ORIGINAL ARTICLE

Efficacy of early administration of levosimendan in emergency department in patients with acute heart failure: a randomized pilot clinical trial

Pere LLORENS[1], Òscar MIRÓ[2], Francisco ROMÁN[1], Pedro ZAPATER[3], José CARBAJOSA-DALMAU[1], Lucía LLANOS[3]

[1]Servicio de Urgencias-UCE, Hospital General Universitario de Alicante, Spain. [2]Àrea de Urgencias, Hospital Clínic. Grupo de investigación "Urgencias: procesos y patologías" IDIBAPS, Barcelona, Spain. [3]Servicio de Farmacología Clínica, Hospital General Universitario de Alicante, Spain.

Correspondence:
Pere Llorens
Servicio de Urgencias-UCE
Hospital General de Alicante
C/ Pintor Baeza, 12
03010 Alicante, España
Email: llorens_ped@gva.es

Received:
20-4-2012

Accepted:
20-5-2012

Conflict of interest:
None

Acknowledgements:
The authors wish to thank Dr. Cristina Fernández Pérez of Hospital Clínico San Carlos de Madrid, who is also a senior lecturer in the Faculty of Mathematics, Universidad Complutense de Madrid, for her guidance on the statistical analysis.

Objective: To compare the efficacy and safety of early levosimendan administration in addition to standard treatment in patients with severe symptoms of decompensated heart failure attended in the emergency department (ED).
Methods: A single-center, prospective, third-party blinded, randomized, placebo controlled, pilot study was performed in 45 patients with advanced heart failure attended in the ED. Patients were randomized 1:1 to receive intravenous levosimendan or placebo in addition to standard care. The primary endpoint was improvement in baseline dyspnea over 24 hours. Improvement of orthopnea, jugular ingurgitation and peripheral edema, cumulated diuresis and changes in systolic and diastolic blood pressure and in heart and respiratory rates were also registered. Adverse events during treatment were recorded. Patients were followed for 7 days and at 1 and 6 months after hospital discharge for all causes of hospital readmission, mortality or both.
Results: Dyspnea improved faster and in more patients with the use of levosimendan ($P<0.05$). Similar findings were found for orthopnea ($P<0.05$), with no differences for the remaining variables. Adverse effects were observed in 20% and 25% of patients in the levosimendan and placebo groups, respectively (P=NS), with no patients withdrawn from the protocol. No differences were seen with respect to readmission, mortality or both outcomes in combination.
Conclusion: Early treatment with levosimendan produces no significant differences in readmission or mortality rates, although it is associated with a significant clinical benefit in terms of improvement in dyspnea and orthopnea compared with placebo. [Emergencias 2012;24:268-276]

Key words: Levosimendan. Acute heart failure. Emergency Department.

Introduction

Current pharmacological treatment of acute heart failure (AHF) is based on the use of diuretics, vasodilators and inotropic agents[1,2]. The latter have demonstrated their efficacy in improving myocardial function, some hemodynamic variables and neuro-hormonal markers. However, certain issues related with increased risk of adverse effects, such as life-threatening arrhythmia[3], have limited their use in different clinical scenarios. Levosimendan is a relatively recent inotropic drug which increases calcium sensitivity of myocytes by binding to cardiac troponin C and thus improves cardiac contractility. It also causes vasodilation by activating potassium channels sensitive to adenosine triphosphate (ATP)[4]. As a result, levosimendan increases cardiac output, coronary and kidney flow, and heart rate (HR), to reduce preload and cardiac afterload. Furthermore, it also has an antiarrhythmic effect and increases cardiac contractility without increasing the risk of ischemia[5-7], which could provide additional benefits in terms of long-term mortality[8-11].

For these reasons, since 2005[12], The European Society of Cardiology (ESC) has included levosi-

mendan in the therapeutic arsenal for symptomatic heart failure and, in the clinical guidelines of 2008, levosimendan was considered the inotropic agent of first choice for treatment of symptoms in patients with AHF with systolic dysfunction, signs of congestion or hypoperfusion and systolic blood pressure (SBP) above 100 mmHg, when symptoms persist after treatment with diuretics and vasodilators (recommendation IIa, level of evidence B)[2].

In the emergency department (ED) however, experience with levosimendan is limited to a few case reports or small case series, with no evidence from controlled studies currently available[13]. In addition, the potential benefit of early levosimendan use in selected patients has not been evaluated. We therefore hypothesized that early levosimendan treatment, initiated at the same time as diuretics and vasodilators, could improve symptoms and signs of AHF and, consequently, short term prognosis. The primary aim of the present study was to assess the efficacy and safety of early levosimendan administration in patients with advanced AHF (New York Heart Association-NYHA-classes III and IV) treated in an ED.

Method

We performed a pilot, placebo-controlled, triple blind, randomized interventional clinical trial with consecutive inclusion of AHF patients at a single center. It was an independent study, designed and promoted by the researchers themselves, without external public or private funding, carried out only with the resources of Hospital General de Alicante. The protocol was registered in the European Clinical Trials Database (EudraCT 2007-002447-25); it was approved by the Ethics Committee of Hospital General de Alicante and was performed according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines of the European Union. All patients gave their written informed consent before inclusion in the trial.

This study was conducted in the ED of Hospital General de Alicante, an urban university hospital attending a population of approximately 300,000 people. The center has 816 beds, 19 in the intensive care unit; it attends approximately 100,000 emergencies a year.

