based on the New York Heart Association (NYHA) classification for congestive HF.

Echocardiographic examination

The examination was carried out by a single cardiologist, blinded to patient details, using a GE Medical Systems Vivid 7 device (Vingmed Ultrasound AS, Horten, Norway) with a 2.5-6 MHz transducer. Left ventricular dimensions were measured by M-Mode imaging. Left ventricular volumes and LV EF were calculated by adopting modified Simpson's method from apical 4- and 2-chamber images.

Laboratory examinations

Blood samples were collected into EDTA tubes and then centrifuged for 15 minutes in 3000 rpm to separate the plasma

from blood. Plasma samples were then stored at -80°C pending laboratory measurements at a preset future date.

Brain natriuretic peptide

Brain natriuretic peptide (BNP) measurements were carried out using ARCHITECT BNP (Abbott Diagnostics Division, Abbott Park, Illinois, USA), a quantitative chemiluminescent microparticle enzyme immunological test for the determination of BNP levels in plasma. Intra-assay and inter-assay coefficients of variation for BNP ranged from 0.9-5.6 percent, and 1.7-6.7 percent, respectively, with a lower limit of detection of 10 pg/mL.

Insulin like growth factor

Plasma IGF-I levels were determined using an IGF-I radio immune assay kit (CIS Bio international, Cedex, France). The intra-assay CV was <5.6%, while inter-assay CV was 8.0% and 9.0% for IGF-I concentrations of 87.9 and 416.8 µg/L, respectively. Assay sensitivity was 2 µg/L and calibration range was up to 1200 µg/L (IRR WHO 87/518).

Reference ranges of IGF-I (µg/L) in our local laboratory are depicted in Table 1. Patients with IGF-I levels lower than 2SD of normal values based on age and sex were stratified into the low IGF-I group, while the remaining patients were included in the normal IGF-I group (17).

Levosimendan application

Levosimendan was administered intravenously as a loading dose of 12 µg/kg/min, given over 10 minutes followed by a maintenance dose of 0.1 µg/kg/min which was continued for 24-hours. During treatment, patients were monitored with close follow-up of ECG and blood pressure.

Post-treatment follow-up

Patients were evaluated 72 hours after conclusion of treatment, including determination of symptom scores and a repeat physical examination for heart rate and blood pressure measurements. Echocardiographic examination was followed by blood sampling for the evaluation of BNP and IGF-I levels.

Statistical analysis

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS) program version 13.0 (Chicago, IL, USA). Normality of distribution of continuous variables was evaluated using the Shapiro-Wilk test, whereas comparisons between groups were performed using the t-test for independent variables or the Mann-Whitney U test, as appropriate. The degree of association between continuous variables was determined by the Spearman's "rho" correlation coefficient. The differences between pre-and post-treatment parameters were evaluated by Wilcoxon Sign Rank test. A p value of less than 0.05 was considered statistically significant.

Table 1. Reference ranges for IGF-I at our laboratory

Age groups	IGF-I concentrations, µg/L	
	Male	Female
29-40 years	302-774	302-774
41-50 years	102-328	137-366
51-60 years	108-330	113-326
61-70 years	100-314	88-262
>70 years	87-195	101-224

IGF-I - insulin-like growth factor 1

Results

Baseline characteristics

A total of 30 patients, 5 (16.7%) of which were female, were enrolled in this study with a mean age of 62.6±10.1 years (range 40-82 years). With an overall mean body mass index (BMI) of 26.1±4.4 kg/m^2 (range 16.5-36.7), only two patients had a BMI <18.5 kg/m^2, whereas 9 patients had a BMI of 18.5-24.9 kg/m^2. Fourteen patients were overweight with a BMI of 25-29.9 kg/m^2 while five (16.7%) had a BMI of ≥ 30 kg/m^2.

The number of patients with NYHA class 3 and class 4 HF was equal (Table 2). The mean baseline IGF-I level was 106.9±47.0 (range 39-258) and 14 out of 30 (46.7%) patients had low pretreatment levels of IGF-I (Table 3), taking into consideration variations associated with age and gender.

Results of post-treatment evaluation

Statistically significant improvements in NYHA class, BNP levels, LVEF and mean LV end-systolic volume (ESV) values were observed after treatment with levosimendan, compared to pretreatment values (p<0.001, p<0.001, p=0.021, and p=0.012, respectively) (Table 4). However, no significant change in mean IGF-I level was observed (p>0.05).

No correlation could be established between pre-treatment IGF-I levels and other parameters such as LVEF, serum BNP levels and NYHA class (Table 5). However, changes in IGF-I and BNP with treatment were found to be correlated with baseline IGF-I levels (r=0.533, p=0.002 and r=0.364, p=0.048), meaning that patients with higher baseline levels of IGF-I manifested a greater decrease in BNP levels compared to those with low baseline levels.

