Levosimendan in Decompensated Heart Failure Patients: Efficacy in a Brazilian Cohort. Results of the BELIEF Study

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Summary

Background: Levosimendan is a new inodilatory agent that enhances cardiac contractility via Ca(2+) sensitization and induces vasodilation through the activation of KATP/BKCa.

Objective: To study the efficacy and safety of levosimendan in a decompensated heart failure (DHF) Brazilian cohort, and in β-adrenergic agonist resistant patients.

Methods: The Brazilian Evaluation of Levosimendan Infusion Efficacy (BELIEF) study was prospective, multicenter, observational and included 182 high-risk DHF patients, all of which received open-label levosimendan. Primary end point was hospital discharge without additional inotropic therapy (responder). Secondary end points were changes in hemodynamics, clinical parameters, and brain natriuretic peptide (BNP).

Results: Mortality rate was 14.8%, and 139 of 182 patients were responders. In non responders it was 62.8%. Systolic blood pressure was a predictor of response. In β-adrenergic agonist resistant group, 55.8% were responders. Overall, 54 patients experienced at least one adverse event; most of them resolved either spontaneously or after levosimendan dose reduction. A significant improvement in quality of life was verified at 2-6 months of follow-up (p<0.0001).

Conclusion: Our results suggest levosimendan infusion as an alternative therapy in the short term management of DHF patients. HF severity can influence the response to levosimendan treatment. Prospective studies are warranted in a Brazilian cohort including Chagas heart disease. (Arq Bras Cardiol 2008; 90(3):182-190)

Key words: Heart failure, decompensated heart failure, levosimendan, inotropic drug, decompensated congestive heart failure, dyspnea, Chagas disease, systolic blood pressure.

Introduction

Decompensated heart failure (DHF) is the admission diagnosis in approximately 400,000 hospitalizations in Brazil annually.[1] In the Brazilian public health system, hospitalization for HF accounts for 33% of all cardiovascular disease hospitalizations and about 23% of cardiovascular disease hospitalization expenditures.

Intravenous inotropic agents are commonly used in DHF treatment despite concerns about their deleterious influence on survival and attenuation of their effects in patients using β-blockers.[2] Levosimendan is an inodilator with a dual mode of action: calcium sensitization through calcium-dependent interaction with troponin C and vasodilation, promoting an ATP-sensitive potassium-channel agonist[3]. Levosimendan can improve hemodynamic condition symptoms, survival, and duration of hospital-stay in DHF[4-8]. The SURVIVE study compared long-term survival between levosimendan and dobutamine-treated patients and found no difference between these drugs. However, atrial fibrillation was found to increase in the levosimendan group [9,10].

In this study, we investigated the efficacy and safety of levosimendan in DHF patients in a Brazilian cohort.

Methods

Design

The Brazilian Evaluation of Levosimendan Infusion Efficacy (BELIEF) study, as part of a levosimendan early access program, was a prospective, multicenter observational study enrolling DHF patients from 35 centers in Brazil. Patients were assigned to receive levosimendan in addition to standard care. Inclusion criteria were patients at least 16 years of age; left ventricular ejection fraction below 35% documented by either 2-dimensional echocardiography or radionuclide ventriculography within 6 months prior to study entry; diuretic resistance and/or low urine output without the presence of hypovolemia; and DHF requiring hospitalization and intravenous inotropic therapy. DHF was defined by the presence of (a) pulmonary congestion; or (b) pulmonary congestion associated with signs or symptoms of

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low cardiac output and without severe arterial hypotension; (c) signs or symptoms of low cardiac output without congestion or severe arterial hypotension. Patients were eligible if they had decompensation due to chronic HF, gradual worsening chronic HF, persistent DHF, or de novo DHF.[1] Patients requiring β-adrenergic agonist infusion for more than 48 hours with no signs of dose reduction and who met entry criteria were also admitted into the study.

Exclusion criteria were the following: severe hypotension [systolic blood pressure (SBP) below 85mmHg at screening] not responding to intravenous fluids; mechanical ventilation; severe renal impairment (creatinine clearance <30 mL/min or creatinine>2.5 mg/dL); hepatic impairment (defined as alanine aminotransferase or aspartate aminotransferase levels 3 times normal); hypersensitivity to levosimendan or any of its excipients; mechanical obstruction affecting ventricular filling and/or outflow; hypokalemia not responding to potassium replacement therapy; acute myocardial infarction; severe or uncontrolled arrhythmias; primary pulmonary hypertension; acute myocarditis; congenital heart disease; pregnant or breastfeeding females; cancer; dementia; any systemic disease that could affect interpretation of the results; or significant hemodynamic instability requiring mechanical support.