The study subjects were included from patients admitted consecutively to the ED for an episode related with AHF. The diagnosis was made according to Framingham criteria[14]. Inclusion criteria were: age 18 years or older, NYHA functional class III or IV, presence of decompensated AHF with symptoms and signs of pulmonary and systemic congestion requiring intravenous therapy and hospitalization, and SBP $\geq$ 90 mmHg on ED arrival. The exclusion criteria were: previous inclusion in this protocol, history of ventricular fibrillation, sustained ventricular or multiple episodes of ventricular tachycardia or torsade de pointes, respiratory distress syndrome, septic shock, cardiac tamponade, restrictive or hypertrophic cardiomyopathy, moderate to severe valve stenosis, liver failure, severe renal impairment (defined as creatinine a clearance < 30 ml/min), hypersensitivity to levosimendan or any of its excipients, pregnancy or breastfeeding. Patients were also excluded if they showed hemodynamic instability requiring mechanical support on ED arrival.

Patients were stratified according to SBP and randomized 1:1 (using a random numbers list) to receive intravenous levosimendan (study group) or glucose solution at 5% (placebo group). Assignment of each patient to one or other group was performed by the clinical pharmacology department and masked for the emergency physicians (EPs) responsible for the study. We informed all EPs of the protocol at 2 meetings before starting the study in order to ensure the presence of an EP familiar with it, 24 hours a day and 7 days a week. The study began in June 2007. EPs who treated patients in the ED screened for potential candidate patients for the study, and when they detected an eligible patient, contacted the principal investigator (PI). The PI immediately verified that the patient met all selection criteria and authorized the request for inclusion in the study. If patient consent was finally obtained, the EP contacted a pharmacologist in the clinical pharmacology department who randomly assigned the patient to one or other treatment group. To ensure blinding, the infusion systems were covered with aluminum foil to prevent evaluator identification by the yellow color of levosimendan. The maximum time from the patient's arrival at the ED to randomization was 2 hours. In all cases, the patient received conventional treatment, including oxygen at a concentration of 28-40%, intravenous furosemide (bolus of 20 mg/6 h) and vasodilators (continuous perfusion of nitroglycerin with initial dose of 10-20 µg/min and gradual adjustment to achieve SBP between 100 and 140 mmHg, with a maximum dose of 200 µg/min). The remaining treatment was prescribed at the discretion of the attending EP in accordance with SEC 2005 clinical guidelines[12]. In patients with SBP> 120 mmHg, levosimendan was started with a loading

dose of 6 mg/kg administered in 10 minutes, followed by continuous infusion of 0.1 µg/kg/min for 24 hours. In patients with SBP between 90 and 120 mmHg, no initial loading bolus was administered. In the placebo group the same procedure was followed using a glucose solution at 5%. In patients who experienced a decline of SBP below 90 mmHg, the perfusion dose was reduced by half, and nitroglycerin tapered gradually to withdrawal if necessary. In those cases where hypotension was symptomatic or persistent after adoption of this strategy, the patient was excluded from the study and the blinding foil was removed. In order to ensure blinding, each randomized patient was controlled by two different senior EPs: one was responsible for carrying out the treatment and controlling the patient's clinical condition, and the other EP performed the measurement of all the outcome variables. Patients treated with placebo who showed no improvement after 24 hours received treatment according to clinical guidelines for managing heart failure[12]. The use of angiotensin converting enzyme (ACE) inhibitors, digoxin, beta blockers, aldosterone antagonists, amiodarone, and antiplatelet agents was permitted. Patients were admitted to the ED-dependent short stay unit, after perfusion was initiated, without invasive monitoring to guide treatment. Echocardiographic assessment was not performed during the study. However, if the patient had undergone echocardiography in the previous 12 months, the type of heart failure was recorded according to the criteria described by Swedberg et al[15].

We recorded demographic and clinical data, and the results of blood tests including troponin-T and NTproBNP and chest x-ray, at the time of patient inclusion in the study. We also recorded data on creatinine and plasma electrolytes at the end of drug infusion.

The primary outcome variable was improvement of dyspnea, quantified according to patient response using a 7-point Likert type scale[16], ranging from "markedly better" to "markedly worse" which was compared with the degree of dyspnea present at the time of starting treatment. Improvement was considered as demonstrated when the score increased by two points on the scale.

We considered eight other secondary outcome variables related a priori to aspects of the efficacy and safety of levosimendan: two were categorical [orthopnea (no/yes) and jugular venous distention (no/yes)], and six were quantitative [peripheral edema (categorized using a six-point scale according to the level of edema: 0: no edema, 1: feet, 2: ankles, 3: knees, 4: thighs 5: anasarca), cumulative urine output (volume in ml), diastolic BP (in mmHg), heart rate and breathing rate (per minute)].

The primary and secondary outcome variables were assessed at baseline, and at 1, 2, 6, and 24 hours after initiation of treatment.

Besides the creatinine and plasma electrolyte data, we also recorded any adverse effects reported by the patient or observed by an investigator at the end of perfusion. This information was obtained using a semi-structured interview focusing on cardiovascular, respiratory, neurological and metabolic systems. Finally, we also followed up all patients by means of electronic medical records and/or telephone calls to record the percentage of readmissions or all-cause mortality in the first week, and the first and sixths month after discharge.