Comparison of patients with low and normal IGF-I levels

A comparison between groups based on IGF-I levels was made in terms of changes in NYHA class, BNP levels, EF and LV-ESV after levosimendan treatment (Table 6). Decreases in BNP were more prominent in patients with normal IGF-I values compared to those with low IGF-I levels (decrease in BNP-650.5±367.2 vs. 340.1±269.0, p=0.014).

Adverse events

Two patients required halving of infusion rate of levosimendan due to decreases in systolic blood pressure below 90 mmHg. One patient developed two non-sustained ventricular tachycardia attacks that did not necessitate treatment. None of the patients had an AF attack during infusion, and no mortalities were reported.

Table 2. Baseline characteristics of study population

Variables	Results
Age, years	62.6±10.1
Gender, female/male	5/25
BMI, kg/m^2	26.1±4.4
Smoking, n (%)	15 (50.0)
DM, n (%)	16 (53.3)
NYHA class (3/4), n	15/15
HR, beats/min	84.0±15.7
SBP, mmHg	115.9±13.5
DBP, mmHg	69.4±9.3
ACEI, n (%)	21 (70)
ARB, n (%)	4 (13.3)
Beta-blocker, n (%)	18 (60)
Spironolactone, n (%)	14 (46.7)
Digoxin, n (%)	16 (53.3)
Anticoagulant, n (%)	4 (13.3)
Antiaggregant, n (%)	25 (83.3)

Data are presented as mean±SD and number (percentage) values
ACEI - angiotensin-converting enzyme inhibitor, ARB - angiotensin receptor blocker, BMI - body mass index, DBP - diastolic blood pressure, DM - diabetes mellitus, HR - heart rate, SBP - systolic blood pressure

Table 3. Baseline laboratory parameters of study population

Variables	Results
Fasting blood glucose, mg/dl	86.2±15.7
Sodium, mmol/L	139.4±4.8
Potassium, mmol/L	4.3±0.5
TG, mg/dl	108.5±76.1
T-C, mg/dl	173.0±41.2
HDL-C, mg/dl	42.4±11.6
LDL-C, mg/dl	109.3±33.3
Insulin, µU/ml	7.0±7.9
Cortisol, ug/dl	15.9±6.3
ACTH, pg/ml	32.3±25.0
Free testosterone, pg/ml	4.2±4.9
Total testosterone, ng/ml	2.6±0.8
GH, µ/l	1.8±3.0
TSH µIU/ml	1.7±3.1
FT3, pg/ml	3.1±0.6
FT4, ng/dl	0.9±0.2

Data are presented as mean±SD values
ACTH - adrenocorticotropic hormone, FT3 - triiodothyronine, FT4 - thyroxin, GH - growth hormone, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol, T-C - total cholesterol, TG - triglyceride, TSH - thyroid stimulating hormone

Discussion

In this study, we managed to establish a GH deficiency prevalence of 46.7% as determined by measurement of IGF-I levels, taking into consideration variations due to age and gender. Levosimendan treatment was associated with improvements in NYHA class scores and decreases in BNP levels of patients with CHF. More significant reductions in BNP levels were observed in patients with higher baseline IGF-I levels, however, we failed to demonstrate a significant change in IGF-I levels.

Conventional inotropic agents utilized in HF are beta-agonists (dobutamine, dopamine) and phosphodiesterase 3 inhibitors. These medications improve cardiac output by increasing pulse volume, but such an increase in contractility comes with the price of greater energy demand and increased oxygen consumption (18, 19). Furthermore, these agents potentiate the cardiotoxic and arrhythmogenic effects associated with elevated intracellular calcium (20). Their hemodynamic and symptomatic benefits are short-lived, and the detrimental effects on mortality in the long-term restrict the use of these agents (21). Levosimendan, on the other hand, stabilizes the cross-bridges, which form between actin and myosin by binding to cardiac troponin C. This stabilization provides a more efficient contraction by prolonging the time both proteins interact together during systole. In contrast to other positive inotropic agents, levosimendan does not increase oxygen demand of the myocardium and no negative effects on diastolic heart function have been reported in association with this agent.

Another feature of levosimendan is that it promotes arterial and venous dilatation by opening ATP-dependent potassium channels in venous smooth muscle cells (22). The resultant decrease in preload and after load consequently leads to drops in right atrial pressure, pulmonary artery pressure, and mean arterial blood pressure. The superiority of levosimendan to both dobutamine and placebo in the setting of acute decompensated HF has been demonstrated in several studies, with particular benefits in terms of hemodynamic and symptomatic improvements, overall survival and tolerability (23, 24). In two recent large-scale studies (REVIVE-2 and SURVIVE), levosimendan was found to be better than placebo in improving symptoms, and then both placebo and dobutamine in reducing BNP levels. With regards to mortality, however, no difference from either placebo or dobutamine was observed (25, 26). In our study, we managed to demonstrate improvements in HF scores and LVEF values, as well as decreases in BNP levels in association with levosimendan treatment, our results being in concordance with previous reports.

