Uso y seguridad de levosimendan en una unidad de cuidados intermedios: revisión de la experiencia de 3 años

Use and safety of Levosimendan in an Intermediate Care Unit: 3-year experience review

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ABSTRACT

Introduction: Levosimendan is an inodilator with positive inotropic effect whose demonstration of hemodynamic and clinical benefits has not always been consistent. The most recent meta-analyzes show stronger evidence of it, especially in some subgroups. The objective was to evaluate the experience in the use of levosimendan, characterizing the mode of prescription, the target population, clinical benefits and adverse effects.

Materials and Methodologies: All patients who took Levosimendan in an Intermediate Care Unit during three full years were included. General clinical and analytical parameters, co-morbidities and characteristics of hospitalization were obtained, as well as readmissions up to 6 months.

Results: There were 39 events. Thirteen admissions were scheduled. Only 4 patients tolerated the maximum recommended levosimendan speed. All completed 12.5 mg of levosimendan, 10 of which required aminergic support. In-hospital mortality was 15.4%. For all the patients who died, admission was urgent.

Conclusions: No patient with scheduled admission required aminergic support or died during hospitalization. It is not possible to infer whether it would be possible to perform the same dose in a shorter period of time, even because of the small number that tolerated the maximum speed. Results of ongoing studies may help assess safety and propose selection criteria for patients suitable for day hospital administration. Particularly in patients with advanced HF, intermittent and repeated administration, as occurred in this study, is a promising option. However, there are still important gaps, namely which is the ideal cumulative dose and the frequency with which it should be performed.

Keywords: Levosimendan, Heart Failure, Intermediate Care Unit, Cardiotonic Agents, Prognosis

RESUMEN

Introducción: El levosimendan es un sensibilizador de calcio con efecto inotrópico positivo cuya demostración de beneficios hemodinámicos y clínicos no siempre ha sido consistente. Los metanálisis más recientes muestran pruebas más contundentes de ello, especialmente en algunos subgrupos. El objetivo fue evaluar la experiencia en el uso de levosimendan, caracterizando el modo de prescripción, la población, los beneficios clínicos y los efectos adversos.

Materiales y Metodologías: Se incluyeron todos los pacientes que tomaron Levosimendan en una Unidad de Cuidados Intermedios durante tres años. Se obtuvieron parámetros clínicos y analíticos generales, comorbilidades y características de la hospitalización, así como reingresos hasta los 6 meses.

Resultados: Hubo 39 eventos. Se programaron trece ingresos. Solo 4 pacientes toleraron la velocidad máxima recomendada de levosimendan. Todos completaron 12,5 mg de levosimendan, 10 de los cuales requirieron apoyo aminérgico. La mortalidad hospitalaria fue del 15,4%. Para todos los pacientes que fallecieron, el ingreso fue urgente.

Conclusiones: Ningún paciente con ingreso programado requirió apoyo aminérgico ni falleció durante la hospitalización. No es posible inferir si sería posible realizar la misma dosis en un período de tiempo más corto, incluso por el pequeño número que toleró la velocidad máxima. Los resultados de los estudios en curso pueden ayudar a evaluar la seguridad y proponer criterios de selección para pacientes adecuados para la administración en un hospital de día. Particularmente en pacientes con IC avanzada, la administración intermitente y repetida, como ocurrió en este estudio, es una opción prometedora. Sin embargo, existen lagunas importantes, a saber, cuál es la dosis acumulativa ideal y la frecuencia con la que debe realizarse.

Palabras-clave: Levosimendan, Insuficiencia cardíaca, Unidad de cuidados intermedios, Cardiotónicos, Pronóstico

INTRODUCTION

Levosimendan is an inodilator that acts to open potassium channels and to sensitize calcium. It has a positive inotropic effect, without increasing myocardial oxygen consumption, vasodilation and cardioprotection, in addition to having an active metabolite with a long-acting effect [1,2].