Given the apparent non-existence of a previous study to assess the effects of early levosimendan use to treat AHF in the ED, the present work was considered a pilot study and the plan was to include 45 patients.

Quantitative variables were described as mean ± standard deviation (Kolmogorov-Smirnov test was used to verify that the distribution was normal) and qualitative variables as frequencies or percentages. For analysis of the baseline characteristics between the groups we used one-way ANOVA for quantitative data and chi-square test or Fisher exact test for qualitative data. Two-way ANOVA was used for continuous variables (peripheral edema, SBP and DBP, heart rate and breathing rate, and cumulative urine output) to compare the effects of treatment over time, while a multivariate conditional logistic regression model was used for categorical variables (dyspnea and orthopnea). All analyses were planned for patients on an intent-to-treat basis. All p values were two-tailed and considered statistically significant when less than 0.05. All calculations were performed using SPSS version 15.0 and STATA version 11.

Results

The recruitment process for this clinical trial lasted 12 months (June 2007-May 2008), as shown in Figure 1. Twenty-five patients were randomly assigned to treatment with levosimendan and twenty to placebo. Thirty two and 35% of patients, respectively, had SBP values between 90 and 120 mmHg. Groups were similar in age, sex, cause of HF, clinical and laboratory parameters (Table 1).

Table 1. Demographic characteristics, clinical and laboratory data of patients included in the present study

	Levosimendan group (N = 25)	Placebo group (N = 20)	P
SBP < 120 mmHg [n (%)]	8 (32)	7 (35)	0.83
Age (mean ± SD)	80.8 ± 7.9	77.6 ± 9.9	0.24
Sex (male/female)	6/19	7/13	0.42
Barthel Index (mean ± SD)	81.8 ± 19.5	84.3 ± 19.7	0.79
Charlson index (mean ± SD)	3.7 ± 1.8	2.4 ± 1.0	0.15
Primary coronary disease [n (%)]	5 (20)	4 (20)	0.71
Primary valvular disease [n (%)]	7 (28)	5 (25)	0.91
Type of heart failure [n (%)]*			0.36
Systolic	2 (8)	4 (20)	
Diastolic	7 (28)	8 (40)	
Mixed	10 (40)	4 (20)	
Unknown	6 (24)	4 (20)	
Diabetes mellitus [n (%)]	14 (56)	7 (35)	0.16
Hypertension [n (%)]	24 (96)	17 (85)	0.19
Smoking (active or ex-smoker) [n (%)]	3 (12)	3 (15)	0.77
Creatinine (mg/dL) (mean ± SD)	1.3 ± 0.4	1.3 ± 0.4	0.96
Patients >1.3 mg/dL [n (%)]	9 (36)	9 (45)	0.76
Sodium (mEq/L) (mean ± SD)	137 ± 5	138 ± 2	0.41
Patients <135 mEq/L [n (%)]	3 (12)	1 (5)	0.62
Potassium (mEq/L) (mean ± SD)	4.5 ± 0.5	4.4 ± 0.8	0.61
Patients <3.5 mEq/L [n (%)]	2 (8)	5 (25)	0.21
Patients >5.5 mEq/L [n (%)]	2 (8)	2 (10)	1.00
Hemoglobin (g/L) (mean ± SD)	11.9 ± 1.8	12.4 ± 1.5	0.26
Troponin T (ng/mL) (mean ± SD)	0.023 ± 0.017	0.017 ± 0.011	0.18
Patients >0.1 ng/mL [n (%)]	0 (0)	0 (0)	–
NT-proBNP (pg/mL) (mean ± SD)	5482 ± 4711	5988 ± 6027	0.65
Concomitant treatment [n (%)]			
Beta-blockers	13 (52)	12 (60)	0.59
ACE inhibitors or ARA	18 (72)	12 (60)	0.40
Furosemide	24 (96)	19 (95)	0.87
Spironolactone	4 (16)	2 (10)	0.68
Digoxin	4 (16)	6 (30)	0.32

*Classification according to Swedberg et al[15] criteria. SBP = systolic blood pressure, SD = standard deviation, ACE = angiotensin converting enzyme, ARA = angiotensin receptor antagonist.

Dyspnea improvement at 1, 3, 6 and 24 hours after initiation of treatment was significantly higher in patients treated with levosimendan compared with those receiving placebo ($p < 0.05$) (Figure 2). After treatment, the dyspnea improved in 22 patients treated with levosimendan, was unchanged in 2 and worsened for I patient. In the placebo group, dyspnea improved in only 11 patients, showed no change in 7 and worsened for 2 patients. The improvement in dyspnea at 24 hours in patients who received levosimendan was recorded in 86%, 50%, 90% and 100% of patients with diastolic, systolic, mixed or unknown HF respectively. These percentages were lower in the placebo group (63%, 25%, 50% and 50% respectively), although the differences were not statistically significant ($p = 0.31$ $p = 0.54$, $p = 0.09$, $p = 0.19$ respectively).

In the initial assessment, 22 patients treated with levosimendan (88%) and 16 with placebo (80%) had orthopnea, and 24 hours after treatment, 16 patients in each group continued to have orthopnea. Surprisingly, 4 of the placebo-treated patients without orthopnea in the initial assessment developed manifestations of orthopnea after the first and third hour after initiation of treatment. The number of patients without orthopnea in the levosimendan treatment group was lower after initiation and maintenance of treatment, as shown in Figure 3. Evolutionary analysis of the data showed greater improvement of orthopnea over time in the group of patients receiving levosimendan (Figure 3).