Patients did not undergo invasive monitoring to guide treatment. Written informed consent was obtained from all patients before entering the study. The Ethics Committee and Review Board of each participating center approved the protocol.

Levosimendan Infusion

Levosimendan was prepared at a concentration of 0.025 mg/mL obtained by diluting 2.5 mg in 500 mL of 5% glucose solution. The loading dose used (6 to 12 μg/kg) was based on the investigator's clinical decision and was administered for 10 minutes, followed by continuous infusion of 0.1 μg/kg/minute for the remainder of the 24 hours. Throughout this period, investigators could up-titrate the dose to a maximum of 0.2 μg/kg/minute or down-titrate it to 0.05 μg/kg/minute. They could also discontinue the infusion at their discretion, based on symptomatic hypotension (SBP below 80mmHg), clinically significant tachycardia, a serious adverse event related to levosimendan, or patient consent to withdraw. During levosimendan infusion, the discontinuation of inotropic drugs, except levosimendan, was tested, unless necessary due to clinical status.

End Points

The primary end point was defined as hospital discharge without additional inotropic therapy after levosimendan infusion.

Secondary end points included changes from baseline in SBP and diastolic blood pressure (DBP), heart rate, respiratory rate, dyspnea, pulmonary congestion, and B-type natriuretic peptide (BNP). Blood pressure (mmHg), heart rate (beats per minute, bpm), and respiratory rate (r/min) were evaluated at baseline (0), 1, 2, 4, 6, 12, 24, 36, and 48 hours after levosimendan infusion was initiated, and every 24 hours thereafter until hospital discharge.

Dyspnea (absent, mild, or severe) and pulmonary congestion (absent, basilar, lower third, and 1/3 up to pulmonary apices) were evaluated at baseline, 1, 2, 4, 6, 12, 24, 36, and 48 hours after the levosimendan infusion was initiated. Serum creatinine (mg/dL), hematocrit (%), hemoglobin (g/dL), sodium (mEq/L), and potassium (mEq/L) were determined at baseline and at later time points.

Analysis of Factors Influencing Response to Levosimendan

To identify potential variables that might have prognostic value in determining clinical response to levosimendan, baseline population characteristics of 2 groups were compared: patients who were responders (R) and those who failed to meet the primary end point (nonresponders - NR).

Safety Assessment

Safety was monitored including adverse events for 31 days after levosimendan infusion. Adverse events were reported as they occurred while patients were hospitalized or by telephone interviews. Changes from baseline SBP and effect of loading dose on SBP were analyzed to assess risk of hypotension.

Hospital Stay and Readmissions, Quality of Life, and Mortality after Hospital Discharge

Patients were followed for 6 months after hospital discharge for hospital readmission, mortality, and quality of life by a specialized nursing team using standardized family and patient telephone interviews. Hospital admissions, clinical events, changes in medication, weight, food and water ingestion, symptoms, exercise, work, and psychological aspects were assessed during the 6-month follow-up. Quality of life was assessed by applying the Minnesota Living with Heart Failure Questionnaire at baseline, 2, 4, and 6 months after hospital discharge[11].

Statistical Analysis

Data were collected and managed by the study sponsor (Abbott Laboratories, Inc, São Paulo, Brazil). Its representatives were involved in data analysis and interpretation. All analyses were performed by Statistika Consultoria (São Paulo, Brazil) and verified by the sponsor and investigators. For continuous variables, equality of variance was tested with the folded F method before analysis by either Student *t* test with pooled variance for equal variances or Satterthwaite's method for unequal variances. Categorical variables were evaluated by Fisher's exact test. Logistic regression modeling was used to determine the probability of treatment failure as a function of baseline characteristics. Repeated measures analyses with spatial power covariance structure and restricted maximum likelihood estimation methods were conducted for continuous variables. Categorical responses across time were analyzed by using a generalized linear model with multinomial response and cumulative logit link function, using the generalized equation estimation methods. Event-free curves were estimated using the Kaplan-Meier function. Data were analyzed using SAS 8.2 statistical software. Any p-value ≤0.05 was considered significant.

Results

Baseline Characteristics

Between February 22, 2002 and April 15, 2003, 182 patients were enrolled in the study (Table 1). The BELIEF study population was predominantly Caucasian (58%) and male (67%). However, the proportion of Afro-Brazilians (36.8%) was also significant. Most patients (81%) had clinical evidence of fluid overload and congestion without hypotension (warm/wet clinical profile). Comorbid conditions included diabetes mellitus type 2 (13.7%) and thyroid disease (4.4%). Anemia and hyponatremia were common. Medications received before levosimendan infusion initiation are detailed in Table 2; 71 patients (39%) had already received inotropic drugs, and 21% of them were receiving β-blockers.