The hemodynamic and clinical benefits that have been presented in several randomized clinical trials have not consistently translated into an improvement of prognosis in the short/medium term [3-5]. However, the most recent meta-analyzes point to stronger, albeit limited, evidence in this regard, especially when used in patients with acute decompensated heart failure (HF) under beta-blockers and in patients with advanced HF [6-12]. Intermittent outpatient administration to patients with advanced HF is an area with positive results but still scarce[10], with at least one larger randomized trial underway, aimed at patients in the post-hospitalization period[13].

Approved in Portugal since 2001, Levosimendan is only administered intravenously and sold in 5mL bottles with a concentration of 2.5mg/mL. The mode of administration, namely the rate of infusion and the use or not of an initial bolus, are hypotheses pointed out as factors of heterogeneity that may have contributed to the disagreement in the results obtained in previous studies.

The aim of the present study was to evaluate the experience in the use of levosimendan, characterizing the mode of prescription, the target population, clinical benefits and adverse effects, as well as readmission and mortality in the short and medium term.

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MATERIALS AND METHODOLOGIES

The study included all patients admitted to our Internal Medicine Intermediate Care Unit between January 1, 2017 and December 31, 2019 who were treated with Levosimendan while in this unit. Each hospital stay was defined as a case. No exclusion criteria were defined.

The following clinical and analytical parameters were obtained: age, sex, KATZ Index of Independence in Activities of Daily Living[14](minimum 0, maximum 6), Charlson co-morbidity index[15,16](minimum 0, maximum 33), pathological history, etiology of heart failure, baseline functional stage in the year prior to hospitalization according to the New York Heart Association classification[17], left ventricular ejection fraction (LVEF) as calculated on the most recent echocardiogram, value of the N-terminal fragment of type B natriuretic peptide (NT-ProBNP) in picogram/milliliter in the last year and 6 months after discharge obtained in routine study (excluding hospitalization or urgency related to heart disease), NT-ProBNP value before starting treatment with levosimendan and at discharge date, usual medication prior to hospitalization, follow-up in a specialized heart failure consultation, number of hospitalizations in the previous year, type of hospital admission (urgent or scheduled), origin of hospital admission, length of stay, day of hospital stay on which levosimendan was started, maximum levosimendan perfusion rate (in microgram/kilo/minute), total dose of levosimendan (in milligrams), need and duration of aminergic support, mortality at discharge date, as well as status and readmission at 3 and 6 months after discharge. The results of the KATZ index were divided into 3 categories: A (score 5-6, high autonomy), B (score 3-4, moderate autonomy) and C (score 1-2, impaired autonomy). The diagnosis of severe chronic kidney disease was admitted in those who had an estimated glomerular filtration rate <30 milliliters/minute/1.73m^2 using the CKD-EPI formula, using the most recent serum creatinine value obtained outside of acute events. The diagnoses of heart failure were divided into 3 categories according to LVEF: preserved, intermediate and reduced to LVEF ≥ 50%, 40-49% and <40%, respectively[18].

Descriptive statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY, USA: IBM Corp). For continuous parametric variables, the values are presented with mean ± standard deviation; for nonparametric, the median (interquartile range) is shown. The normality of distribution in continuous variables was assessed using the Kolmogorov-Smirnov, Shapiro-Wilk tests, as well as asymmetry and kurtosis. To compare paired nonparametric continuous variables, the Wilcoxon test was used. The p-value considered statistically significant was <0.05 and all tests presented are the result of 2-sided tests.

The study was approved by the Ethics Committee of the Hospital Centre under the number 111/2020.

RESULTS

During the stipulated period, there were 39 hospitalizations of 30 patients who met the inclusion criteria. Male gender was more prevalent (n = 31, 79.5%), and the mean age was 70 ± 12 years. Almost 90% (n = 34) had a KATZ index in category A. The median Charlson index was 6 (5-7), corresponding to an estimated 10% survival at 10 years. More than half of the patients had at least 1 hospital stay in the previous year (n = 20).