Regarding the seven secondary outcome variables (Figure 3), significant changes were documented in time with respect to jugular venous distension (decrease, $p < 0.001$), peripheral edema (decrease, $p < 0.001$), SBP (decrease, $p = 0.01$), respiratory rate (decrease, $p < 0.001$) and diuresis (increase, $p < 0.001$). However, there were no significant differences in any of these outcome variables during the 24-hour evaluation period between the levosimendan and placebo groups.

During the first 24 hours after initiating treatment, adverse clinical effects were noted in 20% of patients receiving levosimendan and 25% of those receiving placebo, and electrolyte alterations occurred in 40% and 35%, respectively. A transient decrease in SBP below 90 mmHg was recorded in 2 patients in the levosimendan group and in 3 patients in the placebo group. Table 2 shows the adverse clinical effects and electrolyte changes recorded in the two groups.

Median hospital stay was the same in both groups of patients (median: 3 days, 25 and 75 percentile: 2-4 days, $p = 0.72$). No differences were recorded between groups in terms of readmission or all-cause mortality at 7 days, 1 month and 6 months. There were also no statistically significant differences for the combined outcome variable readmission and mortality (Table 3). Decompensation of HF was the main cause of hospital readmission in the two treatment groups (14 cases treated with levosimendan and 10 in those treated with placebo).

Discussion

The results of this clinical trial indicate the symptomatic utility of early levosimendan administration in selected patients with AHF treated in an ED. The addition of levosimendan to conventional treatment produced better and more rapid improvement in dyspnea in the first 24 hours after initiating treatment, and also relieved orthopnea in a greater percentage of patients.

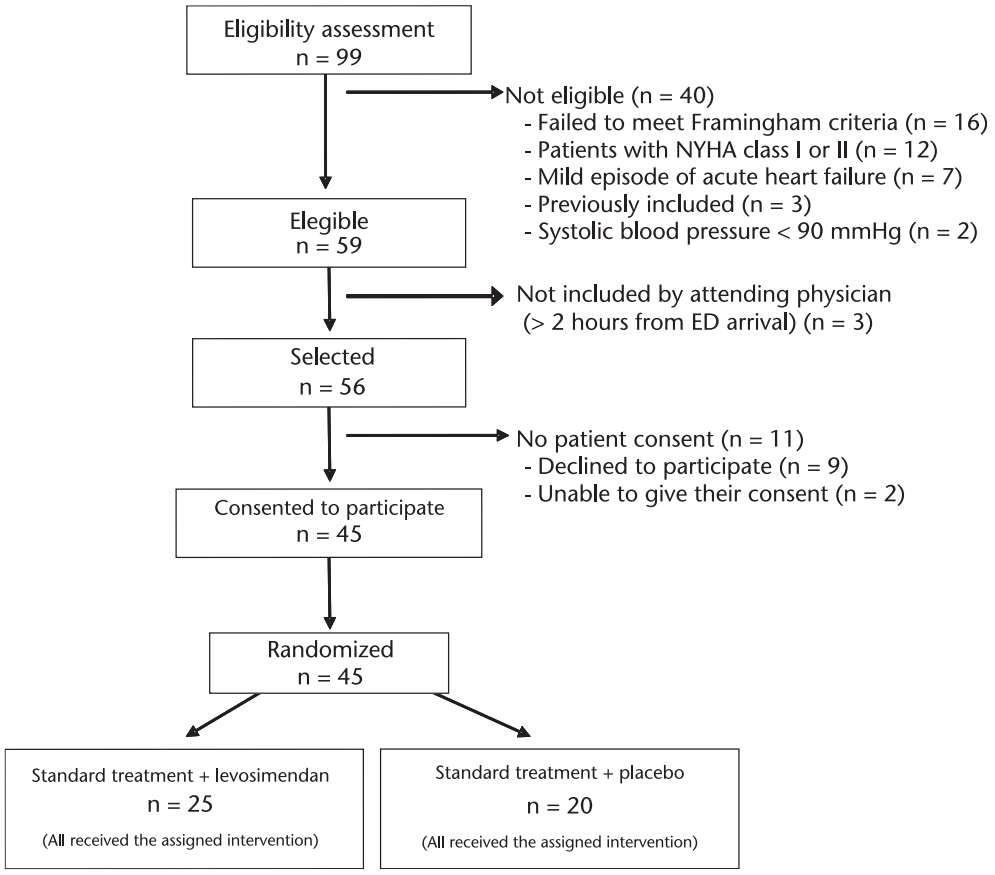

Figure 1. Flowchart of patients included in the study.