Primary End Point

Levosimendan infusion resulted in 139 responders (R) out of 182 DHF patients [76.4%; 95% confidence interval (CI) 69.5%-82.3%]. Twenty-seven patients (14.8%) died during hospitalization (Graphic 1). Sixteen of 43 patients (37%) who failed to meet the primary end point were discharged after rescue therapy (dobutamine in 14 patients, dopamine in 1, and dobutamine and dopamine in 1). Mean hospital stay for all patients was 8 ± 10 days. Seventy-one patients (39%) received β-agonist inotropic drugs for at least 48 hours before levosimendan infusion and failed to improve clinically; 39 of them (55%) subsequently responded to levosimendan (Table 2). Treatment success was achieved in 25 of 30 (83.3%) patients receiving β-blockers (Table 2).

Secondary End Points

SBP reduction from baseline over time was observed in patients who received a loading dose (p=0.0492). Graphic 2 displays SBP changes between treatment groups that received or did not receive a levosimendan loading dose followed by continuous infusion. Mean SBP for R patients at baseline, 1, 12, 24, and 48 hours after levosimendan infusion initiation was respectively 112, 111, 110, 106, and 108mmHg; whereas for NR patients, it was 105, 99, 99, 96, and 96mmHg. No significant different response between groups was detected for DBP, (p=0.0897). No patient was withdrawn from the study because of symptomatic hypotension.

Heart rate (b/min) for R patients at baseline, 12 and 24 hours after levosimendan infusion initiation was respectively 83, 87, and 84, whereas for NR patients it was 89, 86, and 89. This effect on heart rate was not significant (p=0.1), nor was the interaction between groups and time (p=0.6).

A significant decrease was found in respiratory rate over time (p=0.01), but a difference in the rate between groups was not significant (p=0.6). There was no significant interaction between the groups and time (p=0.9).

Pulmonary congestion was present in both groups at baseline evaluation (R patients = 86.8%; NR patients = 70.7%) (Graphic 3a). A significant improvement occurred over time (p<0.0001). After 48 hours, 53.3% of R and 51.5% of NR patients had no pulmonary congestion.

Dyspnea was present in both groups at the beginning of levosimendan infusion (R patients=80.5% and NR patients=83.8%) (Graphic 3b). For dyspnea, a significant interaction between time and groups was observed (p=0.008), and its improvement over time in NR patients was slower. After 48 hours, the proportion of patients with no dyspnea was higher in R (67.5%) than in NR [(42.4%), p=0.014].

BNP serum levels were determined in 28 R and NR patients. A significant decrease in BNP over time was observed in R patients. At baseline and after 24, 48, and 72 hours, values for R and NR patients combined were respectively 1096±867, 740±1187, 827±743, and 474±565 pg/mL. B-type natriuretic peptide levels at baseline and after 24 hours for R patients were respectively 939±617 and 405±240pg/mL (p<0.05), whereas for NR patients levels were 1672±1558 and 2580±2886 pg/mL.

No significant changes in creatinine, hemoglobin, hematocrit, sodium, and potassium levels were observed between groups up to 48 hours.

Analysis of Factors Influencing Response to Levosimendan

The efficacy of levosimendan was not related to the loading dose amount. An average loading dose of 7.1 ± 4.5 μg/kg

Table 1 - Characteristics of patients with decompensated heart failure.

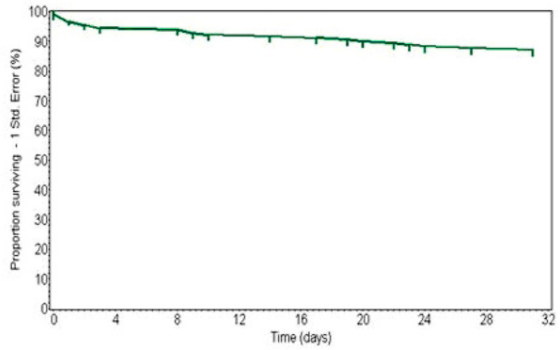
Characteristics	n = 182; n (%) or Value*
Age (years)	55 ± 16
Race (Caucasian/Afro-Brazilian)	106 (58,2%)/67 (36,8%)
Sex (male)	122 (67,0%)
Baseline systolic blood pressure (mm Hg)†	110,6 ± 22
Baseline diastolic blood pressure (mm Hg)†	70,5 ± 13,9
Baseline heart rate† (b/min)	87,4 ± 17,8
Baseline respiratory rate (p/min)	22,8 ± 6,1
Creatinine (mg/dL)	1,25 ± 0,41
Hemoglobin (g/L)	12,68 ± 1,96
Sodium (mEq/L)	135,6 ± 5,2
Potassium (mEq/L)	4,3 ± 0,6
Pulmonary congestion	147 (80,8%)
Cyanosis	38 (20,9%)
Dyspnea	147 (80,8%)
Prior-year hospitalizations	2,81 ± 3,07
Duration of congestive heart failure diagnosis (months)	46±13 (28 a 75)
Atrial fibrillation	31 (17,0%)
Left branch block	44 (24,2%)
Body mass index	24,2 ± 4,6
Chronic comorbidities	
Diabetes mellitus	25 (13,7%)
Thyroid disease	8 (4,4%)