The diagnosis of heart failure was the most frequent isolated pathological history, previously present in all but 2 cases (whose hospitalization was the first presentation). Overall, cardiovascular diseases corresponded to the most common antecedents, and their prevalence, as well as other co-morbidities, is shown in Table 1. This table also shows the frequency of use of drugs in an outpatient setting. The most used diuretics were loop (n = 33). More than ¾ were medicated with beta blocker and ⅔ with angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor antagonist (ARA).

The characterization of heart failure is shown in table 2. Ischemic etiology was present in more than 1/3 of the cases (n = 14), with alcoholic etiology being the second most prevalent (n = 10). About 4 out of 5 cases had a reduced LVEF (n = 31) and half had a NYHA baseline functional stage of 3 (n = 19). The baseline median value of NT-proBNP was 1799 [980-2793] pg/mL, significantly lower than the median value presented before starting levosimendan treatment (p <0.001). Only 7 patients had no previous follow-up in a specialized heart failure consultation.

Table 3 shows the parameters related to hospitalization, including the administration of levosimendan, as well as intra and post-hospital mortality. Only 13 admissions were scheduled, the rest being urgent. All scheduled admissions (plus 6 urgent ones) originated at the outpatient clinic (n = 19). Twelve came from the Emergency Department and the rest were admitted by transferring them from other inpatient services. Most patients (n = 24) started levosimendan within the first 48 hours of hospitalization, although about ¼ only started it after at least 1 week. Only 4 patients tolerated the maximum recommended levosimendan speed (0.20 µg/kg/min) and ⅓ only tolerated 0.05 µg/kg/min. Despite this, all patients completed an ampoule of levosimendan (12.5 mg), although 10 of them required aminergic support, at least partially, during the administration period. No patient with scheduled admission (and only 1 from the outpatient clinic) required aminergic support. The NT-proBNP values at the discharge date were significantly lower than those presented before the start of treatment with levosimendan (p <0.001), but still significantly higher than the baseline values (p = 0.023). However, there were no statistically significant differences between the baseline NT-proBNP values before and after hospitalization (p = 0.605).

In-hospital mortality was 15.4% (n = 6). For all the patients who died, admission had been urgent. During the 30 days after discharge, 2 more patients died, both already being part of the group of scheduled admissions. One of them, the oldest in the study at 92 years old, was admitted to the emergency department, where he died, the day after discharge with a sustained ventricular tachycardia. Another 2 patients were re-admitted within 30 days after discharge. At 6 months after discharge, 23 patients had died (n = 14) or been re-admitted (n = 9) due to heart failure.

DISCUSSION

HF remains the most frequent isolated diagnosis that motivates hospital admission of acute patients[19]. Despite the improvement in survival provided by the introduction of prognostic-modifying therapy, patients with HF maintain a substantial risk of death or recurrent decompensation[20], and the need for inotropic treatment is not rare. Levosimendan is a therapeutic option approved in Portugal that, despite conflicting results in the past, has accumulated evidence of hemodynamic and clinical benefits[12]. It is distinguished from other catecholaminergic inotropes by its 3 mechanisms of action: positive inotropism, vasodilation and cardioprotection. In turn, pharmacokinetics allows hemodynamic and pharmacological actions to be prolonged, due to the presence of its active metabolite. This explains why the cardiovascular effects prevail for days after the end of the infusion[21].

In the present study, most of the patients evaluated had a high Charlson index, associated with a low probability of survival at 10 years. These data reinforce the prevalence of co-morbidities in these patients, which places even more importance on the development of therapies that can reduce the morbidity and mortality associated with HF. To date, no treatment has shown, with significant evidence, to reduce morbidity and mortality in patients with HF with preserved and intermediate LVEF. Despite this, this group has a high prevalence of elderly and very symptomatic patients, changing the therapeutic objective for the relief of symptoms and improvement of quality of life[18]. The population presented here was heterogeneous as to LVEF, but mostly with reduced ejection fraction. Thus, extrapolation regarding the efficacy and safety of this drug, particularly in the population with intermediate or preserved ejection fraction, is limited.