Our findings are consistent with those of previous studies that considered the improvement of dyspnea as a secondary outcome variable. In an American study with dose escalation[17], the improvement in dyspnea at 6 hours after initiation of treatment was significantly higher in levosimendan-treated patients (29%) compared with those receiving placebo (15%). In the REVIVE-2 study, levosimendan produced an improvement in dyspnea at 6 and 24 hours and at 5 days of treatment in patients with decompensated heart failure (ejection fraction < 35%) with dyspnea at rest despite previous treatment with intravenous diuretics[18]. This rapid effect may be due to the loading dose, absent in many previous studies[19], or the additive effect of levosimendan with intravenous diuretics[20,21]. Our data also indicate that this effect was observed regardless of the type of HF, and this is consistent with the results of previous studies which found that levosimendan improves both systolic and diastolic function[7,22]. A significant finding in our study was that improvement in dyspnea and orthopnea was recorded in patients with a high average age (80.8 ± 7.9 years in the levosimendan group and 77.6 ± 9.9 years in the placebo group). Most HF patients treated in the ED are aged 23-25 years, while those included in clinical trials also had a lower average age (RUSSLAN, 67.2 years; REVIVE-II, 63; SURVIVE, 67; LIDO, 59 years)[26]. Interestingly, the safety profile of levosimendan in the elderly patients included in our study was similar to that observed in younger patients included in previous studies. However, the small sample size of our study does not allow conclusive findings in this regard.

We would point out that there were no significant differences in SBP, DBP and HR between the two groups of patients, in contrast to several published studies which reported a higher percentage of hypotension and atrial fibrillation in patients who received levosimendan[5,6]. In our study, a transient decrease of SBP below 90 mmHg was observed in only 2 and 3 patients treated with levosimendan and placebo respectively. One possible explanation for this low number of episodes of hypotension may be the use of a strategy which avoided high loading doses (we used a low-dose bolus of 6 µg/kg, half that initially indicated by the levosimendan manufacturer), as well as decreasing the continuous infusion dose by half

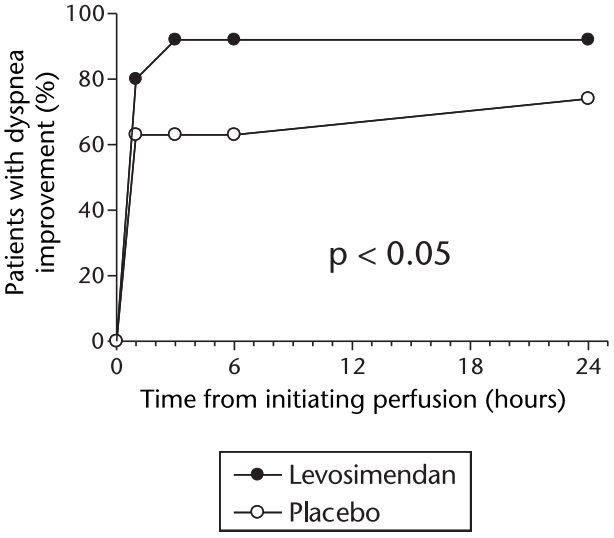

Figure 2. Analysis of improvement in dyspnea over time. The p value indicates the statistical difference between the two groups using multivariate conditional logistic regression.

during any episode of hypotension. High dose levosimendan has been linked to increased hypotensive episodes, arrhythmias and other adverse effects[27,28].

Median hospital stay was similar in the two groups of patients (3 days; p = 0.72). The study REVIVE-II18 showed shorter hospital stay in the levosimendan group (7 ± 4.6 days) compared

with the control group (8.9 ± 8.6 days; p = 0.003). Parissis et al[29] in a study that included 63 patients reported significantly reduced hospital stay in patients receiving levosimendan (3.2 ± 1.7 days) compared with those receiving placebo (5.8 ± 2.1 days) (p < 0.01). In our study, median hospital stay was shorter than that reported in previous studies. This might be due in part to the fact that patients included in most of these studies were hospitalized with severe systolic dysfunction refractory to treatment with diuretics and vasodilators[8-10,18] compared to our series which included few patients with systolic dysfunction and no evidence of resistance to treatment.

Table 2. Adverse clinical effects and electrolyte alterations during study treatment perfusion

Adverse effects	Levosimendan (N = 25)	Placebo (N = 20)	p
Patients with adverse clinical effects [n (%)]	5 (20%)	5 (25%)	0,73
Transient decrease of SBP < 90 mmHg	2	3	
Acute coronary syndrome	–	1	
Chest pain	1	–	
Dizziness	–	1	
Abdominal pain	1	–	
Deterioration of renal function	1	–	
Macroscopic hematuria	–	1	
Patients with hydro-electrolyte alterations [n (%)]	10 (40%)	7 (35%)	0,77
Increased creatinine > 0.3 mg/dL	5	1	
Development of hyponatremia (< 135 mEq/L)	4	2	
Development of hypokalemia (< 3.5 mEq/L)	1	4	
Development of hyperkalemia (> 5.5 mEq/L)	1	4	

SBP: systolic blood pressure.

Table 3. Readmission and mortality at 7 days, one month and six months after discharge

	Levosimendan (N = 25)	Placebo (N = 20)	P
Readmission for any cause			
Within 7 days	2 (8%)	2 (10%)	0.77
In the first month	6 (24%)	5 (25%)	0.79
Within 6 months	18 (72%)	13 (65%)	0.32
All-cause mortality			
Within 7 days	1 (4%)	1 (5%)	0.57
In the first month	2 (8%)	1 (5%)	0.84
Within 6 months	5 (20%)	5 (25%)	0.73
Combinada (mortalidad o reingreso)			
Within 7 days	3 (10%)	2 (12%)	0.36
In the first month	7 (28%)	5 (25%)	0.36
Within 6 months	19 (76%)	13 (65%)	0.52

In a previous clinical trial with 34 patients, which was similar to ours in that the patients included were not candidates for inotropic drugs per se, and which considered the combined outcome variable of death and hospital readmission hospital at 5 months, the authors found that result in 89% of patients of the placebo group and 71% of those in the levosimendan group[7]. In our study, for this combined outcome variable at 6 months, we found slightly lower values (65% and 76%, respectively). However, it is very difficult to attribute any eventual difference found in the long-term to treatment administered during the patient's stay in the ED, since mortality and hospital readmission of HF patients depends on a multitude of factors other than the drugs prescribed in the acute phase of HF decompensation[30-33]. In the opinion of the authors, it is difficult to link events that occur more than a week after pharmacological intervention to the drugs themselves, and for that reason they performed short-term evaluation (7 days). However, when considering this in relation to prognosis, they were also unable to demonstrate any benefit in favor of levosimendan.