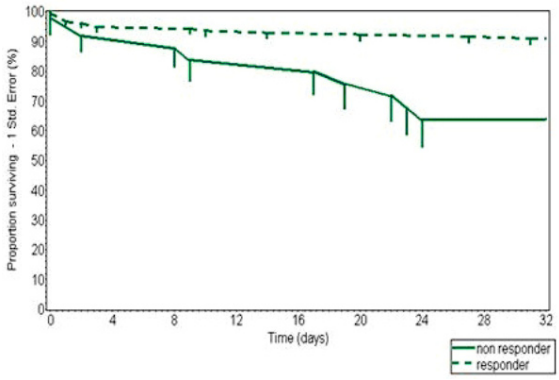
**Some values are means±1SD; n - Patients enrolled in the study; †Baseline systolic blood pressure, diastolic blood pressure, and heart rate were determined immediately before levosimendan infusion start.*

Table 2 - Medications used for decompensated heart failure treatment within the 48-hour period before levosimendan infusion.

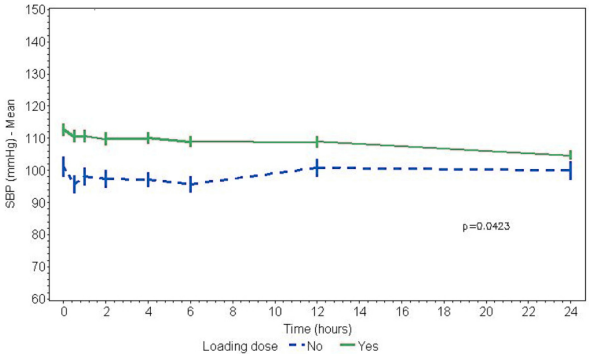
Medication	n = 182* n (%) and/or dose	R n = 139 n (%) and/or dose	NR n = 43 n (%) and/or dose	p
Oral				
Diuretics				
Furosemide	96 (52.7%)	81 (58.3%)	15 (34.9%)	0.00876
Hydrochlorothiazide	19 (10.4%)	16 (11.5%)	3 (7.0%)	0.57023
ACE inhibitor				
Enalapril	37 (20.3%)	30 (21.6%)	7 (16.3%)	0.52142
Captopril	100 (54.9%)	79 (56.8%)	21 (48.8%)	0.38438
Ramipril	1 (0.5%)	1 (0.7%)	0	1.00000
Angiotensin II AT1 receptors antagonists				
Losartan	8 (4.4%)	6 (4.3%)	2 (4.7%)	1.00000
Valsartan	2 (1.1%)	2 (1.4%)	0	1.00000
Candesartan	4 (2.2%)	2 (1.4%)	2 (4.7%)	0.23741
β-Adrenergic receptor blocker				
Carvedilol	30 (16.5%)	25 (18.0%)	5 (11.6%)	0.48032
Metoprolol	3 (1.6%)	2 (1.4%)	1 (2.3%)	0.55681
Atenolol	3 (1.6%)	2 (1.4%)	1 (2.3%)	0.55681
Bisoprolol	2 (1.1%)	2 (1.4%)	0	1.00000
Spironolactone	126 (69.2%)	100 (71.9%)	26 (60.5%)	0.18609
Amiodarone	39 (21.4%)	27 (19.4%)	12 (27.9%)	0.28744
Nitrates	5 (2.8%)	3 (2.1%)	2 (4.7%)	0.33789
Digoxin	109 (59.9%)	88 (63.3%)	21 (48.8%)	0.10967
Statins	6 (3.3%)	4 (2.9%)	2 (4.7%)	0.62775
Warfarin sodium	21 (11.5%)	14 (10.1%)	7 (16.3%)	0.27997
Acetylsalicylic acid (Aspirin)	33 (18.11%)	29 (20.9%)	4 (9.3%)	0.11264
Hydralazine	12 (6.6%)	8 (5.8%)	4 (9.3%)	0.48170
Parenteral				
Dobutamine	59 (32.4%)	34 (24.5%)	25 (58.1%)	0.00007
Lanatoside C/digoxin	7 (3.8%)	6 (4.3%)	1 (2.3%)	1.00000
Dopamine	9 (4.9%)	4 (2.9%)	5 (11.6%)	0.03510
Norepinephrine	3 (1.6%)	1 (0.7%)	2 (4.7%)	0.13949
Heparin/enoxaparin	6 (3.3%)	6 (4.3%)	0	0.33822
Nitroprusside	1 (0.5%)	0	1 (2.3%)	0.23626
Furosemide	121 (66.5%)	93(66.9%)	28 (65.1%)	0.85455
Amiodarone	5 (2.7%)	2 (1.4%)	3 (7.0%)	0.08669
Potassium chloride	3 (1.6%)	3 (2.2%)	0	1.00000
Aminophylline	2 (1.1%)	2 (1.4%)	0	1.00000
Intravenous inotropic drugs at initiation of levosimendan infusion				
Dobutamine	27 (15.9%)	7 (5.0%)	20 (46.5%)	<0.0001
Dopamine	10 (3.8%)	2 (1.4%)	8 (18.6%)	<0.0001
Norepinephrine	4 (1.6%)	1 (0.7%)	3 (6.9%)	0.0416

