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ORIGINAL RESEARCH

Dobutamine versus levosimendan for patients with acute decompensated heart failure

Dobutamina versus levosimendán en pacientes con insuficiencia cardiaca agudizada

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Key words:
Heart failure worsened, dobutamine, levosimendan, LVEF.

Palabras clave:
Insuficiencia cardiaca agudizada, dobutamina, levosimendán, FEVI.

ABSTRACT

Introduction: Heart failure remains a highly frequent cause of hospitalization; with a high morbidity and mortality. **Objectives:** The aim of this study is to compare the 30-day in hospital survival of patients treated with Levosimendan vs. Dobutamine in acute decompensated heart failure. Secondary aims will be to compare the measurement of LVEF before and after inotropic and length of hospital stay. **Material and methods:** Observational, descriptive, retrospective study. All adult patients were admitted to the Hospital Christus Muguerza Alta Especialidad, with acute decompensated heart failure diagnosis and have required inotropic support in the period January 2013 to September 2015 were collected. **Results:** 83 patients were included, however only 38 met the inclusion criteria. Of the 38 patients 20 (53%) were prescribed levosimendan and 18 (47%) dobutamine. The average age in both groups was 62.2 years (± 15.6) of levosimendan versus dobutamine 78.8 years (± 10.6) (p = 0.0005). Survival at 30 days was 100% in levosimendan versus 77.8% in dobutamine (p = 0.0274). In days of hospital stay it was 9.3 days (± 5.1) levosimendan and 13.8 days (± 6.5) in dobutamine (p = 0.02). postinotropic LVEF change was 18.3% (± 6.2) levosimendan versus 18.7% (± 9.9) dobutamine (p = 0.88). **Conclusions:** The use of dobutamine leads to a lower survival to 30 days, in addition to longer hospital stay. However no difference in LVEF values at admission or inotropic post.

RESUMEN

Introducción: *La insuficiencia cardiaca agudizada continúa siendo una causa altamente frecuente de hospitalización con una gran morbimortalidad.* ***Objetivos:*** *El objetivo primario es comparar la sobrevida a 30 días de los pacientes tratados con levosimendán versus dobutamina en insuficiencia cardiaca agudizada. Como objetivo secundario será comparar la determinación de la FEVI pre- y post-inotrópico y días de estancia hospitalaria.* ***Material y métodos:*** *Estudio observacional, descriptivo, retrospectivo. Se recabaron todos los pacientes adultos que hayan ingresado en el Hospital Christus Muguerza Alta Especialidad, con diagnóstico de insuficiencia cardiaca agudizada y que hayan requerido el apoyo de inotrópicos, en el periodo comprendido de enero de 2013 a septiembre de 2015.* ***Resultados:*** *Se documentaron 83 pacientes con diagnóstico de insuficiencia cardiaca agudizada, de los cuales sólo 38 cumplieron con los criterios de inclusión. De los 38 pacientes a 20 (53%) se les indicó levosimendán y a 18 (47%) dobutamina. La media de edad en ambos grupos fue de 62.2 años (±15.6) de levosimendán versus 78.8 años de dobutamina (±10.6) (p = 0.0005). La supervivencia a 30 días fue de 77.8% en dobutamina versus 100% levosimendán (p = 0.0274). En días de estancia hospitalaria fue de 9.3 días (± 5.1) en levosimendán y de 13.8 días (± 6.5) en dobutamina (p = 0.02). El cambio FEVI postinotrópico fue de 18.3% (± 6.2) levosimendán versus 18.7% (± 9.9) dobutamina (p = 0.88).* ***Conclusiones:*** *El uso de Dobutamina conlleva a una menor sobrevida a 30 días, además de tener mayor estancia hospitalaria. Sin embargo no hay diferencia en los valores de FEVI al ingreso ni postinotrópico.*

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INTRODUCTION

The term acute heart failure includes a group of related clinical syndromes, defined as a gradual or rapid change in the signs and symptoms of heart failure, resulting in a need for urgent therapy. It is a critical inability of the myocardium to maintain an adequate cardiac output to meet the demands of the peripheral circulation. Acute Heart failure can present as new onset or worsening of preexisting chronic heart failure.[1]

It is the leading cause of hospitalization in patients over 65 years, the rate of hospitalization is increasing due to the progressive aging of the population and a better management of acute myocardial infarction. Moreover, nearly 50% of patients hospitalized with acute heart failure are readmitted within 6 months after discharge. Hospital mortality is about 5% and the risk of death or rehospitalization within 2-3 months ranges from 20% to 60% depending on the population study.[1]