In our study, both short and long term all-cause mortality was similar in the levosimendan and placebo groups. These findings are consistent with the results of a recent meta-analysis of 6 controlled clinical trials involving a total of 1,578 participants. Comparing levosimendan with place-

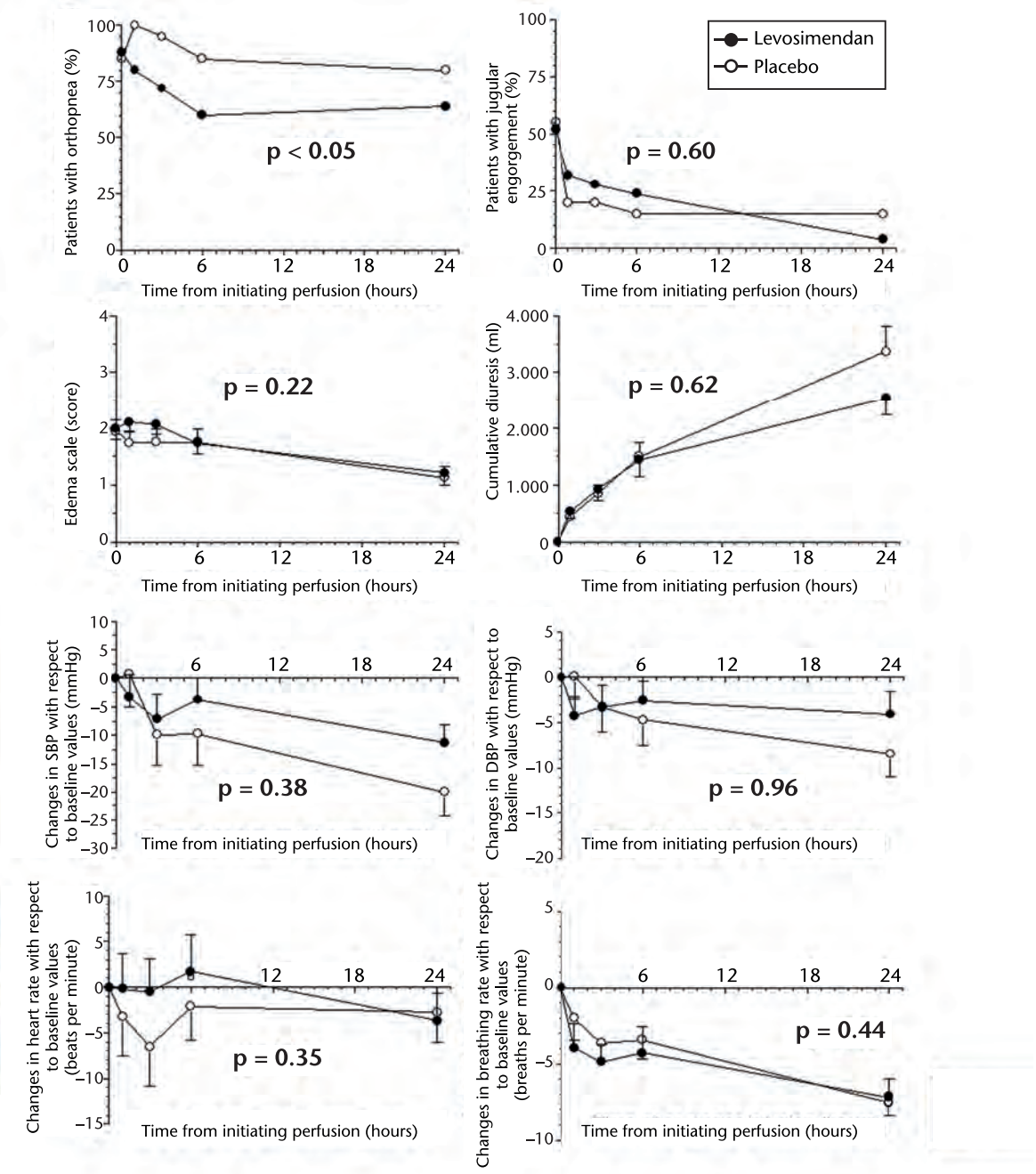

Figure 3. Analysis of changes in the percentages of patients with orthopnea and jugular engorgement (top), peripheral edema and cumulative urine output (upper middle), systolic blood pressure and diastolic blood pressure (SBP and DBP, lower middle), and heart and respiratory rate (bottom) over time. The p value indicates the comparison between the two groups using a multivariate conditional logistic regression model for orthopnea and jugular venous distension, and 2-way ANOVA for the remaining variables. The bars represent standard error.

bo in terms of 1-180 day mortality, the odds ratio for the levosimendan-treated group was 0.83 (95% CI 0.62-1.10, p = 0.20). It would therefore seem that levosimendan is no better than placebo in reducing mortality in patients with AHF[28].