**n - patients enrolled in the study.*





Graphic 1 - Kaplan-Meier estimates of risk of death during 32 days follow-up after initiation of levosimendan infusion. Left: all patients; right, for R (Responders) versus NR Patients (Nonresponders) (Continuos Line) (p=0.001).



Graphic 2 - Effects of levosimendan intravenous infusion added to stantard of care on systolic blood pressure (±1 SD). Loading dose followed by 24-hour continous infusion (continuos line) versus absence of loading dose.

for 10 minutes was administered in 148 patients, and 112 (76%) were responders. Similarly, 27 of 34 patients (79%) who did not receive a levosimendan bolus at the beginning of levosimendan infusion also responded (p=0.4). Furthermore, concomitant use of β-blockers did not influence response rates to levosimendan. Thirty-one of 38 patients (82%) receiving β-blockers responded to levosimendan.

Significant differences were observed between R and NR patients in baseline SBP, creatinine, hemoglobin, and pulmonary congestion (Table 3). Only baseline SBP was a significant predictor of treatment failure (p=0.046) in logistic regression models, and an inverse relation with response to treatment was observed. Predictive ability of the model was improved when SBP was classified as hypotension (SBP< 90mmHg) or normal (p=0.0006).

Analysis of medications administered 48 hours before and during levosimendan administration demonstrated that oral diuretics and angiotensin-converting enzyme inhibitors were used more extensively by R patients; while dobutamine, dopamine, and norepinephrine were used more frequently by NR patients (Table 2).

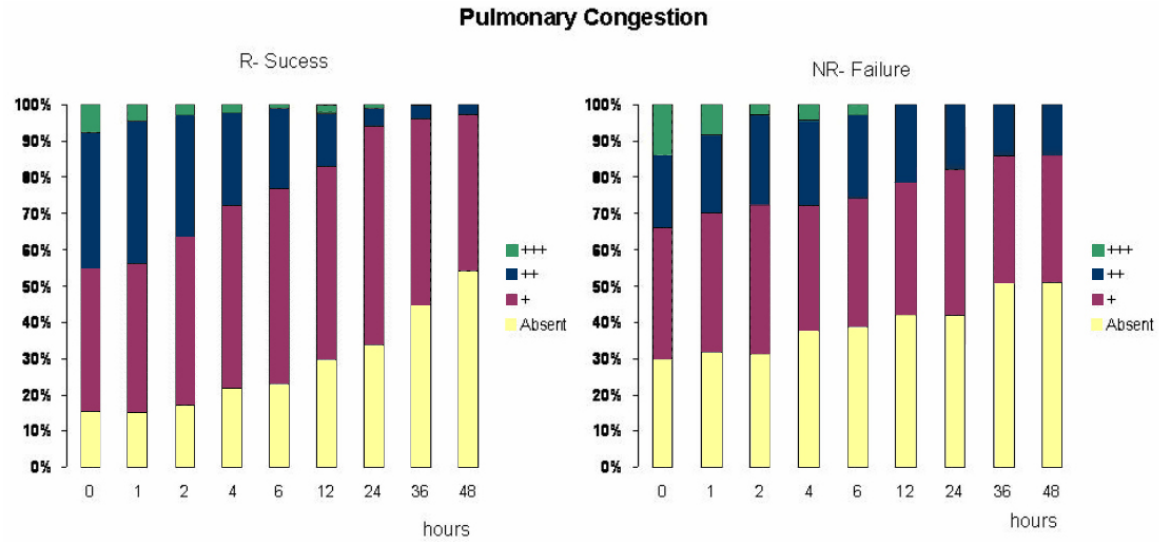
Dobutamine usage within the 48-hour period prior to levosimendan infusion was more frequent in NR (58.1%) than in R patients (24.4%, p<0.0001) (Table 2). No differences were observed in patients receiving β-blockers and intravenous diuretics. Eighty-one percent of patients receiving digoxin were responders, while 70% of patients not receiving digoxin were nonresponders.