Growth hormone is a 191 amino acid peptide hormone released from the pituitary gland, which exerts pleiotropic actions on both growth and maturation of the body spanning throughout life. It also plays a role in the short-term regulation of energetic flux. Its anabolic and stimulatory effects during stress and energy expenditure may be viewed as an attempt at regulating restoration and build-up of energy stores. GH realizes its peripheral effects indirectly through somatomedins, predominantly IGF-I (22) which is produced mainly by the liver and to a lesser extent by peripheral tissues (27).

The prevalence of low IGF-I levels in our study was 46.7%. Numerous studies have reported on decreased levels of IGF-I levels as well as blunted responses to GHRH, both alone or combined with arginine, in patients with severe left ventricular dysfunction (28-31).

Table 4. Comparison of NYHA class, BNP levels and echocardiographic parameters before and after treatment with levosimendan

Variables	Pre-treatment	Post-treatment	p*
NYHA class	3.5±0.5 (3-4)	2.5±0.7 (1-3)	<0.001
BNP, pg/ml	1209.8±398.6 (490.0-2645.0)	704.1±344.6 (208.0-1320.0)	<0.001
IGF-I, µg/L	106.9±47.0 (39.0-258.0)	107.7±40.9 (49.0-250.0)	0.788
LVEF, %	25.7±6.6 (14.8-35.0)	29.0±6.8 (17.0-39.0)	0.021
LV-ESV, ml	164.1±45.7 (99.0-285.0)	152.8±50.6 (87.0-299.0)	0.012

Data are presented as mean±SD (minimum-maximum) values
*Wilcoxon Sign Rank test
BNP - brain natriuretic peptide, IGF-I - insulin like growth factor 1, LVEF - left ventricular ejection fraction, LV-ESV - left ventricular end-systolic volume

Table 5. Correlation between baseline IGF-I levels and various pre-treatment and post-treatment parameters of heart failure

Variables	r	p
On admission		
LVEF	-0.062	0.827
LVESV	-0.109	0.568
BNP	-0.271	0.147
NYHA class	-0.023	0.902
Changes after treatment		
LVEF increase	0.040	0.897
LV-ESV decrease	0.165	0.384
IGF-I increase	0.533	0.002
BNP decrease	0.364	0.048
NYHA class decrease	-0.105	0.582

Spearman correlation analysis
BNP - brain natriuretic peptide, IGF-I - insulin like growth factor 1, LVEF - left ventricular ejection fraction, LV-ESV - left ventricular end-systolic volume

Table 6. Comparison of changes in clinical variables after levosimendan treatment based on baseline IGF-I levels

Variables	Normal IGF-I (n=16)	Low IGF-I (n=14)	p*
BNP decrease, pg/ml	650.5±367.2 (212.0-1325.0)	340.1±269.0 (58-975.0)	0.014
IGF-I change, µg/L	-0.7±16.7 [(-13.0)-37.0]	6.7±10.7 [(-22.0)-38.0]	0.316
LVEF increase, %	3.5±5.7 [(-2.0)-16.0]	3.2±3.0 (0-10.0)	0.209
LV-ESV decrease, ml	8.9±24.6 (2.0-61.0)	21.5±14.3 (12.0-35.0)	0.240
Frequency of decrease in NYHA score, n (%)	11 (68.8)	11 (78.6)	0.311

Data are presented as mean±SD (minimum-maximum) and number (percentage) values
*Mann-Whitney U test and Pearson Chi-square test
BNP - brain natriuretic peptide, IGF-I - insulin like growth factor 1, LVEF - left ventricular ejection fraction, LV-ESV - left ventricular end-systolic volume

Several mechanisms such as reduced somatotropic secretion, increased peripheral GH resistance, hypothalamic somatostatinergic hyperactivity, drug interference (i.e. angiotensin-converting enzyme inhibitors, digoxin, diuretics), nutritional changes, and increased angiotensin 2 and cytokine production, have been postulated to account for this phenomenon in patients with HF (32). Acquired GH resistance is known to occur during the course of a number of catabolic disorders such as sepsis, trauma, surgery, cancer, chronic obstructive pulmonary disease, uremia, chronic liver disease and CHF (33). Moreover, hepatic stasis occurring as a result of biventricular HF has been shown to contribute to low IGF-I levels (34). Patients with hepatic dysfunction and cachexia were excluded from our study, to eliminate any influences they may have on the GH/IGF-I axis.