In this regard, early administration of levosimendan was not associated with a reduction in hospital stay time or short-term prognosis. These findings, together with the fact that levosimendan only improved subjective symptoms and the high cost of treatment (about 600€ per patient in 24 h treatment), limits its usefulness in the ED and should not be routinely used in patients with decompensated AHF.

The study has a number of limitations. First, the main outcome variable was dyspnea, which is liable to subjective bias. This we sought to control, at least in part, with the triple blind study design. In addition, our method of assessing dyspnea has been used successfully in recent studies by other authors[16]. Secondly, we did not perform continuous invasive monitoring, which leaves open the possibility of undetected episodes of cardiac arrhythmia or hypotension. In any case, such episodes were asymptomatic or had minimal clinical impact since they were not evident during the follow-up period. Thirdly, the type of heart failure was unknown in the great majority of cases. This is relatively common in a high proportion of AHF patients attended in the ED. It is important to note that the early improvement observed in our levosimendan study appears to be independent of the type of cardiac dysfunction. Finally, this was a pilot study with a small sample size, which implies a high risk of type II error, especially regarding conclusions on safety issues.

The results of the present study show that the addition of levosimendan to conventional treatment at an early stage had no effect on the short- or long-term prognosis of patients attending the ED for a moderate-severe episode of AHF. However, levosimendan proved useful to obtain faster symptom improvement. The results are of interest for generating hypotheses, but levosimendan should be studied in a clinical trial with a greater sample size before it can be safely recommended for more widespread use.

References

1 Llorens P, Miró O, Martín Sánchez FJ, Herrero Puente P, Jacob Rodríguez J, Gil V, et al. Guidelines for emergency management of acute heart failure: consensus of the Acute Heart Failure Working Group of the Spanish Society of Emergency Medicine (ICA-SEMES) in 2011. Emergencias. 2011;23:119-39.

2 Dickstein K, Cohen-Solal A, Filippatos G, McMurray J, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Eur Heart J. 2008;29:2388-442.

3 Thackray S, Easthaugh J, Freemantle N, Cleland JG. The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure-a meta-regression analysis. Eur J Heart Fail. 2002;4:515-29.

4 Parissis JT, Filippatos G, Farmakis D, Adamopoulos S, Paraskevaidis I, Kremastinos D. Levosimendan for the treatment of acute heart failure syndromes. Expert Opin Pharmacother. 2005;6:2741-51.

5 Antila S, Sundberg S, Lehtonen LA. Clinical pharmacology of levosimendan. Clin Pharmacokinet. 2007;46:535-52.

6 De Luca L, Colucci WS, Nieminen MS, Massie BM, Gheorghiade M. Evidence-based use of levosimendan in different clinical setting. Eur Heart J. 2006;27:1908-20.

7 Parissis JT, Panou F, Farmakis D, Adamopoulos S, Filippatos G, Paraskevaidis I, et al. Effects of levosimendan on markets of left ventricular diastolic function and neurohormonal activation in patients with advanced heart failure. Am J Cardiol. 2005;96:423-6.

8 Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, et al. Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet. 2002;360:196-202.

9 Moiseyev VS, Pöder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB, et al. RUSSLAN Study Investigators. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). Eur Heart J. 2002;23:1422-32.

10 Coletta AP, Cleland JGF, Freemantle N, Clark AL. Clinical trials update from the European Society of Cardiology Heart Failure meeting: SHAPE, BRING-UP 2 VAS, COLA II, FOSIDIAL, BETACAR, CASINO and meta-analysis of cardiac resynchronisation therapy. Eur J Heart Fail. 2004;6:673-6.

11 Follath F, Franco F, Cardoso JS. European experience on the practical use of levosimendan in patients with acute heart failure syndromes. Am J Cardiol. 2005;96:80-5.

12 Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure. Eur Heart J. 2005;26:384-416.

13 Llorens-Soriano P, Carbajosa-Dalmau J, Fernández-Cañadas J, Murcia-Zaragoza J, Climent-Payá V, Laghzaoui F, et al. Clinical Experience With Levosimendan in the Emergency Department of a Tertiary Care Hospital. Rev Esp Cardiol. 2007;60:878-982.

14 Framingham McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med. 1971;285:1441-6.

15 Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J. 2005;26:1115-40.

16 O'Connor CM, Starling RC, Hernández AF, Armstrong PW, Dickstein K, Hasselblad V, et al. Effect of nesiritide in patients with descomensated heart failure. N Engl J Med. 2011;365:32-43.

17 Slawsky MT, Colucci WS, Gottlieb SS, Greenberg BH, Haeusslein E, Hare J, et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Study Investigators. Circulation. 2000;102:2222-7.

18 Cleland JGF, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. Eur J Heart Fail. 2006;8:105-10.

19 Lilleberg J, Laine M, Palkama T, Kivikko, Pohjanjousi P, Kupari M. Duration of the haemodynamic action of a 24-h infusion of levosimendan in patients with congestive heart failure. Eur J Heart Fail. 2007;9:75-82.