Safety

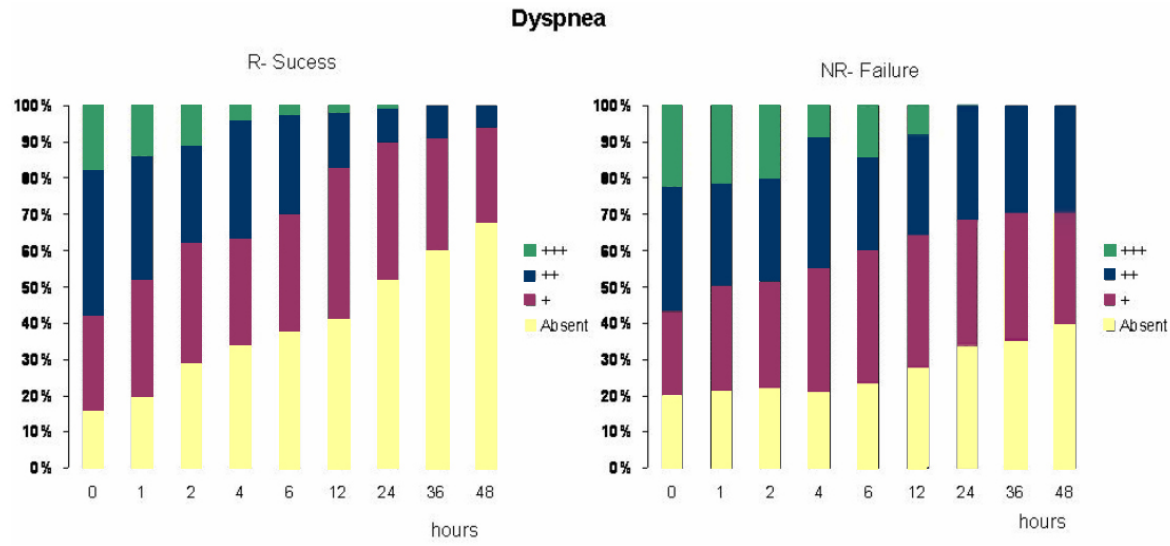
A total of 54 patients had at least one event during hospitalization (Table 4). Most events resolved either spontaneously or after levosimendan dose reduction. No patient had levosimendan infusion permanently or temporarily interrupted, and only 1 patient had the dose reduced. Seventeen patients died from cardiac causes: 7 from either complex arrhythmias or cardiac arrest (2 during infusion) and 10 from the progression of congestive HF. The noncardiac causes of death in 10 patients were pulmonary embolism in 2, pneumonia in 2, sepsis in 4, respiratory failure in 1, and chronic obstructive pulmonary disease in 1.

Hospital Stay and Readmissions, Quality of Life, and Mortality after Hospital Discharge

Graphic 1 shows the proportion of patients who survived to the end of the 32-day follow-up period after levosimendan infusion. Hospital admissions, survival data, heart transplants, and Minnesota Quality of Life Scores were collected for 118 patients over a period of 4.7±1.6 months (range, 1-9 months) after discharge. Forty-two patients (36%) were readmitted to the hospital, 10 died (8%), and 8 (7%) underwent heart transplantation. There was a significant improvement in quality of life from 2-6 months after hospital discharge, with a 26.4 mean decrease in Minnesota Quality of Life Score (p<0.0001) (Graphic 4).



Graphic 3.a - Dyspnea after levosimendan intravenous infusion added to standard of care in R patients (responders; success) versus NR patients (nonresponders; failure).



Graphic 3.b - Pulmonary congestion after levosimendan intravenous infusion added to standard of care in R patients versus NR patients; + means basilar congestion, ++ lower third congestion , and +++ 1/3 up to pulmonary apices congestion.