In HF, in an acute or chronic context, elevated levels of natriuretic peptides correlated with a worse prognosis, namely with a higher risk of death, major cardiovascular event, atrial fibrillation or stroke[22].

During hospitalization, there was a significant reduction in plasma concentrations of NT-proBNP. Although these did not return to baseline values at the time of discharge, this was achieved during the next 6 months. The use of levosimendan may have contributed, together with the other drugs, namely prognostic modifiers, to this improvement. Given their active metabolite with a prolonged effect over time, patients with scheduled and short hospital stays were discharged after the infusion, but with potential beneficial effects not yet fully accounted for. All patients analyzed underwent the infusion in a level two unit. The perfusion under the Day Hospital regime could allow this drug to be made available to more patients and more frequently. No patient with scheduled admission, which would correspond to an approximation of those who would be candidates for admission to a hospital during the day, needed aminergic support or died during hospitalization. Although these data may point to safety in day hospital administration, it is not possible to infer whether it would be possible to carry out the same dose of levosimendan in a shorter period of time, which would necessarily have to happen. Only 4 patients tolerated the maximum recommended levosimendan speed. However, in our Intermediate Unit there is no urgent need of achieving maximum speed, at it might not have been tried in many patients. We need to see the results of ongoing studies regarding use of levosimendan in a Day Hospital that will probably allow the proposal of selection criteria that make it possible to choose subgroups with an adequate safety profile.

Overall, there was a high rate of in-hospital mortality, particularly in patients whose admission was urgent. However, these data were not entirely unexpected since, particularly in this subgroup, patients with advanced HF whose symptoms remain despite the best tolerated therapy are included. This data suggests the relevance of carrying out studies with the earlier use of this drug, particularly in symptomatic patients. Early administration, in an elective way, could be a tool capable of improving the quality of life of these patients, reducing symptoms and the number of hospitalizations due to acute HF.

One of the concerns with the administration of inotropic therapy is related to its arrhythmogenic potential. One of the limitations of the study, due to its retrospective design, was the impossibility of clarifying, in most cases, the cause of death, as well as the absence of a control group that allowed to compare the extent to which the benefits and complications can be attributed only to the levosimendan.

It would be important to carry out real-world studies, namely, with the subgroups of HF that have shown greater evidence of benefit with levosimendan (exacerbated under beta-blockers and advanced HF), with significantly larger sample sizes and with homogeneous administration methodology. Particularly in patients with advanced HF, intermittent and repeated administration, as occurred in several of the patients in the present study, is an option that looks promising[10,23].

There are still important gaps to fill, namely which ideal cumulative dose and to identify the frequency with which it should be performed[24].

Table 1. Descriptive statistics of demography, pathological history and usual medication.

Variables		n (%)
Age (years)	mean ± SD	70 ± 12
Sex (Male)		31 (79,5)
KATZ index (category A)		34 (87,2)
Charlson index	median [IQR]	6 [5-7]
Hospitalizations in the previous year		
0		19 (48,7)
1-2		18 (46,5)
3-4		2 (5,1)
Pathological history		
Heart Failure		37 (94,9)
Acute myocardial infarction		13 (33,3)
Diabetes mellitus		12 (30,8)
Stroke		10 (25,6)
Chronic obstructive pulmonary disease		9 (23,1)
Peripheral artery disease		7 (17,9)
Severe chronic kidney disease		1 (2,6)
Active solid neoplasm		5 (12,8)
Active lymphoma		2 (5,1)
Usual medication		
ACEI/ARB		26 (66,7)
Beta blockers		30 (76,9)
Aldosterone antagonist		17 (43,6)
Neprilisin Inhibitor		8 (20,5)
iSGLT2		1 (2,6)
Nitrate		17 (43,6)
Ivabradine		7 (17,9)
Loop diuretic		33 (84,6)
Metolazone		4 (10,3)
Triamterene		1 (2,6)

Values presented in n (%) format except when specified. IQR - interquartile range; ARB - angiotensin II receptor blocker; SD - standard deviation; ACEI - Angiotensin converting enzyme inhibitor; iSGLT2 - Renal sodium-glucose co-transporter 2 inhibitors

Table 2. Descriptive statistics of variables associated with heart failure.