20 Goebel JA, Van Bakel AB. Rational use of diuretics in acute decompensated heart failure. Current Heart Failure Reports. 2008;5:153-62.

21 Felker GM. Diuretic Management in Heart Failure. Congestive Heart Fail. 2010;16(supl):S68-S72.

22 Branzi G, Malfatto G, Villani A, Ciambellotti F, Revera M, Giglio A, et al. Acute effects of levosimendan on mitral regurgitation and diastolic function in patients with advanced chronic heart failure. J Cardiovasc Med (Hagerstown). 2010;11:662-8.

23 Jacob J, Llorens P, Martín-Sánchez FJ, Herrero P, Álvarez A, Pérez-Durá MJ, et al. Prognostic value of emergency department testing for N-terminal fragment of brain natriuretic peptide in patients with acute heart failure. The PICASU-1 study. Emergencias. 2011;23:183-92.

24 Miró O, Jacob J, Martín-Sánchez FJ, Herrero P, Pavón J, Pérez-Dura MJ, et al. Prognostic implications on the possibility to urgent testing for N-terminal fragment of brain natriuretic peptide in emergency department in patients with acute heart failure: the PICASU-2 study. Emergencias. 2011;23:437-46.

25 Miró Ò, Llorens P, Martín-Sánchez FJ, Herrero P, Pavón J, Pérez-Durá MJ, et al. Short-term prognostic factors in elderly patients seen in emergency department for acute heart failure. Rev Esp Cardiol. 2009;62:757-64.

26 Delaney A, Bardford C, McCaffrey J, Bagshaw SM, Lee R. Levosimendan for the treatment of acute severe heart failure: A meta-analysis of randomised controlled trials. Int J Cardiol. 2010;138:281-9.

27 Mebazaa A, Gheorghiade M, Piña I, Harjola VP, Hollenberg S, Follath F, et al. Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. Crit Care Med. 2008;36(supl):S129-39.

28 Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, et al. SURVIVE Investigators. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA. 2007;297:1883-91.

29 Parissis JT, Papadopoulos C, Nikolaou M, Bistola V, Farmakis D, Paraskevaidis I, et al. Effects of Levosimendan on quality of life and emotional stress in advanced heart failure patients. Cardiovasc Drug Ther. 2007;21:263-8.

30 Miró Ò, Llorens P, Martín-Sánchez FJ, Herrero P, Jacob J, Pérez-Durá MJ, et al. Predicting the risk of reattendance for acute heart failure patients discharged from Spanish Emergency Department observation units. Eur J Emerg Med. 2010;17:197-202.
31 Teerlink JR, Metra M, Zacà V, Sabbah HN, Cotter G, Gheorghiade M, et al. Agents with inotropic properties for the management of acute heart failure syndromes. Tradicional agents and beyond. Heart Fail Rev. 2009;14:243-53.
32 Parissis JT, Rafouli-Stergiou P, Paraskevaidis I, Mebazaa A. Levosimendan: from basic science to clinical practice. Heart Fail Rev. 2009;14:265-75.
33 Holley AD, Ziegenfuss M. Levosimendan: A new option in acute cardiac failure. Emerg Med Australas. 2006;18:505-9.

Eficacia de la administración precoz de levosimendán en urgencias en pacientes con insuficiencia cardiaca aguda: un ensayo clínico piloto aleatorizado

Llorens P, Miró O, Román F, Zapater P, Carbajosa-Dalmau J, Llanos L

Objetivo: Comparar la eficacia y la seguridad de la administración precoz de levosimendán junto con la terapia convencional en pacientes con síntomas graves de insuficiencia cardiaca aguda (ICA) atendidos en un servicio de urgencias (SU).
Método: Estudio piloto de intervención controlado con placebo, aleatorizado, triple ciego, unicéntrico, y que incluyó 45 pacientes con ICA avanzada atendidos en un SU. Los pacientes fueron aleatorizados 1:1 para recibir levosimendán o placebo añadido al tratamiento convencional. El objetivo primario fue la mejoría de la disnea basal las primeras 24 horas. También se registró la mejoría de la ortopnea, la ingurgitación yugular, el edema periférico, la diuresis acumulada, las modificaciones en la presión arterial sistólica y diastólica y en la frecuencia respiratoria y cardiaca. Se recogió los eventos adversos durante la administración del tratamiento. Se realizó un seguimiento de todos los pacientes a los 7 días, y en el primer y sexto mes tras el alta hospitalaria, y se registró la mortalidad y los reingresos hospitalarios por cualquier causa o su combinación.
Resultados: La disnea mejoró más rápido y en más pacientes con la administración de levosimendán ($p < 0,05$). Resultados similares se encontraron con la ortopnea ($p < 0,05$), sin diferencias significativas en el resto de las variables. Aparecieron efectos adversos en el 20% y en el 25% de los pacientes con levosimendán y placebo respectivamente ($p = NS$), pero en ningún caso motivó la retirada del paciente del estudio. No se observó diferencias respecto al reingreso, la mortalidad o la variable combinada.
Conclusiones: El tratamiento precoz con levosimendán no produce diferencias estadísticamente significativas respecto el reingreso o la mortalidad, aunque sí se asocia con un beneficio clínico significativo en términos de mejoría de la disnea y la ortopnea comparado con placebo. [Emergencias 2012;24:268-276]

Palabras clave: Levosimendán. Insuficiencia cardiaca aguda. Servicio de urgencias.