Discussion

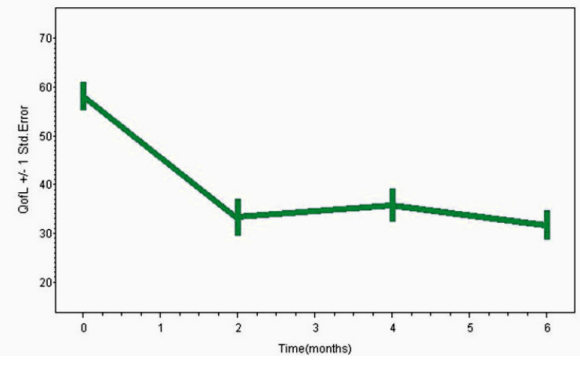
The BELIEF study results support the use of levosimendan as an effective alternative therapy in the short-term management of DHF. Levosimendan infusion may be effective in select patients in which β-adrenergic agonist therapy is not successful. Its concomitant use with β-blockers did not affect the percentage of patients with a favorable response to levosimendan. The only baseline variable demonstrated to be of prognostic value for determining clinical response to levosimendan was SBP; patients with hypotension (SBP < 90mmHg) were 4 times more likely to fail to respond to levosimendan.

The beneficial effects of levosimendan can be explained by the improvement in hemodynamic variables, including systolic and cardiac diastolic functions, reduction of ventricular filling pressures, and increase in cardiac output[3-10,12-25]. Additional attributes include vasodilation of the pulmonary circulation,[3] reduction in myocardial ischemia and infarct size, improvement

Table 3 - Characteristics of patients who responded (R) and achieved the primary end point compared with those who did not respond (NR).

Characteristic	R n=139 n (%) or Value*	NR n=43 n (%) or Value*	p Value
Age (years)	54.8 ± 18	55.4 ± 14.8	0.8
Race			
Caucasian	85 (61.2%)	21 (48.8%)	0.2
Afro-Brazilian	48 (34.5%)	19 (44.2%)	
Sex (male)	91 (65.5%)	31 (72.1%)	0.4
Diabetes mellitus	21 (15.1%)	4 (9.3%)	0.4
Baseline SABP (mmHg)†	104.7 ± 20.9	112.4 ± 21.7	0.043
Baseline DABP (mmHg)†	68.3 ± 13.2	71.2±14.2	0.2
Baseline heart rate† (b/min)	90.6 ± 20.8	86.4 ± 16.8	0.1
Baseline respiratory rate (p/min)	23.1 ± 6.5	22.7 ± 6	0
Creatinine (mg/dL)	1.38 ± 0.47	1.21 ± 0.4	0.023
Hemoglobin (g/L)	11.9 ± 1.9	12.9 ± 1.9	0.005
Sodium (mEq/L)	134.9 ± 6	135.8 ± 4.9	0.3
Potassium (mEq/L)	4.3 ± 0.7	4.3 ± 0.6	0.7
Pulmonary congestion	118 (84.9%)	29 (67.4%)	0.03
Cyanosis	26 (18.7%)	12 (27.9%)	0.2
Dyspnea	114 (82.0%)	33 (76.7%)	0.6
One year previous hospitalizations	3.73 ± 4.21	2.54 ± 2.61	0.097
Atrial fibrillation	24 (17.3%)	7 (16.3 %)	1
Left bundle branch block	38 (27.3%)	6 (14.0%)	0.1
Body mass index	23.5 ± 5.19	24.4 ± 4.4	0.3
Variables during postlevosimendan infusion			
SBP 2 hours after levo initiation	110.67 **± 21.91**	98.60 **± 16.19**	0.0003
DBP 2 hours after levo initiation	70.72 **± 12.87**	61.13 **± 9.95**	<0.0001
Hb (g/L) 36 hours after levo initiation	12.89 **± 2.00**	11.39 **± 2.00**	0.003
Use of loading dose	112 (80.6%)	36 (83%)	0.82
No loading dose	27 (19.4%)	7 (16.3%)	

**Some values are means±1SD; Hb - hemoglobin (g/L); SBP - systolic blood pressure; DBP - diastolic blood pressure.*



Graphic 4 - Quality of life in 6-month follow-up after hospital discharge (Minnesota living with heart failure questionnaire).

in left ventricular-arterial coupling[20], improvement in antistunning effects, energetically favorable profile-enhancing cardiac output without oxygen consumption increase[22], and improvement in neurohormonal proinflammatory profile including reductions in renal endothelin-1, atrial natriuretic peptide, and rennin[23-26].