In theory, inotropic agents improve hemodynamic parameters, increasing cardiac output and reducing the filling pressure of the left and the right ventricle by increasing myocardial contractility. Consequently, they are indicated for treating both patients with peripheral hypoperfusion and water retention caused by deterioration of cardiac contractility.[2-4]

Dobutamine is a synthetic catecholamine acting primarily through stimulation of β1 receptors and partly through β2 receptors to produce positive inotropic and chronotropic depending of the dose.[5-7]

Levosimendan is a pyridazinone-dinitrile derivative acts by increasing the affinity of troponin C to calcium and stabilizes the conformation of troponin C. By improving the sensitivity of the contractile apparatus to intracellular calcium, it has positive inotropic properties without impairing relaxation ventricular nor induce cytosolic calcium overload.[8-12]

There are multiple studies in which the effectiveness of these two drugs are compared, but in Mexico there is no reported series.[13-19]

OBJECTIVE

The aim of this study is to compare the 30-day in hospital survival of patients treated with levosimendan versus dobutamine in acute decompensated heart failure. Secondary aims will be to compare the measurement of LVEF before and after inotropic and length of hospital stay.

MATERIAL AND METHODS

Observational, descriptive, retrospective study. Study Data was collected from the records of the department of statistics. Were selected all patients who entered with the diagnosis of acute decompensated heart failure during the period from January 2013 to September 2015 at Christus Muguerza High Specialty Hospital.

All information was collected from medical records and include all patients over 18 years with the diagnosis of acute decompensated heart failure who have required inotropic support and have had oliguria. Patients with persistent systolic BP < 85 mmHg, persistent heart rate > 130 bpm and a history of arrhythmias were excluded.

The Excel program and Medcalc program was used. To compare survival, the Kaplan-Meier curve was used. Comparison of Means Using Student's t-Test and chi-square calculations to compare proportions. Medical records were used to look for 30 days survival, comorbidities, base treatment, length of stay in hospital, age. For the calculation of LVEF aPhillips hd7 echocardiogram was used and by a biplane method the LVE was calculated, the result was obtained from medical records.

As operational definitions: acute heart failure: patient who meets exacerbation of dyspnea in addition to a LVEF of 50% found by transthoracic echocardiography. Oliguria: patient presenting diuresis less than < 0.5 mL/kg/hr.

The study followed the ethical guidelines in accordance with the ethical standards of the Helsinki Declaration of 1975 with last update in 2013 and the Scientific and Ethics Committee of the institution where it was made.

No external sources of finance were required. There are no conflicts of interest.

RESULTS

During the period from January 2013 to September 2015, 83 patients diagnosed with acute

Table I. Baseline characteristics of the patients.

General population n = 38		
Gender	Male	14 (37%)
	Female	24 (63%)
Age (years)		70.1 (± 15.7)
Comorbilities	DM	20 (53%)
	HTN	20 (53%)
	AMI	10 (26%)
	AF	4 (11%)
	Cardiomyopathy	2 (5%)
	Malignancies	4 (11%)
	CKD	6 (16%)
	Rheumatolology	4 (11%)
	Hypothyroidism	4 (11%)
Baseline treatment	BB	14 (37%)
	ARB	8 (21%)
	ACEi	14 (37%)
	CCB	2 (5%)
	Diuretic	10 (26%)
	ARA	4 (11%)
	Digoxin	4 (11%)
	Nitrates	4 (11%)
	Statins	6 (15%)
	Antiplatelets	12 (32%)
	Insuline	8 (21%)
	OA	8 (21%)
	Others	8 (21%)

DM = Diabetes mellitus, HTN = Arterial hypertension, AMI = Acute myocardial infarction, AF = Atrial fibrillation, CKD = Chronic kidney disease, BB = Beta-blockers, ARB = Angiotensin receptor blocker, CCB = Calcium channel blockers, ACEi = Angiotensin converting enzyme inhibitors, ARA = Aldosterone receptor agonist, AO = Oral antidiabetic.

Table II. Baseline results of the patients.

General population n = 38		
Inotropic	Levosimendan	20 (53%)
	Dobutamine	18 (47%)
Days of intrahospital stay		11.5 (± 6.2)
Death		4 (11%)
Initial LVEF		27% (± 10%)
Final LVEF		46% (± 9.6%)
% change LVEF		18.5% (± 8%)

LVEF = Left ventricular ejection fraction.

heart failure were selected, of which only 38 met the inclusion criteria.