Previous clinical investigations revealed an association between serum IGF-I levels and heart disorders such as HF and coronary artery disease (particularly myocardial infarction) (35-39). Furthermore, recent experimental data suggest that GH and IGF-I manifest their beneficial effects in HF by decreasing the extent of apoptotic cardiomyocyte death (12, 13, 40).

Current evidence supports the use of natriuretic peptides in the diagnosis of HF and when investigating patients suspected of being at risk for cardiac events (41, 42). Brain natriuretic peptide and N-terminal (NT)-proBNP are the most frequently used natriuretic peptides in clinical practice. In the chronic phase of myocardial infarction, plasma BNP reflects hemodynamic loads, ventricular remodeling and HF (43).

Growth hormone/IGF-I may have a direct suppressive effect on the secretion of NT-proBNP from the myocardium, independent of ventricular wall tension. This is supported by results of an in vitro study on cultured rat cardiomyocytes in which reduced expression of natriuretic peptide mRNA in response to IGF-I was demonstrated (44). Additionally, patients with acromegaly were found to have low levels of NT-proBNP, related to elevated levels of GH/IGF-I in this patient group. More interestingly, a marked increase in NT-proBNP was observed in patients under treatment for acromegaly, with values peaking after 3 months (45). Renal clearance of BNP is increased in patients with acromegaly, which also contributes to the decreased levels seen in this patient group. On the other hand, besides the attenuated inhibitory effect associated with the decreased activity of the GH/IGF-I system in patients with HF, the disrupted renal perfusion brought about by the poor cardiac pump function leads to decreased renal clearance of BNP which in turn translates into elevated serum levels (46, 47).

In our study, patients with normal IGF-I levels seem to have responded better to levosimendan as reflected by a more significant decrease in BNP levels compared to those with low baseline IGF-I levels. We managed to establish a correlation between low baseline levels of IGF-I levels and the extent of decrease in BNP levels with levosimendan treatment. This may be attributed to the presence of several stimulatory factors on BNP, such as increased ventricular wall pressure, which overshadow the direct suppressive effect of pre-treatment IGF-I. Treatment with levosimendan effectively eliminates most of

these stimulatory factors, allowing for the inhibitory effects of IGF-I to manifest, which may help explain why patients with higher baseline IGF-I levels had a more pronounced response in terms of decrease in BNP, compared to patients with low baseline IGF-1 levels.

In the REVIVE-2 and LIDO studies, whose subjects shared many characteristics with our patient population, only a particular group of patients showed symptomatic and/or hemodynamic improvement with levosimendan treatment (22, 24). In fact, more patients than not failed to respond, or even deteriorated despite treatment. Our study results suggest that as a predictor of response, determination of baseline IGF-I levels may play a role in the decision making process while contemplating levosimendan treatment. In the above studies, while the number of patients with normal IGF-I levels was greater in responders to treatment, patients who failed to respond to treatment had lower baseline IGF-I levels.

To date, no parameter has been shown to accurately predict treatment response to levosimendan. In one study, decreases in BNP levels were predictive of re-hospitalization rates after levosimendan treatment (48). In the SURVIVE study, decreases in BNP were found to be predictive of mortality in patients receiving levosimendan (49).

Clinical implications

Our aim while undertaking this study was to investigate the value of measuring baseline IGF-I levels in predicting response to levosimendan treatment. As such, our study results seem to suggest that determination of baseline IGF-I levels may help guide clinicians when making the decision to administer a positive inotropic agent such as levosimendan in patients admitted with a diagnosis of decompensated HF. In this study, we only assessed short-term response to levosimendan treatment. In future studies, a longer follow-up period would help establish whether the beneficial effects of levosimendan are sustained in the long run, particularly with regards to heart failure-related hospitalization rates.

Study limitations

The small sample size is the biggest drawback of this study. However, levosimendan is not used very frequently in general clinical practice, making enrollment of a larger number of patients who fulfilled the necessary criteria for inclusion in this trial during the study period unattainable. There is a dire need for more comprehensive clinical trials.

Low IGF-I levels are prevalent in patients with chronic HF, and we strongly believe that. The GH/IGF-I axis has an important prognostic role in this patient population. Cost-effectiveness analysis was not a part of our study objectives, and was therefore not conducted. We do not recommend routine determination of IGF-I levels prior to administration of levosimendan as a means of predicting response to treatment. Future studies on cost-effectiveness analysis would require long-term post-treatment follow-up, comparing outcomes in patients with low and normal IGF-I levels.

Conclusion

In the present study, we managed to demonstrate improvements in HF symptom scores and LVEF measurements, as well as a decrease in BNP levels with levosimendan treatment. Patients with higher baseline levels of IGF-I levels showed the most benefit with levosimendan treatment, indicated by greater decreases in serum BNP levels. Our results also suggest that in patients with decompensated HF, normal baseline levels of IGF-I may be associated with a better response to levosimendan treatment.

Conflict of interest: None declared.

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