Heart Failure	n (%) or median [IQR]
Etiology	
Alcoholic	10 (25,6)
Ischemic	10 (25,6)
Ischemic + Valvular	3 (7,7)
Ischemic + Hypertensive	1 (2,6)
Valvular	5 (12,8)
Cardiotoxicity after chemotherapy	5 (12,8)
Viral cardiomyopathy	3 (7,7)
Hereditary	2 (5,1)
LVEF	
≥ 50%	3 (7,7)
40-49%	5 (12,8)
<40%	31 (79,5)
NYHA stage	
1	7 (17,9)
2	12 (30,8)
3	19 (48,7)
4	1 (2,6)
NT-proBNP (baseline)	1799 [980-2793]
Previous specialized heart failure consultation	
Cardiology	15 (38,5)
Cardiology + Internal Medicine	2 (5,1)
Internal medicine	12 (30,8)
Private	3 (7,7)
No follow-up	7 (17,9)

IQR - interquartile range; LVEF - left ventricular ejection fraction; NYHA - New York Heart Association; NT-proBNP - N-terminal fragment of type B natriuretic peptide; NT-proBNP value presented in picogram / milliliter

Table 3. Descriptive statistics of variables associated with hospitalization and prognosis

	n (%) or median [IQR]
Admission	
Urgent	26 (66,7)
Scheduled	13 (33,3)
Origin	
Ambulatory	19 (48,7)
Emergency Service	12 (30,8)
Another internment	8 (20,5)
Total length of stay (days)	5 [2-26]
Length of stay at Intermediate Unit (days)	3 [2-8]
NT-proBNP at start of Levosimendan	14763 [3965-35519]
Time until start of Levosimendan	
<48 hours	24 (61,5)
2-7 days	5 (12,8)
>7 days	10 (25,6)
Maximum levosimendan perfusion rate	
0,05	13 (33,3)
0,08	1 (2,6)
0,10	21 (53,8)
0,20	4 (10,3)
Need for aminergic support	10 (25,6)
Length of aminergic support	
2-3 days	2 (20,0)
4-6 days	7 (70,0)
≥ 7 days	1 (10,0)
NT-proBNP at discharge	4816 [1739-6882]
NT-proBNP baseline after discharge	1088 [635-3242]
In-hospital mortality	6 (15,4)
30-days mortality	8 (20,5)
30-days readmission	2 (6,4)
3-months mortality	11 (28,2)
3 months readmission	5 (17,8)
6-months mortality	14 (35,9)
6 months readmission	9 (36,0)

IQR - interquartile range; NT-proBNP - N-terminal fragment of type B natriuretic peptide; NT-proBNP value presented in picogram / milliliter; maximum infusion rate of Levosimendan presented in microgram / kilo / minute; the percentage calculation of readmissions is adjusted to the total denominator to the number of patients alive at the calculated date

CONCLUSIONS

There is more sustained evidence of the usefulness of levosimendan in some subgroups. When used in a programmed manner (mainly in the subgroup of advanced HF), it presented a good safety profile and very low risk of adverse effects. Its use in this population aims to improve the quality of life, and the high mortality at 6 months was expected. The data obtained favor the possibility of its administration in a day hospital, although there is limited evidence of the tolerance of higher administration speeds, necessary in this context.

CONFLICT OF INTEREST

There is no conflict of interest.

SOURCE OF FUNDING

This research had no funding sources.

ETHICAL ASPECTS

All participants submitted a consent form to be included in this study.
The study was approved by the Ethics Committee of the Hospital Centre under the number 111/2020.

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