A 37 % of them were males and 63% females. The average age was 70.1 years (±15.7). Among the most frequent comorbidities, diabetes mellitus (53%) and arterial hypertension (53%) were the most prevalent. About base treatment of patients, it was evidenced that beta-blockers (37%) and ACE inhibitors (37%) were the most prevalent. The rest of the characteristics of the study population can be found in *table I*.

In 20 patients of 38 (53%) were prescribed with levosimendan and 18 (47%) with dobutamine *(Table II)*. The average of hospital stay was 11.5 days (± 6.2); of the total of patients there were 4 (11%) who died. The average income of LVEF was 27% (± 10%), post-inotropic management was 46% (± 9.6), having a mean change in LVEF of 18.5% (± 8%).The average of LVEF during income was 27% (± 10%), post-inotropic management was 46% (±9.6), having a mean change in LVEF of 18.5% (± 8%).

By comparing levosimendan versus dobutamine groups *(Table III)*, it was demonstrated that the proportion of female was 50 versus 78% (p = 0.15) respectively. The average age in both groups was 62.2 years (± 15.6) of levosimendan versus 78.8 years (± 10.6) (p = 0.0005). Among the comorbidities in which exist a statistically significant difference was in the proportion of patients with diabetes mellitus, which was 20 versus 83% levosimendan with dobutamine (p = 0.0004). Regarding the base treatment there was not found significant difference in the use of Beta-blockers (50% levosimendan and versus dobutamine 22%; p = 0.15) nor ACE inhibitors (30% levosimendan and versus dobutamine 44%; p = 0.58); the base treatment in which there was found significant difference it was in the use of calcium channel antagonists (40% levosimendan and versus dobutamine 0%; p = 0.009).

Survival analysis of Kaplan-Meier method was performed *(Figure 1)*, where survival within 30 days was of the 77.8% in patients treated with dobutamine versus 100% with levosimendan (p = 0.0274).

Comparing both therapeutic measures are summarized in *table IV*, it was found that there is not statistically significant difference in the

Table III. Comparative description of patients according to study group.

General population comparative				
Inotropic		Levosimendan n = 20	Dobutamine n = 18	p
Gender	Male	10 (50%)	4 (22%)	0.15
	Female	10 (50%)	14 (78%)	0.15
Age (years)		62.2 (± 15.6)	78.8 (± 10.6)	0.0005
Comorbilities	DM	4 (20%)	16 (83%)	0.0004
	HTM	10 (50%)	10 (56%)	0.96
	AMI	6 (30%)	4 (22%)	0.85
	AF	2 (10%)	2 (11%)	0.67
	Cardiomyopathy	2 (10%)	0 (0%)	0.51
	Malignancies	4 (20%)	0 (0%)	0.14
	CKD	4 (20%)	2 (11%)	0.75
	Rheumatology	0 (0%)	4 (22%)	0.09
	Hypothyroidism	0 (0%)	4 (22%)	0.09
Baseline treatment	BB	10 (50%)	4 (22%)	0.15
	ARB	8 (40%)	0 (0%)	0.009
	ACEi	6 (30%)	8 (44%)	0.58
	CCB	2 (10%)	0 (0%)	0.51
	Diuretic	8 (40%)	2 (11%)	0.09
	ARA	2 (10%)	2 (11%)	0.67
	Digoxin	2 (10%)	2 (11%)	0.67
	Nitrates	4 (20%)	0 (0%)	0.14
	Statins	0 (0%)	6 (33%)	0.02
	Antiplatelets	6 (30%)	6 (33%)	0.88
	Insuline	2 (10%)	6 (33%)	0.18
	OA	4 (20%)	4 (22%)	0.8
	Others	4 (20%)	4 (22%)	0.8