In vitro mechanisms of action reported for levosimendan include (a) increment in myofilament calcium sensitivity by binding to cardiac troponin C in a calcium-dependent manner[5], (b) enhanced release and reuptake of calcium in the sarcoplasmic reticulum[14], (c) arteriolar and venous dilation by activation of ATP- and glibenclamide-sensitive potassium channels via calcium desensitization of peripheral smooth muscle cells in vessel walls[6,16,17], (d) and phosphodiesterase inhibition above therapeutic levels[5,19,26,27]. In vivo mechanisms of action for levosimendan are not known[28]. Pathophysiological

conditions can change myofilament response to a specific intracellular concentration of calcium. In guinea pig hearts, the cardiotonic calcium effects of levosimendan may be influenced by β-adrenergic stimulation[29]. Also, mechanisms involved in increased inotropy may be species-dependent[18,19].

Our results confirm and extend the findings on efficacy of levosimendan in DHF patients[7-10,30] and also demonstrate that reduction in respiratory rate and congestion support findings of the REVIVE II study, but contrast with findings of the RUSSLAN study[8]. However, improvements in dyspnea have been reported with short-term (6-hour) and long-term (24-hour) levosimendan infusions[4,7].

In our patient cohort, baseline SBP was a good predictor of clinical response to levosimendan, especially when patients were categorized with SBP above or below 90mmHg. Reduced SBP was found to be a powerful predictor of adverse outcomes in HF patients[31,32]. It is likely that negative consequences of further vasodilation in hypotensive patients requiring sympathomimetic inotropic agents to maintain SBP may overcome the favorable effects of increased cardiac contractility. Furthermore, the magnitude of increased myofibrillar calcium sensitivity might be reduced in patients with severe cardiomyopathy[33]. Other studies[32,34] on HF have also demonstrated reduced treatment success rates in the presence of other markers of worse prognosis, such as anemia, renal dysfunction, pulmonary congestion, and also the use of inotropic drugs that increase intracellular calcium levels, eg, β-agonists. The lower creatinine and hemoglobin serum values in responders observed in our study, however, contradict this concept.

The finding that levosimendan did not negatively affect renal function concurs with previous reports[30,35]. This is encouraging because renal function decreases in approximately 21% of patients hospitalized with HF[36]. Because kidneys excrete 20% of the levosimendan metabolites, metabolism of the medication is only minimally impacted by decreased renal function[37]. Moreover, worsening of renal failure was associated with more than a twofold increase in the incidence of adverse events[35].

The reported adverse event rate demonstrates that levosimendan is acceptably tolerable for high-risk patients with severe DHF. Our results are consistent with the previous reported incidence of significant dose-dependent hypotension.[7] The incidence rate for other events was also similar to those previously reported except for the incidence of atrial fibrillation, ventricular fibrillation, and hypotension/cardiogenic shock, which was lower than that observed in the SURVIVE study[4,7-9,30,35]. The reasons for this finding are unknown, but the characteristics of the Brazilian cohort may have contributed to these differing results.

Of particular note was the sustained improvement in Minnesota Quality of Life Scores within our patient cohort. The 24.6 point improvement from 2-6 months during follow-up after hospital discharge exceeded the improvement reported by 31 other HF trials and was matched by only one trial[38]. Our readmission results were consistent with those previously reported demonstrating high hospital admission rates after hospital discharge. Nonetheless, unlike patients in other studies, our patients reported a consistent, stable improvement in quality of life after 6 months[39]. Pharmacological effects of the active levosimendan metabolite OR-1896, with an elimination half-life of approximately 80 hours, are sustained but cannot be expected to prevent late rehospitalizations[40].

Clinical Implications

Levosimendan is a promising alternative drug for DHF treatment because it can combine inotropic and vasodilatory effects and the following actions: efficacy is maintained in patients on β-blockers, absence of tachyphylaxis, and minimal increase in heart rate.

Study Limitations

This study was limited by its open-label and nonrandomized design. Furthermore, the lack of a placebo group prevents determination of cause and effect relationships between treatment and outcomes. Nonetheless, the consistency of favorable treatment results and the low incidence of adverse events must be attributed to levosimendan, even in patients receiving numerous pharmacological agents. Also, BNP results should be interpreted with limitations because the BNP serum levels were determined in a subgroup of patients; and comparison of SBP reduction from baseline over time between patients who received a loading dose versus patients without bolus infusion, should be analyzed with caution due to different baseline SBP.

Conclusion

This study suggests that levosimendan is an attractive therapeutic option in short-term management of DHF, even in patients resistant to other inotropic drugs or taking β-blockers. Patients presenting with SBP ≥ 90mmHg seem to benefit the most from levosimendan therapy. Our results should stimulate interest in a specific trial for a DHF Brazilian cohort including Chagas' heart disease patients.

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