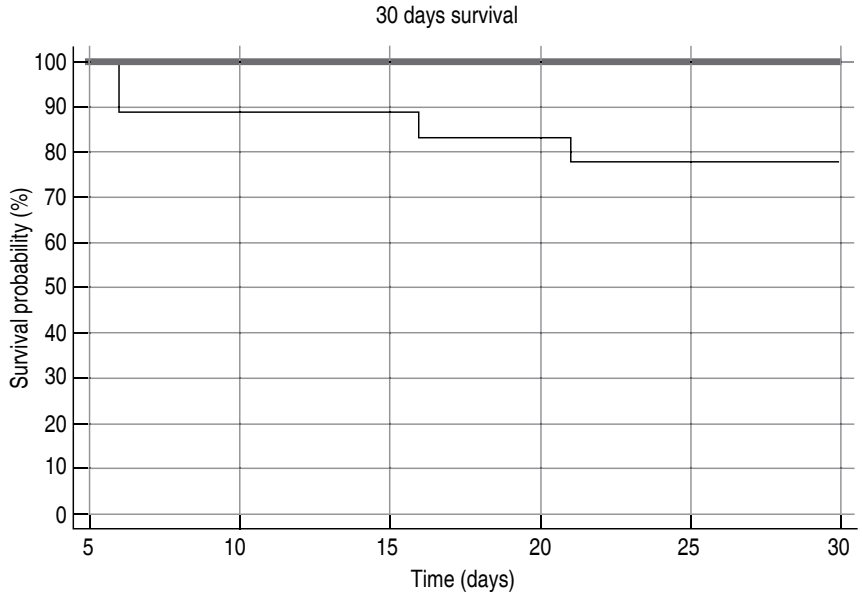
DM = Diabetes mellitus, HTN = Arterial hypertension, AMI = Acute myocardial infarction, AF = Atrial fibrillation, CKD = Chronic kidney disease, BB = Beta-blockers, ARB = Angiotensin receptor blocker, CCB = Calcium channel blockers, ACEi = Angiotensin converting enzyme inhibitors, ARA = Aldosterone receptor agonist, AO = Oral antidiabetic.

hospital stay, reporting an average of 9.3 days (± 5.1) levosimendan and 13.8 days (± 6.5) in dobutamine (p = 0.02). About mortality, there was not found significant difference (0 versus 22% levosimendan and dobutamine; p = 0.09), nor in the variation of the change in LVEF with both drugs (18.3% [± 6.2] levosimendan versus 18.7% [± 9.9] dobutamine; p = 0.88).

DISCUSSION

The main objective of this study was to demonstrate the survival to 30 days in both therapeutic measures. There was found statistically significant difference between these two groups; patients who were treated with dobutamine got shorter survival; However, in the literature revised,[15] says there is not difference between these groups. It might consider that this lower survival in the dobutamine group, it is because patients were older and had more comorbidities such as diabetes mellitus.

Although most patients died in the dobutamine group, there was no significant difference, which is related to what was stated by Mebazaa A, et al[16] despite the length in the administration of inotropic it was similar, patients treated with levosimendan had a shorter hospital stay.



Survival within 30 days was of the 77.8% in patients treated with dobutamine versus 100% with levosimendan (p = 0.0274).

Figure 1.

30-day survival Kaplan-Meier curve of levosimendan versus dobutamine.

Table IV. Table of results between levosimendan versus dobutamine.

Treatment comparative			
Inotropic	Levosimendan n = 20	Dobutamine n = 18	p
Dose (µg/kg/min)	0.065 (± 0.023)	3.5 (± 0.85)	< 0.0001
Treatment duration (hours)	48 (± 19)	46.6 (± 23.6)	0.84
Intrahospital stay (days)	9.3 (± 5.1)	13.8 (± 6.5)	0.02
Death	0 (0%)	4 (22.2%)	0.09
Initial LVEF	29.1% (± 10.5%)	25.3% (± 9.4%)	0.25
Final LVEF	47.4% (± 10)	44% (± 9.1)	0.28
% change LVEF	18.3% (± 6.2)	18.7% (± 9.9)	0.88

LVEF = Left ventricular ejection fraction.

Regarding LVEF, there were no significant differences in baseline LVEF compared after administration of the drug, neither a mean improvement of this. This was stated already.[18]

As discussed previously the groups were not entirely homogeneous, because the dobutamine group patients were older, in addition to this, between the comorbidities there were found statistically significant difference in the fact of suffer diabetes.

It is remarkable that beta blockers and ACE inhibitors were the base treatment in these two groups, being the main drugs that handles the medical reviews for optimal management of patients with heart failure. There were no differences in the use of these measures in the two groups; however levosimendan treated patients had greater use of ARBs, compared to the dobutamine group, which is also considered first-line management of this disease.

This study has limitations such as is purely descriptive and observational, therefore the patients were not randomized, and the decision to use either drug was based on each physician. Another limitation is that the calculation of LVEF is through an echocardiogram, which as is well known is operator dependent, so the results provided are approximations. However in our search this is the first Mexican series that reports the comparison between these two therapeutics.

CONCLUSION

The use of dobutamine leads to a lower survival to 30 days, in addition to longer hospital stay. However, there is not difference in LVEF values at admission or postinotropic effect.

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